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Determination of Eligibility in Related Pediatric Hematopoietic Cell Donors: Ethical and Clinical Considerations. Recommendations from a Working Group of the Worldwide Network for Blood and Marrow Transplantation Association

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A B S T R A C T

Related donors for hematopoietic cell (HC) transplantation are a growing population in recent years because of expanding indications for allogeneic transplantation. The safety and welfare of the donor are major concerns for the transplantation community, especially for related sibling donors of young recipients who are children and, thus, not able to fully consent. Because donation of HC does not improve the donor's own physical health and carries a risk of side effects, careful assessment of medical risks specific to the individual donor, as well as consideration of ethical and legal aspects associated with donation from a child, must be considered. In addition, donor centers must balance the needs of both the donor and the recipient, understanding the inherent conflict parents may have as they can be overly focused on the very sick child receiving a transplant, rather than on the relatively less significant health or emotional problems that a sibling donor may have, which could impact risk with donation. Likewise, consideration must be made regarding the nature of the relationship of the sibling donor to the recipient and also aspects of performing research on pediatric HC donors. In this article, as members of the Donor Issues Committee of the Worldwide Network for Blood and Marrow Transplantation, we review key ethical concerns associated with pediatric donation and then give recommendations for screening potential child donors with underlying health conditions. These recommendations are aimed at protecting the physical

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and emotional well-being of childhood donors and arise out of the Third International Conference on Health and Safety of Donors sponsored by the Worldwide Network for Blood and Marrow Transplantation.

INTRODUCTION

Allogeneic hematopoietic cell (HC) transplantation is an acceptable therapeutic tool for a growing number of pediatric medical indications. HLA-matched siblings are considered to be the best donors for both practical and biological reasons, including superior availability before and after transplantation [1-6]. Thus, when the recipient is a child, potential sibling donors may be children themselves. Moreover, in rare cases, children may also be considered as potential donors for an adult sibling, parent, or other family member. Worldwide data demonstrate that more than one third of children undergoing allogeneic transplantations receive grafts from siblings under the age of 18 [7,8]. All 3 major sources of stem cells, bone marrow (BM), peripheral blood stem cells (PBSC), and cord blood (CB), are routinely obtained from pediatric donors, but BM-derived cells are the preferred source for many indications [7,8]. According to an European Group for Blood and Marrow Transplantation (EBMT) estimate, approximately 600 to 700 children in Europe become hematopoietic stem cell donors for their siblings every year [9].

The key issue that must be addressed with childhood HC donors is their initial inability to understand and voluntarily consent. Understanding increases as they age into an ability to assent, then finally to legally consent. Because HC donation can benefit their sibling more than any other tissue source, and because the procedure can be performed with limited risk, sibling donation under parental consent has been considered appropriate by many, and an extensive literature has developed that addresses the ethical underpinnings of this practice [10]. Authors have suggested that this act is necessary "involuntary altruism" in one not capable of recognizing the need [11]; others have suggested the parents are providing "substituted judgment" of what an adult would do under similar circumstances [12], and yet others have preferred framing the donation as something done in the "best interest" of the child, given the impact on the family framework of nondonation [11,13,14]. Another proposed framework uses the "intrafamilial principle," where members of a family have an obligation to other family members, making trade-offs for the good of the family as a whole; a variation to this is the "intimate attachment" principle, where because of a close attachment, the good of the donor is bound up in the good of the recipient. Though ethical frameworks may vary, all agree that such donation is reasonable but safeguards are necessary to protect the psychological and medical health of the child, to consider the health and the implications of the donation distinctly from the ill sibling, and to respect the child donor's developing sense of autonomy and ability to assent.

The Worldwide Network for Blood and Marrow Transplantation believes that minors can physically and ethically participate as hematopoietic stem cell donors. This statement reviews consensus recommendations of an international working group regarding 3 important areas of medical ethics associated with pediatric HC donation and then addresses concerns regarding pre-existing medical issues that some potential pediatric donors may have, which could affect their safety during stem cell donation. With a global perspective, we provide recommendations for how donors should be approached regarding advocacy and parental rights, and then we outline conditions when it may not be in the best interest of a child to be a donor for HC therapy. This article is not an exhaustive review; instead, we have chosen to focus on limited areas we think are of importance. Our intent is to begin an active process of recommendations regarding pediatric donor guidelines that will be updated regularly.

ADVOCACY VERSUS PARENTAL RIGHTS

Donation of BM from a sibling or close family member who has not reached legal status for offering independent informed consent has been practiced for nearly 4 decades and is considered by most experts and ethicists to be an appropriate procedure as long as care is taken to ensure the health and safety of the donor [14,15]. Donation of PBSC by sibling minors using granulocyte colony–stimulating factor (G-CSF) has also been widely practiced for more than 15 years, has extensive safety data, and is considered standard by many centers and countries, although there are variations in the acceptability of the approach dependent on the age of the donor [9,10,16]. The main safeguards of the interest of the healthy sibling donor since the inception of the practice have been the parents and the physicians involved in the procedure, generally part of the transplantation team caring for the affected child. (Although some countries and states have used court-appointed advocacy systems, these have been the exception, rather than the rule). However, concern has arisen that conflicts of interest could possibly lead to the performance of HC collection in situations that would favor the health of the sicker recipient sibling over that of the donor. This has led to statements both from the American Academy of Pediatrics (AAP) [15] and the World Marrow Donor Association (WMDA) [17] calling for (1) an unbiased health screening and consent process performed by physicians or equivalent health care providers who are not involved in the care of the sibling, and (2) assessment of the relative risks and benefits of collection of a given donor by an independent advocate, who may or may not be the health professional screening the patient.

Although smaller transplantation programs may find it difficult to identify and schedule individuals qualified in donor screening who are not involved in the recipient's evaluation and care, this approach makes sense and will soon become standard practice. A survey performed by the Center for International Blood and Marrow Transplant Research Donor Health and Safety Committee published in 2010 showed that physicians at 70% of centers were involved in overlapping care of the donor and the recipient during the donor evaluation, clearance, and collection phases. Their publication included an admonition that "the transplant community … eliminate [this] potential for conflict-of-interest. [Donor clearance should be performed by] physicians whose fiduciary responsibility is to only one individual as is required by the NMDP for unrelated donors and by the [solid] organ transplantation field" [18]. An observation by

the EBMT Nurses Group confirmed similar situations in Europe [19]. These publications and statements, along with the AAP and WMDA pronouncements, have led to incorporation of this principle into the next (6th) edition of the Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee—the International Society for Cellular Therapy (Europe) and EBMT standards, requiring all certified centers to adopt this approach.

Although medical screening by an independent practitioner can protect donors from harm if they have significant medical issues, there is a lingering question about whether medical screening alone is adequate and about whether true advocacy for the donors is being performed. The WMDA statement calls for the donor to be screened by someone with a "documented advocacy role." The AAP statement states that "the donor advocate should help the parents weigh the risks and benefits for the healthy child to serve as a hematopoietic donor for an ill family member *and not just weigh the risks and benefits from the perspective of the potential recipient or from that of the family as a unit*." What this implies is that the donor advocate should have the ability to look at the potential harm, even if relatively minor compared with that for the sick sibling, and potentially advise against donation if there is a reasonable risk of either physical or psychological harm to the donor. Furthermore, if there is either medical history or clinical findings that raise concern, the advocate could suggest that a second opinion be obtained.

This shift in focus away from medical screening alone to independent advocacy by either the screening physician or another designated advocate means that there is the potential for conflict between the donor advocate and the parent or between the donor advocate and the screening physician regarding whether a sibling should be able to donate. This conflict could even occur between the sibling and the advocate if the sibling is old enough to offer assent. How can such conflicts be resolved? In states or countries where a court has already assumed a protective role for a donor, an advocate could easily appeal to a judge as part of the standard approval process. When the court is not a standard part of such proceedings, we recommend appeal to the independent ethics board, associated with most pediatric hospitals that are transplantation centers. If deliberations of such a board are felt to be inadequate by either contesting party, however, such a board will not have legal authority, and a court would be necessary for a legally binding decision.

If an advocate is given power to perform the roles outlined in the AAP and WMDA statements, who should fill this role? The most important qualifications are (1) training regarding potential psychological and physical consequences of donation, (2) understanding the ethical and legal basis (according to country/state of origin) of voluntary HC donation, and (3) independence from conflicts of interest that would allow unbiased assessment of the welfare of the child donor. We believe that not only medical personnel trained in advocacy could perform this function, but also social workers or mental health professionals trained to understand medical issues (or in consultation with independent medical health professionals) could fill this role. Health professionals associated with a transplantation team are well equipped to accept the role as donor advocate as long as they are not simultaneously involved in direct care for the affected sibling. Individuals independent from the transplantation team could also perform this role, but they must be trained sufficiently and perform the duty often enough to be competent in the role.

NATURE OF THE RELATIONSHIP OF THE SIBLING DONOR TO THE RECIPIENT

The AAP statement regarding HC donation advises that specific conditions be met for collection from a minor sibling donor to be permissible. Condition 2 requires that there has to be a "strong personal and positive relationship, or in the case of directed cord blood transplant, that a strong personal and positive relationship has to be anticipated." According to the statement, this will "increase the likelihood that the donor will experience some psychological benefit." Our committee disagrees with the premise of this condition and would like to propose a modification.

The AAP statement argues that "it would be morally problematic to ask a minor to serve as a donor to an unknown, emotionally distant, or emotionally abusive relative." Examples are given of (1) a case of a child asked to donate to a sibling they were unaware of and (2) a case of a sibling who was required to donate to an older sibling who had sexually assaulted her. In the first case, it is possible that a donor could experience a significant benefit from learning of and establishing a relationship with an unknown sibling. In the second case, however, the likelihood of psychological harm is so high that most experts would agree that the child should never have been HLA typed. The major challenge with the AAP statement is that it is very difficult to assess whether given sibling's relationships are positive—such relationships vary tremendously through the years and have the possibility of being strengthened by a donation procedure. Rather than assuming that a personal and positive relationship will more likely result in a psychological benefit to the donor, we think it makes more ethical sense to focus on avoiding psychological harm.

Practically, how can this is approached? First, if siblings have no personal relationship with each other (parents live separately and do not desire any interaction of the children now and in the future), it is best to avoid the conflict by not performing HLA typing. On the other hand, if separated parents want to use this as an opportunity for siblings to get to know each other, and a future relationship potentially desirable to both individuals could occur, then as long as the child assents, HLA typing and donation are reasonable. In such a circumstance, the likelihood of psychological harm is low.

What about siblings with negative relationships? If the relationship is extremely negative, such as in the case of sexual or repeated physical or emotional abuse, HLA typing should not be performed. Although parents may not be aware of such abuse, a donor advocate should screen for these rare issues. How about the more frequently encountered situation, where siblings fight regularly and currently don't like each other? If such siblings have the possibility of a positive or nonsignificantly negative relationship, and if the potential donor is at the age of assent and voluntarily assents, donation seems reasonable. Obviously, situations where siblings/relatives don't know each other personally should be carefully assessed by an advocate before HLA typing is performed. All siblings should be screened for seriously negative relationships as they go through the donation screening process, preferably before HLA typing, as well.

PERFORMING RESEARCH ON PEDIATRIC HC DONORS

The Ethics and Clinical Working Groups of the WMDA recently published guidelines outlining what they think should and should not be classified as research related to unrelated donors [20]. Because products obtained from the

standard procedures of BM and cytokine-mobilized PBSC collection can be used in many ways, it is sometimes difficult to determine when a donor should be considered a research subject and required to undergo research consent, according to the principles of the Declaration of Helsinki. The WMDA groups suggested 2 categories where donors are undergoing research. The first is the more obvious category, "where there is an intervention or interaction with the donor for research purposes." Examples of interventions/interactions include use of a new cytokine designed to mobilize PBSC, randomization between collection approaches, or participation in a survey about donor attitudes. Because of the direct interaction and collection of research data, research consent is obviously necessary. The second category of research includes studies that gather individually identifiable research material, even if coded, that are beyond the standard demographic data on patients gathered by registries. The WMDA position paper gives relevant examples that clarify these statements [20]. Donors should not be considered research subjects simply because the recipients are enrolled on research protocols. Our committee agrees with these recommendations and believes that applying them to the related donor setting is appropriate.

Once a pediatric donor has been declared a research subject, regulations regarding research in pediatric subjects (subjects not fully able to undergo consent) apply. Such regulations vary by country or state, but all regulatory frameworks struggle to offer protection to the healthy donor because of the following: (1) collection procedures involve a small risk of serious complications and a moderate risk of temporary discomfort, (2) these procedures are well established and considered standard procedures potentially not subject to research regulation, (3) there is controversy about whether a donor has a "condition" because they are generally healthy bystanders in the process of a disease their sibling is fighting, and (4) it is difficult to assess whether the donor will gain direct benefit from a collection procedure, as many ethicists are hesitant to consider possible indirect psychological benefit gained from contributing to a family need as something that would meet a standard of direct benefit.

An example of the challenges faced in fitting HC donor research from healthy minors into regulatory rules designed for children who have an illness or health condition is found in United States regulations. For research to be performed on children, (1) the donor must experience direct benefit (known as the 405 rule) (Figure 1), or (2) the research must represent at most a minor increase over minimal risk and address a "condition" the subject has (406 rule) (Figure 1), or (3) if either of these conditions don't apply, a special panel must be convened to decide whether the research is appropriate; if the panel agrees, the research will then be approved by top officials in the federal government. *Minimal risk* is defined as risk not greater than the average risks children face in life. Because a collection procedure is more than minimal risk, a change in such a procedure for research can often be construed as much more than minimal risk. Because it is difficult to define a benefit to the donor from the procedure, some reviewers find it difficult to approve any research on donors under rule 405. Other reviewers object to calling the state of being an HLA-matched sibling of a person with a disease a "condition" that research can address, thus making approval under rule 406 problematic. The only other avenue, if this line of interpretation of these regulations is followed, is a rule 407 review (Figure 1). Obviously, research regulations that require almost all new research to convene a government panel to address merit and obtain approval from highest levels is not practicable.

	Minimal Risk (MR)	Minor Increase over MR	More than Minor Increase over MR
Prospect 'Direct' Benefit	46.404 Approvable by IRB for all children	46.405 Approvable by IRB if prospect of 'direct' benefit justifies risks	
NO Prospect 'Direct' Benefit		46.406 Approvable by IRB if research concerns subject's condition	46.407 Approvable only by Government Panel*

*Special panel is being convened to decide whether the research is appropriate; if the panel agrees, the research will then be approved by top officials in the federal government.

Figure 1. United States Pediatric Risk-Benefit Regulations (45CFR46, Subpart D).

As a committee, we feel that research that will (1) improve the collection process by making it safer or more efficient, (2) allow biological correlation of donor and/or recipient characteristics that will better define outcomes of 1 or the other, or (3) improve survival of the recipient based upon minor changes in collection or manipulation of the product should be encouraged. We feel that because collection of BM and PBSC is a well established, safe procedure, judgments made about the safety of a research procedure should start with the inherent risk associated with the accepted procedure as a baseline. In other words, because the donor could be having a BM harvest as a standard procedure, does a change in the procedure proposed as research result in increased risk to the donor above the baseline risk, and if so, is it a minimal increase in risk?

We also believe that some consideration should be made to the reality that when a family donor is identified as being an appropriate HLA match (or a haploidentical match in the case of this form of transplantation), if they assent (if old enough), and if they are otherwise healthy, that child will likely participate in a collection procedure, whether or not research is involved. Although being a donor is not a medical condition, it is a situation where an individual both desires to help and has a special ability to help "save" their family member. A reasonable term to refer to this condition would be "willing and eligible donor," and because he or she is going to donate in a standard of care fashion if research is not involved, as long as the research is deemed minimal risk above the procedure he or she would have otherwise, it seems reasonable and appropriate to allow such research to occur. Along a similar vein, if the direct purpose of the proposed research is to improve the collection process by making it safer or more efficient (decreasing risk by having fewer or shorter collection procedures), a study may provide a potential benefit for the "condition" of being a donor. Therefore, in this circumstance, it may be reasonable to consider risks that are more than minimal risk.

CLINICAL ISSUES WITH THE DONOR THAT COULD INCREASE RISK

Over the last few decades, research has concentrated more on psychosocial effects than on physical outcomes of pediatric donors. We think that there are many clinical issues often seen in normal pediatric HC donors that should be addressed to avoid unnecessary risk. It is important to

remember that the process of HC donation exposes a healthy child to a potentially harmful medical procedure with no direct clinical benefit, and therefore, in spite of the good that can be done for the donor's ill sibling, because other donor sources can be used, the donor's safety must be top priority.

Clinical dilemmas may be subdivided according to the timeframe of the donation: before, during, and after donation. In this section, we will deal mainly with the "before" topics, including situations where the potential donor carries a medical problem/disease but normal BM, as opposed to the situation where a potential donor carries a problem in her/his BM but has no physical limitation to donation. We will also point out medical risks that one should pay attention to while taking care of a pediatric donor.

Medical Risks and Benefits

Currently, most medical ethicists agree that the act of donation provides no direct medical benefit to the donor. However, risks for the healthy donor occur in every type of donation. Approximately 1.1% of donation procedures will have some type of significant complication; the estimated death incidence is 1 per 10,000 donations, although deaths have not been reported in pediatric donors [21,22]. The source of the stem cell donation has the greatest influence on what type of adverse events will emerge. Side effects include pain, either from G-CSF treatment, placement of central venous catheter (CVC) or the direct punctures made when harvesting bone marrow. Most young donors will require a CVC, thus exposing them to potential risks such as bleeding, pneumothorax, and complications of sedation or general anesthesia [9,16]. Blood product transfusion is yet another risk. Younger age and higher harvest volume put the donor in higher risk for requiring allotransfusion, potentially exposing donors to risk of transfusion transmitted infection including bacteria, viruses, parasites, and prions. Even without receiving blood products, donors often need iron supplementation after donation.

PBSC as a graft source from pediatric donors became more popular in the last decade [23-25]. Though still not the major source for stem cells, peripheral blood–derived stem cell harvesting requires special attention in children, with the use of growth factors being the main issue. Long-term adverse effects from a brief treatment course with G-CSF for the harvest of PBSCs is being studied in on-going investigations, but to date no convincing evidence has shown significant health risks [10,26]. That said, one has to keep in mind the long life expectancy of children compared with that of adult donors, and this issue should be followed closely. Therefore, we recommend that G-CSF be used with caution only when needed, and we emphasize the need for long-term follow-up for these donors as published previously [27].

If a Donor has Significant Issues, Avoid HLA Typing

A question has been made regarding the timeframe of medical examination and HLA typing. Today, HLA typing precedes physical examination of the potential donor. Centers first screen for potential donors and physically examine those found to be matched. We suggest that centers should consider performing an independent medical screening that would remove children with potentially serious medical problems before HLA typing. If there is a medical contraindication that does not allow a BM or PBSC collection, we recommend that HLA typing should not be performed. This can avoid guilt on the part of an individual who cannot safely donate.

Donors with Medical Problems

The AAP statement referenced previously recommended that children may serve as stem cell donors only if they are "medically appropriate." No further details were provided. We feel that this issue should be described with more precise criteria. We will discuss 2 broad areas that address this issue: pediatric donors with medical problems, but with normal BM, and pediatric donors with known or possible genetic issues that may impact their recipient.

Donors with medical problems but normal BM

As a basic rule, it is preferable that a pediatric donor has no major medical problems. The question of including potential donors or deferring them starts when medical signs and symptoms are discovered. In the Netherlands, for example, many donors are accepted for PBSC donation despite the presence of conditions for which they would be deferred if they were unrelated donors [28]. Because siblings with health problems and their parents and donor centers are motivated to use them as donors in spite of these medical conditions, it is important to establish inclusion and exclusion criteria to clarify what is appropriate. These criteria need to be backed up by medical literature. However, in the absence of literature addressing rare conditions, consensus recommendations can be given.

The decision of whether to collect stem cells from BM or from peripheral blood is usually dictated by the clinical indication and approach to transplantation of the patient. But one should also consider the donor's safety in this choice, especially when outcomes of the recipient are very similar between the 2 stem cell types. Donors are excluded from donating BM if there is contraindication for general anesthesia. This may be a challenge for PBSC in pediatrics, as some centers require general anesthesia for CVC placement.

How should one approach donors with cardiac, lung, or gastrointestinal illnesses? What about children with diabetes [29]? We recommend that these individuals undergo a thorough evaluation by specialists in these organ systems or diseases and engage in a dialogue with the medical professional clearing the donor about potential harm to the donor if a given harvest procedure is performed. If it is clear that there is a moderate risk of significant harm, the donor should be deferred. We recommend that transplantation centers designate specialists in each of the above-mentioned disciplines who can become familiar with the special needs of stem cell donation, and, thus, may better decide how and what to recommend in each case. There are a number of scoring systems for anesthesia risk that can be employed [30].

In addressing the issue of when to defer, there is a need for clarification of how much risk is acceptable in a normal donor. Clearly, the medical and legal communities have judged that standard BM and, in most countries, PBSC donation procedures provide an acceptable risk profile for a pediatric donor. The standard that we would then suggest is that if any medical condition is present in a pediatric donor that alters the safety profile of the BM or PBSC collection procedure in such a way that more than a minimal increase of risk occurs, the donor should be deferred.

Table 1
Pediatric Donors with Known or Possible Genetic Issues that May Impact Recipient

Disease	Reference	Statement
Glucose-6-phosphate dehydrogenase deficiency	Pilo F, et al. Bone Marrow Transplant 2013;48:36-39.	A G6PD-deficient but otherwise healthy volunteer can be selected as an HSC donor.
Sickle cell disease	[31,32] Kang EM, et al. Blood 2002;99:850-855.	There were no G-CSF–related unanticipated adverse events, severe adverse events, or technical difficulties with HSC products collected from donors with the sickle trait
Thalassemia major	Mathews V, et al. Hematol Oncol Clin North Am 2014;28:1187-1200.	Sibling donors are encouraged but carrier status is not specifically mentioned
Primary immune deficiencies	Filipovich AH. Bone Marrow Transplant 2008;42:S49-S52.	Sibling donors are encouraged but carrier status is not specifically mentioned
Hurler syndrome	[33,34]	Although information on the carrier status (1 mutated gene) of the MSDs is lacking, it is expected that the many of the published donors were carriers, which has lead to the observed lower enzyme levels in engrafted MSD patients.
Stem cell failure syndromes	Tolar J, et al. Biol Blood Marrow Transplant 2012; 18:S166-S171.	Sensitive and specific diagnostic tests are now available and it is essential to screen sibling donors, to ensure that an affected sibling is not used as a stem cell donor.
Myelodysplastic syndrome/familial acute myelogenous leukemia	[35,36]	Outcomes using affected sibling donors are suboptimal, with failure in PBSC mobilization, slow and incomplete engraftment, graft failure, early relapses and predisposition to donor-derived myeloid malignancies.
Wiskott-Aldrich syndrome	Ozsahin H, et al. Blood 2008;111:439-445. Okuya M, et al. Bone Marrow Transplant 2010;45:607-609.	Successful transplant was performed for X-linked thrombocytopenia from a mild symptomatic carrier.
Chronic granulomatous disease	Soncini E, et al. BJH 2009;145:73-83.	Sibling donors are encouraged but carrier status is not specifically mentioned

HSC indicates hematopoietic stem cells; MSD, matched sibling donor.

We choose this standard because survival outcomes with unrelated donors in most situations are approaching that of related donors, and in spite of a higher risk of GVHD, if the donor's health is potentially in peril, use of an unrelated donor (even if not fully matched) is a viable alternative that could both offer curative therapy to an ill sibling and protect a child donor with an underling condition who is at increased risk of harm.

Pediatric donors with known or possible genetic issues that may impact their recipient

When children with known or suspected genetic disorders undergo transplantation from siblings, great care needs to be taken to ensure that sibling donors either do not have the condition or, in some cases, are not carriers. Table 1 shows disorders where carrier siblings have been shown either to be acceptable or not recommended for transplantation. These recommendations may vary over time as we learn more about specific diseases, especially disorders where high-level expression of enzymes is important to clinical outcome.

There are other disorders where children may be undergoing transplantation and there is a suspicion that the child's condition may be congenital, such as a child presenting with aplastic anemia and some somatic characteristics that could suggest an undiagnosed congenital marrow failure syndrome. This is also the case in many pediatric myelodysplastic syndromes [35-37]. In such cases, the sibling should be carefully assessed for BM function, and in some cases BM testing may need to be performed to ensure that the marrow is healthy. Such assessment may include measurement of CD34 numbers or colony-forming units and/or morphologic characteristics that would suggest that the "normal" donor may carry the same disease in an earlier stage.

Some carrier states of diseases may present specific health risks to the donor. A number of reports have suggested that PBSC not be collected on carriers of sickle cell disease [29,38,39]. On the other hand, more recent publications have demonstrated no adverse events in sickle cell carrier donors receiving G-CSF and donating from peripheral blood [31,32]. Likewise, potential donors who are not euthyroid at baseline may be at risk for severe deterioration in their thyroid-related hormonal state after injections of G-CSF [29,40-42], albeit this was documented in adults and was not studied in pediatric donors. For Hurler syndrome carriers, there is evidence that normal expression levels of enzyme after transplantation are important in improving outcomes of the recipient, and that lower chimerism and lower levels have been noted using siblings who are carriers. Thus, there is a suggestion that siblings who are carriers may not be the best donor for these patients [33,34].

There are many other major diseases, including primary immunodeficiencies, chronic granulomatous disease, or thalassemia, where there is strong support for matched sibling donors, but carrier status is not specifically mentioned in reports. One should expect that for autosomal recessive diseases or x-linked diseases (receiving female sibling BM transplantation), one half of the transplantations will have utilized carriers. In all these cases, we feel that in the absence of data to suggest otherwise, use of a sibling in a carrier state is appropriate.

Finally, there is debate concerning use of children with Down syndrome or other congenital syndromes resulting in severe developmental delay. There is evidence to show poor outcomes from BM donated by Down syndrome children [43,44]; therefore, this practice is not recommended. If the disorder leading to developmental delay is not known to lead to poor outcomes in the recipient, then donation can be considered, but because many of these children have

pulmonary, cardiac, or other medical issues, a careful review of the risks they may encounter should be performed by trained individuals as outlined above, and if their risks are increased, they should be deferred as donors.

"CREATING DONORS" AND FAMILY CB BANKING

Parents will sometimes consider the option of "creating" donor siblings via embryo selection with preimplantation genetic diagnosis for CB or BM donation. This complex medical and ethical issue deserves further discussion but is beyond the scope of this manuscript. A review of this issue, along with considerations regarding direct and family CB banking, has been published previously [45].

CONCLUSIONS

Pediatric donors of HC can almost always safely donate with parental consent and greatly benefit their recipients and their families. To protect them from rare situations when their psychological or medical health may be at risk, we recommend advocacy and careful medical review. Potential family sibling donors with medical or psychological reasons not to donate should not be HLA typed. Those with medical conditions should be carefully examined by skilled professionals, and if their risks of complications with collection are increased, they should be deferred. Following these simple principles, transplantation professionals can fulfill their obligation to the generous normal childhood donors under their care to "Primum non nocere" —first, do no harm.

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