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Report

Meeting the Demand for Unrelated Donors in the Midst of the COVID-19 Pandemic: Rapid Adaptations by the National Marrow Donor Program and Its Network Partners Ensured a Safe Supply of Donor Products

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A B S T R A C T

The impact of the coronavirus disease 2019 (COVID-19) pandemic on hematopoietic cell transplant (HCT) donor registries and transplant center (TC) practices is underreported. This article reports on the National Marrow Donor Program (NMDP) Be The Match Registry and its coordinating the provision of unrelated donor (URD) products to domestic and international TCs during the initial 3 months of the COVID-19 pandemic (March through May 2020). Specifically, NMDP data are presented for disease indications for transplant, URD search volumes and availability, graft requests and processing, courier utilization and performance, and conversion rates from formal donor search and workup to graft collection and shipment. Data following the onset of COVID-19 are compared to the immediate 3 months prior to the COVID-19 pandemic (December 2019 through February 2020) and the same quarter 1 year prior to COVID-19 (March through May 2019). During the initial onset of COVID-19 and compared to 1 year prior, TCs requested and the NMDP performed less donor searches. More multiple URD and direct to workup requests were processed by the NMDP, which likely reflected reductions in donor availability. Yet TCs continued to perform allogeneic transplants for acute disease indications like acute leukemia and myelodysplasia, using more cryopreserved grafts than before COVID-19. In comparison to prepandemic patient cycle conversion rates and durations, the NMDP was able to convert patient cycles at nearly the same or higher rates and in similar or shorter periods of time. Last, despite significant challenges caused by the pandemic, including interruptions in domestic courier services and travel restrictions, graft products were delivered to and received by TCs in similar periods of time than before COVID-19. Taken together, these data show that NMDP service line operations continued to function effectively during the early phases of the COVID-19 pandemic, ensuring requests for and delivery of URD products to domestic and international allogeneic HCT recipients.

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory virus syndrome coronavirus 2 (SARS-CoV-2) has had catastrophic effects on human life and the global economy. As a result, the pandemic has caused major interruptions in daily life, including disruptions in the provision of essential goods and medical care to millions [1] as well as revealing social and racial inequalities [2]. Similarly, the COVID-19 pandemic created many challenges for hematopoietic cell transplant (HCT) patients and families, medical caregivers, and transplant centers, apheresis/bone marrow collection centers, and donor registries [3].

To address some of these challenges, new care guidelines for managing HCT recipients and donor grafts rapidly emerged from transplant societies and donor registries to mitigate the risk of obtaining and transmitting SARS-CoV-2 [4-6]. Modifications to these guidelines were frequent, reflecting the need for rapid dissemination of new knowledge and practices [7]. Communications from transplant societies and registries occurred

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almost daily, directing medical caregivers on how best to ensure minimal risk to donors and patients.

Yet how profound an impact that the COVID-19 pandemic has had on transplant center practices as well as donor registry operations remains undefined [8]. Herein we provide the first report on the effect of the COVID-19 pandemic on the service line operations of the National Marrow Donor Program (NMDP) during the initial 3 months of the COVID-19 pandemic. We outline many of the rapid measures taken by the NMDP and its network partners to ensure the safe delivery of unrelated donor (URD) products.

METHODS

NMDP: Be The Match Network

The NMDP is a nonprofit organization that operates and manages the Be The Match Registry. Since its inception in 1987, the NMDP has facilitated over 100,000 URD HCTs. Specifically, Be The Match is the hub of a global transplant network that connects 467 leading centers worldwide, including 155 transplant centers in the United States and 38 international transplant centers [9]. The NMDP has formal business relationships and collaborates with 47 international registries in 40 countries, 10 international donor centers in 9 countries, 20 donor centers in 16 states, 18 national cord blood banks, and 23 national recruitment centers. All centers within the network meet quality standards designed to ensure that donors and patients receive high-quality care as well as to meet government standards [10].

Data Definitions

A preliminary patient search requested by the transplant center (TC) is the initial step for identifying and securing a HLA-matched or mismatched URD through Be The Match. The NMDP provides a preliminary report of potential URD candidates to the transplant physician. A formal donor search occurs once the patient is medically determined to need an URD graft, at which point blood for HLA confirmatory typing (CT) is requested and collected from potential donors at the donor center. Once the TC physician chooses a specific URD, a donor workup (WU) occurs when the donor is cleared for future bone marrow (BM) or peripheral blood (PB) harvest, which happens at the collection center (CC) or apheresis center (AC), respectively. Once collected, the graft is shipped to the TC for infusion into the transplant recipient (ie, graft infusion). HLA-matched cord blood grafts also provide an alternative if an URD is not the preferred product. *Direct to work-up* refers to no CT performed or requested for the patient-donor pair before proceeding to donor WU.

A *complete patient cycle* for each transplant recipient is considered from initiation of preliminary search until graft infusion. Individual components of a complete cycle include time (days) from preliminary to formal search, time from formal search to donor WU/graft order, time from WU/graft order until graft collection/shipment, and time from graft shipment until graft infusion.

Conversion rates from formal donor search and WU to graft collection and shipment are calculated for each patient cycle. Conversion rate refers to the percentage of patients who ultimately progress to the next stage from preliminary search to formal search, from formal search to donor WU, and from requesting donor WU to donor collection.

Transportation leg refers to the transport of a donor product between 2 scheduled stops. Usually, 1 courier is assigned to complete transport of a donor product from the AC/CC to the transport center (ie, single leg). When 1 courier is unable to complete the entire trip, a hand-off to another courier or additional leg is necessary.

Acute disease indications for allogeneic HCT included acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and myelodysplasia (MDS). All other malignant diseases were not included given their significantly lower frequency as disease indications for allogeneic HCT [11]. *Nonacute disease indications* for allogeneic HCT included all nonmalignant diseases (eg, bone marrow failure syndromes, hemoglobinopathy).

NMDP Network Announcements, Policy Changes, and Legislative Accomplishments during COVID-19

The first laboratory-confirmed case of COVID-19 in the United States was on January 21, 2020 [12]. On January 30, 2020, the World Health Organization declared the COVID-19 disease outbreak a public health emergency of international concern [13]. The World Health Organization declared COVID-19 a pandemic on March 11, 2020 [13], and the COVID-19 outbreak was declared a national emergency in the United States on March 13, 2020 [14].

With the rapid progression of the COVID-19 pandemic, the NMDP recognized the need to inform and update the transplant community with changes in policies of URD searches, collections, and graft processing and infusions, which reflected and accounted for rapid changes in COVID-19 epidemiology, including travel restrictions. To this end, the NMDP distributed network announcements frequently to TCs, which contained actionable and informative pandemic-related content (Supplementary Table S1). A complete list of NMDP network announcements related to COVID-19 can be found on the NMDP network website [15].

Between March 11 and May 31, 2020, the NMDP legislative and patient advocacy group obtained waivers, classifications, clearances, and authorizations chiefly due to its designation in federal law as the nation's bone marrow registry. Several of these legislative accomplishments were critical to mitigate disruption of delivery of NMDP products and are listed in Supplementary Table S2.

Data Time Periods and Statistical Analysis

Analysis of existing data initially gathered for operations was collected and statistically analyzed by the NMDP. A formal request for the review of data used in this report was submitted to the NMDP institutional review board and was deemed exempt by the institutional review board based on federal guidance for human subjects research. Data collected included preliminary and formal searches for domestic and international donor workups, disease indications for transplant, graft requests and infusions, cryopreserved grafts, requests for multiple donors, and donor availability. Conversion rates from preliminary search to donor graft infusion were also collected.

The main time period of interest, March 1 through May 31, 2020, was compared to 2 time periods: December 1, 2019, through February 29, 2020, which sought to define NMDP operations before the pandemic peaked in the United States, and March 1 through May 31, 2019, which controlled for seasonal differences.

Pairwise proportion tests were used to assess the impact of COVID-19 on donor availability at confirmatory typing, donor availability at workup, and acute versus nonacute patient disease types at formal search and collection/shipment. Impacts on conversion rates from preliminary to formal search, formal search to workup, and workup to collection were also tested using pairwise proportion tests. The Holm correction was used with all pairwise proportion tests to adjust for multiple comparisons.

Initially on March 9, 2020, the NMDP strongly recommended cryopreservation of URD products, but due to worsening conditions from March 23, 2020, to August 10, 2020, the NMDP mandated the cryopreservation of all URD products with limited exceptions. Cryopreservation was not considered a factor in the analysis comparing the time periods on outcomes. Adjusting for the cryopreservation mandate likely would not affect the estimates but may increase the error rate and affect the level of confidence of the estimates.

Odd ratios were calculated to determine whether COVID-19 had an impact on the type of graft source requested, number of postponements, or number of cancellations. Kruskal-Wallis tests were performed to test the impact COVID-19 had on preliminary searches, formal searches, and donor travel distances. Dunn's post-tests were performed along with the Kruskal-Wallis tests to focus on the specific associations between the time period of interest and 2 control timeframes. All analyses were completed using the R statistical analysis software (version 4.0.2).[24]

RESULTS

Preliminary and Formal Donor Searches Decreased with the Onset of COVID-19

We first determined the impact of COVID-19 by first measuring the number of preliminary and formal donor searches submitted from TCs to the NMDP before (March to May 2019) and after (March to May 2020) the onset of the COVID-19 pandemic. An overall drop in preliminary and formal searches for both domestic and international TCs was noted at the onset of the pandemic (Table 1). For domestic searches, there was a significant decrease in submitted searches by 13.2%, which was similar to the decrease observed in international searches (14.6%). In addition, there was a significant drop in the number of formal searches initiated by domestic TCs (14.6%) but less than the 2-fold greater decrease initiated by international TCs (31.4%). During the time period immediately prior to the onset of COVID-19 (December 2019 to February 2020), domestic and international preliminary and formal searches were within 5% of respective searches from March to May 2019. Data for June and July 2020 suggest slight increases for both preliminary and formal searches, but the 2-month timeframe is not comparable for accurate comparison (data not shown). Together, these data show that the TCs performed less donor searches immediately following onset of the COVID-19 pandemic.

Table 1
Donor Searches and Disease Indications for Allogeneic HCT

Preliminary and Formal Searches				
	March to May 2019	March to May 2020	% Change (counts)	December 2019 to February 2020
Domestic TC				
Preliminary	3873	3359	−13.2%*	3680
Formal	2437	2081	−14.6%*	2314
International TC				
Preliminary	4366	3729	−14.6%*	4448
Formal	1756	1204	−31.4%*	1785

Disease Indications				
By Formal Date	March to May 2019	March to May 2020	% Change (Overall)	December 2019 to February 2020
Acute indications	**2706 (65%)**	**2193 (67%)**	**−19% (+2%)**	**2679 (65%)**
Domestic TC	1636	1415	−14%†	1516‡
International TC	1090	778	−29%†	1163
Nonacute indications	**1427 (35%)**	**1092 (33%)**	**−23.5% (−2%)**	**1420 (35%)**
Domestic TC	828	681	−18%†	817‡
International TC	619	411	−34%†	603
Total	**4133**	**3285**	**−20.5%**	**4099**
By collection date				
Acute indications	**1090 (68%)**	**1149 (72%)**	**+5.4% (+4%)**	**3361 (69%)**
Domestic TC	953	1015	7%§	932‡
International TC	137	134	−2%§	171
Nonacute indications	**510 (32%)**	**442 (28%)**	**−13.3% (−4%)**	**1479 (31%)**
Domestic TC	421	362	−14%§	411‡
International TC	89	80	−10%§	94
Total	**1600**	**1591**	**−0.01%**	**4440**

Counts refer to number of patients. Acute indications included ALL, AML, and MDS. Nonacute indications include all nonmalignant diseases (eg, bone marrow failure syndromes, hemoglobinopathy). All other malignant diseases were not included in the analysis given their significantly lower frequency as disease indications for allogeneic HCT.

* March to May 2019 versus March to May 2020, $P < .01$, Kruskal-Wallis test.

† March to May 2019 versus March to May 2020, $P > .05$, Kruskal-Wallis test.

‡ March to May 2020 versus December 2019 to February 2020, $P > .05$, Kruskal-Wallis test. Similar comparisons for international TCs were insignificant due to correction methods.

§ March to May 2019 versus March to May 2020, $P > .05$, Kruskal-Wallis test.

Disease Indications for Allogeneic HCT during COVID-19

The most common malignant disease indications for allogeneic HCT are ALL, AML, and MDS [11]. At the start of the pandemic, we hypothesized that these acute disease transplant indications would be prioritized over nonacute disease indications for proceeding with allogeneic HCT as recommended by the American Society of Transplantation and Cellular Therapy [4] and the European Society for Blood and Marrow Transplantation [6]. To determine if such a change in practice occurred among TCs, we compared the frequencies that acute and nonacute diseases were listed as transplant indications before and after the onset of COVID-19. Although there was an overall decrease in the number of patients who submitted a formal search after COVID-19, a 2% increase in patients who had acute disease transplant indications was noted (Table 1). Collection numbers between periods were similar and consistent with the increase in formal searches, and the percentage of collections for patients with acute disease also increased after COVID-19 (4%) (Table 1). These data suggest that TCs were less likely to delay activation of formal searches and collections for patients with acute disease indications for transplant consistent with recommendations from international transplant consortia [4-6].

Graft Types, Cryopreservation, and Infusion following COVID-19

Given increased hardships that hospitals located within COVID-19 epicenters experienced with respect to the influx of patients and more availability for procedures at ACs than CCs, the NMDP recommended limiting BM products as a means to accommodate the network's capabilities as well as the donors' limitations in travel (Supplementary Table S1). To determine the impact of this recommendation, we analyzed the types of grafts requested by TCs and infused immediately before and after the onset of COVID-19. For domestic TCs, the number of PB requests increased by nearly 15%, while the numbers of BM and cord graft requests decreased by 30.4% and 20.2%, respectively (Table 2). Of note, the total number of requested donor grafts by domestic TCs increased by 5.4% following the onset of COVID-19 (1400 from March to May 2020 versus 1328 from March to May 2019). In contrast to domestic TC graft requests, international TCs requested more cord blood and less BM and PB grafts (Table 2). Note that due to the recent time period of this analysis, not all requests had moved forward to collection before completion of this report.

With rapid changes in SARS-CoV-2 epidemiology resulting in numerous travel restrictions in the early phases of the COVID-19 pandemic, as well as the potential for transplant candidates and their donors to contract COVID-19 prior to admission for transplant, the NMDP on March 23, 2020, required that URD grafts be cryopreserved prior to initiation of conditioning with limited exceptions [15]. As shown in Table 3, both domestic and international TCs substantially increased requests for cryopreserved BM and PB grafts. There were rare occasions when fresh product infusion was approved to accommodate patients where evidence suggested improved

Table 2
Graft Requests and Infusions

Graft Requests				
Domestic TC	March to May 2019	March to May 2020	% Change (Counts)	December 2019 to February 2020
BM	240	167	−30.4%*	250
PB	944	1075	+13.8%	913
Cord	198	158	−20.2%	131
Total	**1328**	**1400**	**+5.4%**	**1294**
International TC				
BM	44	27	−38.6%	53
PB	179	158	−11.7%	166
Cord	24	51	+113%	27
Total	**247**	**236**	**−4.5%**	**246**
Graft infusions				
Domestic TC				
Infused	1512	1453	−3.9%	1449
Not infused	8	65	Pending more to infuse	14

Counts refer to number of unrelated donor or cord requests (graft requests) or number of product infusions (graft infusions). Graft infusion data are as of August 4, 2020. Of the 65 cryopreserved products, some may not be infused yet as awaiting readiness of transplant recipient. Of note, 16 will not be infused given refusal for reasons including but not limited to low cell counts, problems with cryopreservation process, and poor mobilization.

* Odds ratios were calculated to determine whether COVID-19 had an impact on the proportion of marrow or peripheral blood stem cell requests made. Domestic TC requests were 37% less likely to be for marrow during March to May 2020 relative to both December 2019 to February 2020 and March to May 2019 (95% confidence interval, 27% to 46%). Of note, while the proportion of cord requests was reduced in domestic TCs, the reduction was not statistically significant. Additionally, while decreases in BM requests were also seen for international patients, the decrease was not significant.

Table 3
Graft Cryopreservation

Domestic TC	Graft Types	March to May 2019	March to May 2020	% Change (Counts)	December 2019 to February 2020
Not cryopreserved	BM	229	69	−69.9%	236
	PB	872	228	−73.9%	835
Cryopreserved	BM	11	99	+800%	15
	PB	95	865	+811%	98
International TC					
Not cryopreserved	BM	42	4	−90.5%	49
	PB	172	40	−76.7%	153
Cryopreserved	BM	2	24	+1100%	4
	PB	13	120	+823%	19

Counts refer to number of products.

long-term outcomes such as severe aplastic anemia and other BM failure syndromes [16].

We next sought to determine if less grafts were actually infused post-COVID. Only 3.9% less grafts were infused at domestic TCs after the onset of COVID-19 (1453) versus during the same time period prior to COVID-19 (1512) (Table 2). Data for international graft infusions are unavailable. However, an increase in postponement of collections occurred in March 2020 at the beginning of COVID-19, most notably at domestic TCs, but also seen at international TCs (Supplementary Figure S1). Specifically, significant increases in the number of domestic "unknown cause" postponements were observed during the initial onset of COVID-19 (March to May 2020) (Supplementary Table S3). Compared to the 3 months prior (December 2019 to February 2020), URD collections were 4.6 (95% confidence interval, 3.3 to 6.6) times more likely to be postponed for unknown causes than patient reasons and 2.5 (95% confidence interval, 1.7 to 3.9) times more likely than donor reasons (Supplementary Table S3). Similar increases were seen in the likelihood of international postponements for unknown causes as well (data not shown). However, small sample size precluded analysis for international TCs.

These data show that domestic and international TCs requested different graft types early after the onset of the COVID-19 pandemic but requested cryopreserved BM and PB grafts at similar rates. Delays in graft infusions that peaked in March 2020 decreased in subsequent months, resulting in the overall number of graft infusions being minimally decreased relative to pre-COVID-19 levels.

Multiple URD Requests and Use of Related Donors Increased at the Onset of COVID-19

The NMDP recommended that TCs identify backup URDs for allogeneic transplant candidates [15]. Therefore, we assessed the number of multiple donors for WU requested by domestic and international TCs before and after the onset of COVID-19. As shown in Table 4, 41% of domestic TCs requested multiple URDs at WU during COVID-19 (March to May 2020), an increase of 7% compared to pre-COVID (March to May 2019, 34%). Similar increases by international TCs for multiple URD requests were noted but to a lesser degree than domestic TC requests (Table 4).

Direct to WU requests also substantially increased at the onset of COVID-19 (Table 4). The increase in direct to WU

Table 4
Requests for Multiple Donors for Workup and Direct to Workup

Domestic TC	March to May 2019 (% Total)	March to May 2020 (% Total)	Overall % Change	December 2019 to February 2020 (% Total)
Patient requested multiple donors	502 (34%)	628 (41%)	+7%	476 (33%)
Direct to WU requests	119 (8)	356 (23)	+15%	146 (10)
Direct to WU—unrelated	92 (6)	252 (17)	+11%	98 (7)
Direct to WU—related donor	27 (2)	104 (7)	+5%	48 (3)
International TC				
Patient requested multiple donors	24 (7%)	27 (10%)	+3%	32 (10%)
Direct to WU requests	3 (1)	16 (6)	+5%	11 (3)
Direct to WU—unrelated	2 (1)	14 (5)	+4%	11 (3)
Direct to WU—related donor	1 (<1)	2 (1)	+1%	0

Direct to workup refers to no CT or CT request for patient-donor pair before proceeding to workup.

requests was mostly requested by domestic TCs, and in particular for URDs, given that many related donors inherently move directly to WU with CT not always being facilitated by the NMDP (Table 4).

To maintain donor safety during the pandemic, the NMDP accommodated URDs by having them travel closer to an AC/CC. When a donor needed to travel into an area restricted by stay-at-home orders, the NMDP provided documentation that detailed the donor's exemption to the order given their participation in a life-saving mission. In addition, the NMDP made a concerted effort to minimize donor exposure to COVID-19 by reducing numbers of donor visits (eg, blood draws at donor center), particularly in an area with high prevalence of COVID-19. With respect to related donors, facilitation of domestic related donor collections by the NMDP dramatically increased with COVID-19 onset (76; March to May 2020) in comparison to pre-COVID-19 (21; March to May 2019), likely reflecting a related donor's desire to avoid air travel

Table 5
Donor Availability at the Time of Workup and Confirmatory Typing

Donor Workup				
Domestic Donors	March to May 2019 (% Total)	March to May 2020 (% Total)	% Change (Counts)	December 2019 to February 2020 (% Total)
Available	775 (63%)	833 (51%)	+7.5%	695 (60%)
Unavailable	192 (16)	445 (27)	+131.7%	185 (16)
Canceled	263 (21)	269 (16)	+2.3%	264 (23)
Open	1 (0)	189 (5)	Resolve as time passes	22 (2)
Total orders	**1231**	**1636**	**+32.9%**	**1166**
% AV	**80%**	**65%**	**−15% (overall % change)**	**79%**
International donors				
Available	678 (61%)	528 (53%)	−22.1%	662 (56%)
Unavailable	102 (9)	119 (112)	+16.6%	121 (10)
Canceled	334 (30)	254 (26)	−24%	313 (26)
Open	4 (<1)	94 (9)	Resolve as time passes	92 (8)
Total orders	**1118**	**995**	**−11%**	**1188**
% AV	**87%**	**82%**	**−5% (overall % change)**	**85%**
Donor Confirmatory Typing				
Domestic Donors	March to May 2019 (% Total)	March to May 2020 (% Total)	% Change (Counts)	December 2019 to February 2020 (% Total)
Available	3968 (49%)	2709 (36%)	−31.7%	3517 (46%)
Unavailable	3343 (41)	3535 (48)	+5.7%	3681 (48)
Canceled	831 (10)	1137 (15)	+36.8	442 (6)
Open	1 (<1)	50 (1)	Resolve as time passes	4 (<1)
Total orders	**8143**	**7431**	**−8.7%**	**7644**
% AV	**54%**	**43%**	**−11% (overall % change)**	**49%**
International donors				
Available	3995 (68%)	2107 (58%)	−47.3%	3687 (64%)
Unavailable	1486 (25)	1001 (28)	−32.6%	1596 (27)
Canceled	423 (7)	486 (13)	+14.9%	482 (8)
Open	4 (<1)	40 (1)	Resolve as time passes	41 (1)
Total Oorders	**5908**	**3634**	**−38.5%**	**5806**
% AV	**73%**	**68%**	**−6.8% (overall % change)**	**70%**

Counts refer to the number of donor WU or donor CT requests. The percent available (% AV) is defined as AV/(AV + UN). Canceled and open cases do not count in % AV. Open case data are as of August 4, 2020.
UN indicates unavailable.

(Supplementary Table S4). To assess this concern, we looked more broadly at both related and unrelated primary donor travel patterns. The distance between the primary donor address and AC/CC was analyzed for both related and unrelated donors and substantially decreased with the onset of COVID-19 (Supplementary Table S4).

These data show that TCs requested multiple URDs and direct to WU requests during the initial onset of COVID-19, streamlining transplant processes in order to take patients as quickly as possible to HCT. In addition, accommodations were made for both related and unrelated donors to minimize travel to AC/CC.

Changes in Donor Availability Early after the Pandemic

We next analyzed the impact of COVID-19 on donor availability at the time of donor WU and CT (Table 5). For domestic donors, a 32.9% increase in total domestic donor WU requests was noted, potentially due to selection of multiple donors at WU or backup selection by TCs as well as a decline in availability of donors at WU. Overall, donor WU availability was 15% lower following the onset of COVID-19 (65%; March to May 2020) as compared to the year before at the same time (80%; March to May 2019). In contrast to the increase noted in domestic donor WU requests, total international WU requests decreased by 11% (Table 5), as some international registries were unable to facilitate WU requests for periods of time during the onset of COVID-19. Similar to domestic donors, overall donor WU availability for international donors decreased, but less profoundly (5%), following COVID-19 (Table 5).

Donor volumes at CT were affected greatly following the onset of COVID-19, with domestic (−8.7%) and international (−38.5%) significantly lower (Table 5). This is in part a reflection of patients proceeding directly to WU due to the process change protecting healthy donors from having to present for additional blood draws in high-risk areas (Supplementary Table S1). In addition to the decrease in CT requests, the availability of donors at CT was also affected by COVID-19. Specifically, domestic donor availability decreased by 11% and international donor availability by 6.8% (Table 5).

Conversion Rates for Domestic and International Patients following the Onset of COVID-19

With TCs changing their practices to prioritize patients with acute diseases, decreases in donor availability, and interruptions in domestic courier service utilization, we assessed the impact of COVID-19 on NMDP operations by analyzing domestic and international (cases where international centers requested donors from the NMDP registry) conversion rates for patient cycle times (Supplementary Table S5). Duration (median days) of domestic and international patient cycles during the early onset of COVID-19 (March to May 2020) was either similar to or shorter than the pre-COVID-19 timeframe (March to May 2019) (Figure 1). While international TCs showed a significant drop in the conversion rates from preliminary to formal search from March to May 2019 to 2020 (40% versus 32%, $P < .01$, Kruskal-Wallis test), the conversion rates for domestic TCs were not significant (63% versus 62%, $P = .39$, Kruskal-Wallis test) (Figure 1). However, conversion rates from formal search to workup/order cycle significantly increased for both domestic and international TCs (domestic TCs 62% versus 71% and international TCs 19% versus 24%, both comparisons $P < .01$, Kruskal-Wallis test). For the workup/order to collection/shipment cycle, we observed a significant increase in conversion rates for domestic TCs (84% versus 88%, $P < .01$, Kruskal-Wallis test). For international TCs, the change

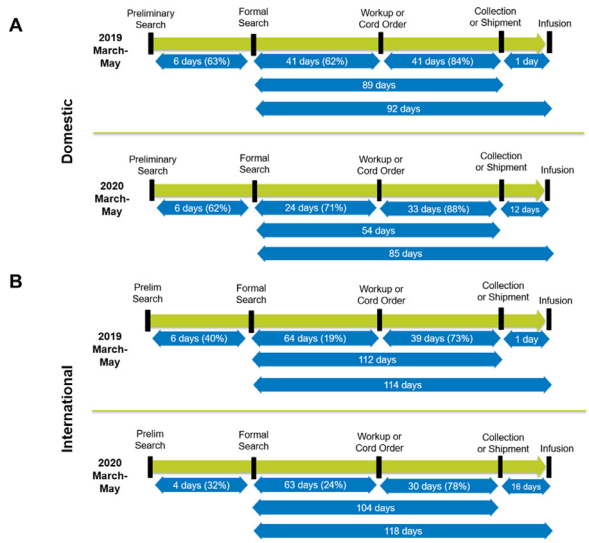

Figure 1. Conversion rates in domestic (A) and international patient (B) cycle times during the COVID-19 pandemic. A *complete patient cycle* for each transplant recipient is defined from initiation of preliminary search until graft infusion. Individual cycles (in days) comprising a complete cycle include time from preliminary to formal search, time from formal search to donor WU/graft order, time from WU/graft order until graft collection/shipment, and time from graft shipment until graft infusion. *Conversion rates* from formal donor search and WU to graft collection and shipment are also recorded for each patient cycle. The median days between each patient cycle is shown. The number of patients at each stage varies depending on TC location, numbers of patients who make it to the next stage of the patient cycle, and the time range of interest (Supplementary Table S4).

in workup/order to collection/shipment conversion rate was not significant (73% versus 78%, $P = .48$, Kruskal-Wallis test). Last, we observed a substantial prolongation in the time from product collection to infusion, likely due to receipt of products for cryopreservation prior to the initiation of recipient conditioning (Figure 1).

These data collectively show that NMDP conversion rates for most patient cycles were similar to or higher than pre-COVID-19 rates and that duration in completion for patient cycle times was similar to or shorter than pre-COVID-19 cycle times.

Domestic Courier Utilization and Performance following Onset of COVID-19 Pandemic

Given constraints that the pandemic placed on regional, national, and international travel, we next looked at domestic courier utilization by the NMDP as a surrogate marker of travel interruptions caused by the pandemic (Figure 2). The NMDP primarily utilizes volunteer and commercial (ie, On Time Courier Service and Time Matters) couriers. Three observations are made from these data. First, total assigned volunteer and staff couriers increased over pre-COVID-19 levels until May 2020 when commercial usage began to resume, given commercial vendors were closed early after the onset of COVID-19. Second, total number of assigned couriers increased over time in parallel with cancellations, likely reflecting interruptions in travel, especially in March 2020, when total cancellations peaked at 163 (Figure 2). Cancellations decreased in subsequent months when total cancellations in April and May 2020 were 112 and 93, respectively. Last, the lowest percentage for completed assigned couriers was in March 2020 with a subsequent rise in May 2020 (Figure 2).

Together, these data show despite significant interruptions in domestic courier utilization causing cancellations in

	February 2020						March 2020						April 2020						May 2020					
Trip Type	Completed		Cancelled		Total Assigned		Completed		Cancelled		Total Assigned		Completed		Cancelled		Total Assigned		Completed		Cancelled		Total Assigned	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
On-Time	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%	0	0.0%	1	0.2%	21	5.9%	2	2.2%	23	5.1%
Time Matters	3	1.7%	0	0.0%	3	1.2%	3	1.4%	0	0.0%	3	0.8%	0	0.0%	0	0.0%	0	0.0%	5	1.4%	0	0.0%	5	1.1%
Staff	5	2.8%	4	4.9%	9	3.5%	5	2.3%	10	6.1%	15	3.9%	60	15.9%	11	9.8%	71	14.5%	50	11.0%	11	11.8%	61	13.6%
Volunteers	169	95.5%	78	95.1%	247	95.4%	213	96.4%	153	93.9%	366	95.3%	316	83.8%	101	90.2%	417	85.3%	280	78.7%	80	86.0%	360	80.2%
TOTAL	177	100%	82	100%	259	100%	221	100%	163	100%	384	100%	377	100%	112	100%	489	100%	356	97%	93	100%	449	100%
Percent Completed of Total Assigned	68.3%						57.5%						77.1%						79.3%					

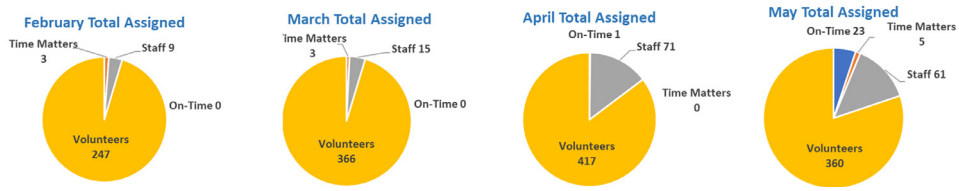

Figure 2. Domestic courier utilization by the NMDP during the COVID-19 pandemic. Types of commercial (On Time Courier Service and Time Matters), staff, and volunteer couriers utilized by the NMDP for shipment of graft products from February through May 2020. Total assigned, completed, and cancelled courier trips are listed for each month. Volunteers comprised the majority of couriers utilized during the initial onset of the COVID-19 pandemic with commercial vendors increasing in April and May, as these businesses started to reopen.

itineraries, the NMDP service line was able to ensure delivery of graft products during the early phase of the COVID-19 pandemic, largely due to the efforts of volunteer couriers.

DISCUSSION

Donor registries are lifelines for transplant recipients, as they are responsible for identifying and securing URDs from around the world and coordinating donor graft collections and product shipment to TCs. The COVID-19 pandemic has had an immense impact in terms of human casualties and economic devastation. Despite the pandemonium caused by the pandemic, data herein show that TCs made modifications in practice required to continue to safely provide their patients with a potentially life-saving treatment option and, in concert with the NMDP, enacted many rapid adaptations required to continue to provide safe and essential donor registry services, while both confronted significant logistical challenges to their respective service lines. Furthermore, in a remarkable display of humanism and selflessness, volunteer donors continued to donate despite risks, and NMDP volunteers and staff continued to serve as couriers, ensuring safe collection and transportation of URD products from around the world for use in HCT recipients.

Changes in TC practices following COVID-19 could be grouped into 3 categories: transplant volumes and disease indications for transplant, donor search and selection, and graft selection and processing. With regards to overall performance of allogeneic HCTs, TCs initially performed less HCTs and may have had less new patient referrals following the onset of COVID-19. These changes in patient volumes were reflected by our data showing, in decreased preliminary and formal URD searches, reduced acute and nonacute disease indications for allogeneic HCT, as well as decreased infusion of hematopoietic stem cell grafts. TCs focused on transplanting acute hematologic diseases (ALL, AML, MDS) during the early phases of COVID-19, reflecting both institutional and transplant society recommendations [7].

Based on recommendations from the NMDP, TCs were advised to have backup URDs available for each transplant recipient. This recommendation, along with challenges with donor availability, translated into increased requests for multiple donors at workup. TCs also had increased utilization of direct to workup requests, primarily with domestic URDs, likely due to decreased timeframes and changes in confirmatory typing process. The NMDP experienced an increase in related donor facilitation requests given restrictions in travel and desire of donors to stay closer to home. The NMDP's extensive AC/CC network enabled donors to be collected at a facility closer to home, which helped alleviate restrictions and donor concerns.

Last, numbers of requested and infused cryopreserved PB and BM grafts dramatically rose during the early phases of the pandemic, clearly reflecting initial recommendations followed by a requirement from the NMDP network to cryopreserve grafts and maintain grafts prior to initiation of recipient conditioning. Over 95% of the grafts collected have been cryopreserved at the TCs following receipt (data not shown). The requirement for cryopreservation was made to ensure a viable product was delivered to the TC prior to conditioning, so no patient was left without a graft to infuse following conditioning. There essentially was no other choice at the onset of the pandemic given the need to protect patient safety. While all cord blood units are cryopreserved, the impact of cryopreservation of allogeneic adult donor products on clinical outcomes remains unclear. Prior published experience on cryopreservation of allogeneic donor grafts suggested no deleterious effects on engraftment or immune reconstitution [17-19]. Of note, numbers of cryopreserved PB grafts were higher than cryopreserved BM grafts, likely reflecting the NMDP's recommendation to limit BM collections given logistical challenges early after the pandemic but also TC preference. Since August 10, 2020, the NMDP has relaxed the requirement for product cryopreservation unless certain clinical scenarios necessitated its use [20]. But given continued changes in SARS-CoV-2 epidemiology and recurrent epicenter activity, cryopreservation will need to remain a viable option for the foreseeable future [21]. Together with its research program, the Center for International Blood and Marrow Transplant Research, the NMDP has been evaluating the impact of cryopreservation on outcomes and has adapted its recommendations accordingly. While

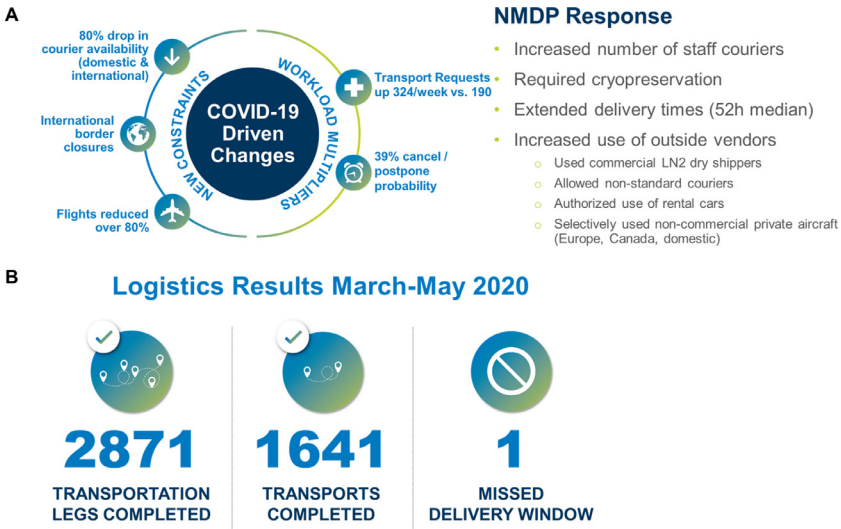

Figure 3. Summary of NMDP logistics during the early onset of the COVID-19 pandemic. (A) COVID-19-driven changes affecting NMDP operations (left) and response from the NMDP to address these changes (right). (B) Summary of NMDP operation logistics early after the onset of COVID-19.

there is no apparent impact in patients with malignant conditions receiving post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis, retrospective data in patients with severe aplastic anemia suggested worse overall survival in recipients of cryopreserved grafts [16,22]. When we obtained these data, we adjusted our recommendations to allow for use of fresh BM if it could be obtained safely. Further investigation will be needed to confirm the safety and efficacy of using cryopreserved products and their effects on short-term and long-term transplant outcomes, particularly in cryopreserved products having prolonged storage time or product manipulation before cryopreservation [23]. Plans are currently under way using the Center for International Blood and Marrow Transplant Research database to study long-term effects of cryopreservation on patient outcomes, specifically during the pandemic.

With these significant practice changes and the inherent challenges of the COVID-19 pandemic, the question arises as to how nimble and effective the donor registry can function. Conversion data suggest that rapid adaptions made by the NMDP were quite efficient. We observed higher conversion rates over shorter periods of time throughout the NMDP network with the exception of duration between collection and subsequent product infusion. However, this increase was anticipated due to our requirement for cryopreservation prior to the initiation of conditioning. Despite these obstacles, the NMDP service line completed over 2800 transportation legs and completed over 1600 graft transports, and only 1 product was delivered outside the requested time window from March to May 2020 (Figure 3). In addition to effective operational adaptations, credit needs to be given to volunteer and staff couriers who completed these routes.

Several limitations are apparent in this work. First, self-reporting and analysis by the NMDP resulted in the data shared in this article. Second, the data presented reflect the experience of only 1 donor registry, and other experiences could vary. Third, data are lacking on how the pandemic affected transplant operations at individual TCs and how this was reflected in choice of transplant conditioning intensity or methods of graft-versus-host disease prophylaxis. Fourth, data are also lacking on the impact of these changes on patient outcomes or donor adverse events, including donors becoming infected by SARS-CoV-2. These data are critical but inherently lagging, so they will be presented in a follow-up to this report. Fifth, conclusions are limited by limitations in the data themselves, including the short timeframes of comparisons. Last, TC practices continue to evolve and future changes could affect the results observed thus far.

Despite these limitations, this report affords a window into how one of the world's largest hematopoietic stem cell donor registries was affected and yet continued to function quite effectively during the early stages of the COVID-19 pandemic. Such insight is helpful to gain a practical perspective in an integral service provided to the HCT field. Finally, we should be reminded that without the heroism of our donors, none of these successes would have been possible.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2020.10.014.

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