To the Editor:

In his commentary,¹ Devine describes the position of the National Marrow Donor Program (NMDP) of the United States regarding cryopreservation of allogeneic hematopoietic cell grafts during the Covid-19 pandemic. We thank the author for addressing this important topic, which constitutes undoubtedly one of the biggest challenges for unrelated stem cell donor registries during the Covid-19 pandemic. The NMDP and DKMS (German Bone Marrow Donor Center or Deutsche Knochenmarksspenderdatei) as two globally leading registries are working closely together on this and other pandemic-related issues.² Nevertheless, both organizations seem to have had somewhat different experiences with cryopreservation during the pandemic, which then led to partially different assessments and conclusions, as we will describe.

Based on our experience with DKMS donors from Germany, we have seen a substantially higher rate of non-transfused cryopreserved products than mentioned in the commentary by Devine³: Between March 1, 2020 and November 15, 2020, 2396 of the 3960 stem cell products collected (60.5%; 63.2% of peripheral blood stem cell (PBSC) and 36.7% of bone marrow (BM) products) were cryopreserved. Of these cryopreserved products, 79 (3.3%; 3.0% of PBSC and 8.1% of BM products) will definitely not be transfused (data retrieval date: November 23, 2020). Another 178 cryopreserved products (7.4%) have not yet been transfused, and many of these products have already passed the originally planned transplantation date. At this time, we expect that ultimately 5%–8% of the cryopreserved products will not be transfused. This rate is not substantially higher than it was before the Covid-19 pandemic (3.1%–6.9% in 2019; the uncertainty results from cases that are still open). However, only 4.7% (262/5603) of all stem cell products were cryopreserved during that period. Therefore, the expected absolute number of non-transfused cryopreserved products collected in 2020 is about one order of magnitude higher than in 2019 (8–18).³

Of course, each DKMS donor must agree to the cryopreservation of their stem cell product prior to collection with the understanding that it may not be transfused. It is rare that a donor refuses this consent. Accordingly, donors who are informed that their product will not be transfused are generally disappointed but understanding. These observations from donor registry practice indicate that the communication challenges associated with non-transfused stem cell products from unrelated donors may generally be manageable. However, all parties operate under the ethical obligation of avoiding these cases as much as possible. Moreover, stem cell donations are associated with small but existing risks as well as inconveniences such as side effects of stem cell mobilization for PBSC donors and postoperative pain for BM donors.⁴,⁵

We propose that three aspects must be considered in order to minimize the risk of non-transfusion of unrelated donor products and thus to do full justice to the altruistic commitment of unrelated donors:

First, a careful case-by-case assessment must be made as to whether cryopreservation is really necessary to ensure that the stem cell product will be available at the transplant center at the required time. This is because the restrictions imposed by the Covid-19 pandemic vary greatly in terms of time and geography.

In the initial phase of the pandemic in March 2020, for example, the transport of stem cell products across national borders was uncertain for a few days before new processes were quickly established.⁶ Since then, these processes have enabled the safe handling of transports between many countries, especially those with many donors and recipients of stem cell products such as Germany and the USA. Even the second wave of the pandemic, which has hit Europe hard for several weeks now, has not changed this situation. As a result, no conditioned patient waiting for a stem cell product from a donor registered with DKMS Germany was left without that product due to logistical or transport issues.

In addition to the safety of product transport, the impact of the pandemic on donor availability is also a factor that must be considered when deciding for or against cryopreservation in each individual case. At DKMS Germany, the pandemic has not significantly affected donor non-availability rates at the workup level, that is, at the final process...
step before stem cell collection. The corresponding values are 19.3% (1340/6943) for 2019 and 19.4% (955/4915) during the Covid-19 pandemic (from March 1, 2020 to November 15, 2020). Until November 15, 19 donors were not available at workup level for SARS-CoV-2 related reasons. This represents only 2.0% of all cases of donor non-availability at work-up level during the same period. Again, no conditioned patient was left without stem cell product due to donor non-availability.

Second, it is important to keep the planned time between collection and transfusion of cryopreserved products as short as possible. Ideally, conditioning of the patient should begin immediately after the product has been received and cryopreserved. This implies especially that the recipient’s transplant eligibility needs to be confirmed before the collection procedure starts, as required by the World Marrow Donor Association. We emphasize this point because the deterioration of the patient’s status (including patient death) was – in clear distinction to the dataset described by Devine – by far the most frequent reason for non-transfusion of cryopreserved products during the pandemic (62 cases; 78.5%). In several of these cases, the patient’s transplant eligibility was not verified shortly before the collection, thus causing unnecessary stem cell collections from unrelated donors. It is our experience that this specific problem was less frequent before the Covid-19 pandemic. However, even then, the deterioration of the patient status was the main reason for not transfusing cryopreserved products.

Third, cryopreservation should be avoided if there is a high probability that process-related cell count and/or viability losses will lead to a product that is not used. Dissatisfaction with product characteristics as cell count or viability is the second most common cause of non-transfusion (11 cases; 13.9%). Risk factors include an unfavorable donor/patient weight ratio, bone marrow as stem cell source and a long transport time before cryopreservation. The latter issue can be resolved by cryopreservation at or near the collection center. Of the 2396 cryopreserved products from German DKMS donors, 96 (4.0%) were cryopreserved at or near the collection center. Therefore, we believe that it is not necessary to select a slightly inferior (“roughly equivalent”) domestic donor in such cases as proposed by Devine.

In summary, cryopreservation of stem cell products from unrelated donors was and is an important tool to overcome the logistical challenges associated with the Covid-19 pandemic and to ensure that conditioned patients receive the stem cell products they need safely and on time. However, the resulting significant increase of non-transfused unrelated donor stem cell products is problematic and requires careful consideration of the best approach in each individual case. After the end of the pandemic, it is essential to return to the conventional practice with predominantly fresh products from unrelated donors.

FUNDING INFORMATION
None.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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