Donor Evaluation for Hematopoietic Stem and Progenitor Cell Collection

4

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4.1 Introduction

Hematopoietic cell transplantation (HCT) remains a potentially curative treatment for life-threatening hematological and non-hematological diseases. Over the last several years, the total number of HCTs performed worldwide has exceeded 60,000 a year (Niederwieser et al. 2016; Gratwohl et al. 2010). Autologous hematopoietic cell transplantation (auto-HCT) accounts for the majority of all procedures performed, and in the United States, the number continues to increase at a fast rate, mainly from transplants performed for plasma cell and lymphoproliferative disorders extending to older patients (Gratwohl et al. 2010; Center for International Blood and Marrow Transplant Research (CIBMTR) 2016). Allogeneic HCTs (allo-HCT) have exceeded 30,000 per year worldwide with the number of transplant recipients surpassing 8000 a year in the United States (Center for International Blood and Marrow Transplant Research (CIBMTR) 2016). Approximately 70% of allogeneic transplants use hematopoietic progenitor cells (HPCs) from volunteered unrelated donors (URDs). Advances in HLA typing, new immunosuppressive protocols, improved supportive care, and the administration of nonmyeloablative (NMA) or reduced-intensity conditioning (RIC) regimens contribute to the increased frequency of HCT. The observed continuous annual increase of around 10% is mainly because of a rise in allo-HCT from URDs (Gratwohl et al. 2010, 2013). There has also been an increase in alternate donor sources with HLA-haploidentical donors now exceeding umbilical cord blood transplants (Center for International Blood and Marrow Transplant Research (CIBMTR) 2016).

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Although $CD34^+$ cell donation by apheresis is considered a relatively safe procedure with very low rates of serious adverse events (Schmidt et al. 2017), the risk of both physical and psychological harm exists. At the same time, there is also potential harm to any recipient through the infusion of the graft, especially by communicable diseases. For allogenic donors, it is important to optimize the whole donation experience as these donors will undergo a procedure for which they will not be receiving any direct benefit. There is however a potential sense of satisfaction derived from this altruistic act (Boo et al. 2011). Therefore, for URD, an excellent reputation of a safe and efficient process is needed to ensure adequate number of donors being maintained and joining the national registries (Billen et al. 2014).

Pretransplant donor evaluation is an essential process to safeguard the quality and safety of donation. The primary goals of allo-HCT donor evaluation are to ensure that a) there is minimal risk to the health of the donor from the collection procedure and b) to protect the recipient from transmissible diseases.

4.2 Regulatory Guidance, National Registries, and Accreditation Agencies

On May 25, 2005, the US Food and Drug Administration (FDA) implemented comprehensive regulations governing the collection and manufacture of human products for transplantation and immune modulation, as well as a variety of other cellular- and tissue-based human products (Food and Drug Administration 2005). These regulations are based on the FDA's responsibility to limit the transmission of infectious diseases through the administration of these products and apply to peripheral blood stem cells, cord blood, and donor lymphocytes. The responsibility for bone marrow regulations has been assigned to the Health Resources and Services Administration (HRSA).

The FDA regulations include the requirements for establishing donor eligibility and apply not only to products collected or manufactured within the country, but also to those imported from outside the United States (Food and Drug Administration 2005). Other international regulatory bodies, for example, European Directives for Donation of Tissues and Cellular Therapy Products (Human Tissue Authority (HTA) Regulations 2007) also have detailed requirements for donor evaluation to ensure the safety of the product for the recipient; however, unlike FDA regulations, they do not address donor safety issues.

Given the extensive international collaboration and exchange of HPC products, most regulatory agencies work closely with national registries, such as the National Marrow Donor Program (NMDP) and the World Marrow Donor Association (WMDA). These national registries develop and establish appropriate guidance to ensure HPC donation is performed safely and ethically in volunteer URDs and have published their recommendations for donor evaluation (Sacchi et al. 2008; Lown et al. 2014; National Marrow Donor Program (NMDP) n.d.-a). Donors are assessed

as to their suitability and eligibility to donate HPCs. Donor suitability refers to the general health or medical fitness of any autologous or allogeneic HPC donor to undergo the collection procedures. Donors are evaluated as to their risk and overall safety to donate. Donor eligibility refers to issues that relate to an allogeneic donor for who all screening and testing has been completed in accordance with applicable laws and regulations and who has been determined to be free of risk factors for relevant communicable diseases. URDs are only eligible if they are unrestrictedly healthy. Often however, physicians struggle with decision making as to the suitability of a relative as a donor that would not otherwise meet the suitability criteria for unrelated donation. The suitability criteria for related donors (RDs) is often less strict and with considerable variability between transplant centers. Differences between RDs and URDs may exist in mobilization and collection practices (Sacchi et al. 2008; Confer et al. 2011; O'Donnell et al. 2010; Clare et al. 2010). Published data suggest that the risks for serious adverse events and reactions might be higher for RDs than for URDs, but the amount of adequate prospective data in the RD setting is still limited (Halter et al. 2009; Kodera et al. 2014). Many institutions have developed their own processes for the evaluation of RDs; historically, there had been no national guidance available. In 2015, the Worldwide Network for Blood and Marrow Standing Committee on Donor Issues developed a consensus document with recommendations for donor workup and final clearance of family donors that would otherwise not be able to serve as URD because of age or preexisting diseases (Worel et al. 2015).

The FACT-JACIE (Foundation for the Accreditation of Cellular Therapy/Joint Accreditation Committee ISCT and EBMT) international standards were founded in 1994 to address obstacles faced when transplantation involves donors and recipients in different countries. This voluntary organization establishes international guidelines for the collection and transfer of hematopoietic stem cells. Members include donor registries, cord blood registries, and numerous individuals working together to advance HCT. FACT/JACIE addresses issues, including donor evaluation criteria, a donor follow-up policy, and the requirement that "Allogeneic donor suitability should be evaluated by a physician who is not the physician of the recipient." Accreditation is the means which a center can demonstrate that it is performing a required level of practice in accordance with agreed standards of excellence. Essentially it allows a center to certify that it operates an effective quality management system. In many countries, however, accreditation is not mandatory for centers assessing RDs. Improved compliance with internationally recognized donor care paradigms have been seen in centers with FACT-JACIE accreditation; however, important practice gaps in all centers irrespective of accreditation continue to be seen (Anthias et al. 2016a, b). Other organizations that provide additional insight into US regulations regarding donor evaluation include the AABB, the American Society for Blood and Marrow Transplant (ASBMT), the International Society for Cellular Therapy (ISCT), and the Center for International Blood and Marrow Transplant Research (CIBMTR).

4.3 Donor Assessment

4.3.1 Donor Eligibility

Similar to blood transfusion, HPC donation has the potential to transmit a wide range of blood-borne diseases. For example, hepatitis B (Lau et al. 1999), hepatitis C (Strasser and McDonald 1999; Shuhart et al. 1994), human T-lymphotrophic virus type 1 (HTLV-1) and type 2 (HTLV-2) (Kikuchi et al. 2000; Ljungman et al. 1994), Chagas disease (Villalba et al. 1992), malaria (Mejia et al. 2012), syphilis (Naohara et al. 1997), and brucellosis (Ertem et al. 2000) have all been reported to be transmitted by HPCs. In the United States, strict federal regulations regarding the evaluation of HPC donors are laid out in Title 21 of the Code of Federal regulations; Part 1271 (Human cells, Tissues and Cellular- and Tissue-Based Products). Subpart C is Donor Eligibility Determination and lays out the requirements for donor screening and testing for "relevant" communicable disease agents and diseases (RCDAD) (Table 4.1). Relevant communicable disease agents and diseases (RCDADs) are identified by the FDA as having the potential to cause significant pathogenicity to recipients of human cells, tissues, and cellular- and tissue-based products and are defined as infections that

Table 4.1 Current relevant communicable disease agents and diseases (RCDADs) for viable leukocyte rich human cells, tissues, and cellular- and tissue-based products

RCDAD	Evaluation	
Specifically listed in CFR	Screening	Testing
HIV types 1 and 2	X	X
Hepatitis B	X	X
Hepatitis C	X	X
HTLV types 1 and 2	X	X
Creutzfeldt-Jakob disease (CJD)/ variant CJD	X	
Treponema pallidum (syphilis)	X	X
Risks associated with xenotransplant	X	
CMV		X
Not specifically listed		
WNV (June 1–October 31)[a]	X	X
ZIKV	X	
Trypanosoma cruzi (Chagas)[b]	X	X
Sepsis	X	
Vaccinia virus infection	X	

HIV human immunodeficiency virus, *HTLV* human T-cell lymphotropic virus, *CMV* cytomegalovirus, *WNV* west nile virus, *ZIKV* zika virus

[a]In US FDA requires NAT testing for WNV between the months of June 1 and October 31

[b]Evaluation for Chagas disease in draft guidance

1. Bring risk of transmission to the recipient
2. Have a severe effect on the recipient if transmitted
3. Have available appropriate screening measures or tests to identify the potential donor's risks of exposure to and/or possible infection with the disease

The FDA identifies specific RCDADs by listing them either specifically in the CFR or by publishing a guidance document to communicate any changes. Some institutions and accreditation bodies may choose to include evaluation of other agents or diseases such as malaria.

To determine eligibility, donors need to be screened and tested for RCDADs. Assessing the risk of disease transmission involves three components (Food and Drug Administration 2005):

1. Targeted screening history
2. Examination for physical signs of disease
3. Laboratory testing for specific pathogens or traits

A **screening history** involves interviewing the donor about their medical history and relevant social behavior. It includes the review of relevant medical records for clinical evidence of RCDADs. The FDA recommends that the screening interview be a documented dialogue, administered by phone or in person, with appropriate follow-up or verification by a trained individual if the donor health history is self-administered. Various registries have developed HPC donor-screening questionnaires and their use recommended, to elicit medical history and to identify high-risk behaviors associated with risk of disease transmission (AABB n.d.-a; National Marrow Donor Program 2002). The screening history should also include communicable disease risks associated with xenotransplantation. One such questionnaire that is freely available is the hematopoietic progenitor cell (HPC), Apheresis and HPC, Marrow Donor History Questionnaire (DHQ) (Appendix 4.1) developed by the AABB Inter-organizational DHQ-HPC Task Force to provide establishments with a standardized tool to screen allogeneic HPC donors for communicable disease risk factors in accordance with requirements of the FDA, AABB, FACT, and the NMDP (AABB n.d.-a).

These DHQ materials are periodically reviewed to ensure continued compliance with regulatory and accrediting agencies. Companion documents provide rationale for the questioning and recommendations for evaluation of responses (AABB n.d.-b). Institutions are notified of any changes as well as the timeline for implementation through existing publications and websites maintained by members of the task force. When a new version of the documents is posted, the previous version is maintained for a period of time to allow facilities to transition to the new version. The NMDP has developed similar medical history questionnaires to support its work with unrelated donors (https://network.bethematchclinical.org/workarea/download-asset n.d.).

In the process of completing the DHQ, clinical staff must verbally interact with the donor to review and verify donor's responses to the DHQ and to ensure the DHQ

was signed and dated. All donors should have appropriate age-related donor health questionnaires with a parent or legal guardian (proxy) when required for age. Appropriate arrangements must be made for donors with developmental delays, appropriate interpreters for nonnational-speaking patients. Donors who are not English or native speaking in the country of assessment should have a medical interpreter who is not a family member or friend of the family.

A **physical examination** should be performed to identify any signs or stigmata that may indicate high-risk behavior for or infection with RCDAD(s). The examination should include recent tattoos, piercings, or signs of intravenous drug use, as well as signs of significant illnesses to determine eligibility for the donation procedure. Several institutions have developed a supplemental examination checklist (Appendix 4.2) to ensure a thorough examination for signs or stigmata of RCDADs.

In accordance with FDA regulation, **laboratory testing** using FDA-approved assays must be performed on the donor' blood for, at least, the following infectious disease agents: human immunodeficiency virus 1 and 2 (HIV 1 and 2), hepatitis B virus (HBV), hepatitis C (HCV), *Treponema pallidum* (syphilis), human T-cell lymphotrophic virus I and II (HTLV I and II), and cytomegalovirus (CMV). The FDA has provided core requirements for laboratory testing (Table 4.2). For emerging infectious diseases including the Zika virus (ZIKV), severe acute respiratory syndrome (SARS), and West Nile virus (WNV), additional screening questions were emergently added to the donor qualification process in the United States, based upon recommendations from the FDA. WNV is only infectious during the viremic phase and NAT testing must be performed concomitantly with product collection (or within 7 days before or after collection). While it might not be possible to prevent the infusion of an infected product, knowing that a product was infected with WNV would provide an opportunity to develop a preemptive treatment strategy. In the United States, WNV testing is to be performed specifically between June 1 and October 31 of each year. For all other establishments and intending to import human cells, tissues, and cellular- and tissue-based products into the United States, testing of human cells, tissues, and cellular- and tissue-based products donors for WNV should be performed year-round.

It is also desirable to perform testing for prior infections with varicella zoster virus (VZV) and Epstein-Barr virus (EBV) and possibly others, such as

Table 4.2 FDA core requirements for laboratory testing

– Use appropriate FDA-licensed, FDA-approved, or FDA-cleared donor-screening tests (Table 4.3)
– Laboratories used for laboratory testing must be certified under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS)
– Testing must be performed in accordance with the manufacturer's instructions for use (IFU)
– For Hematopoietic Stem/Progenitor Cell (HSPC) Donors the laboratory specimen to be used for donor testing may be collected up to 30 days prior to or within 7 days after human cells, tissues, and cellular- and tissue-based products recovery. For all other cells or tissue from the donor, laboratory testing must be performed at or up to 7 days before or after recovery

Table 4.3 Examples of FDA-licensed donor-screening tests

Pathogen	FDA-licensed screening test
HIV-1	• Anti-HIV-1 or combo test for anti-HIV-1 and anti-HIV-2, **AND** • NAT test for HIV-1 or combination NAT testHIV-2
HIV-2	• Anti-HIV-2 or combo test for anti-HIV-1 and HIV-2
HTLV-I/II	• Anti-HTLV-I/II
HBV	• Hepatitis B surface antigen (HBsAg), **AND** • Total antibody to hepatitis B core antigen (IgG & IgM; anti-HBc) • NAT test for HBV
HCV	• Anti-HCV • NAT test for HCV or combination test
WNV	• NAT test for WNV
Treponema pallidum	• Nontreponemal or treponemal
CMV	• Anti-CMV, total IgG, and IgM

HIV human immunodeficiency virus, *HTLV* human T-cell lymphotropic virus, *CMV* cytomegalovirus, *WNV* west nile virus, *ZIKV* zika virus

toxoplasmosis. Positive tests for exposure to these agents may not preclude donation or make the donor ineligible but may modify the transplant approach or post-transplant surveillance strategies.

All RCDAD screening results should be communicated effectively to the collection center as well as to the physician responsible for accepting the human cells, tissues, and cellular- and tissue-based products. This notification should be part of a standard procedure and clearly documented. Any human cells, tissues, and cellular- and tissue-based products donor whose specimen tests positive (or reactive) using any of the assays is considered ineligible (exception syphilis and CMV screening). Confirmatory tests should be considered when a positive (or reactive) screening test result is received for such purposes as donor counseling or investigating discordant test results. If a confirmatory test is performed and is negative or nonreactive, these results would not override a positive or reactive screening test and the donor still remains ineligible. Screening tests for syphilis are the exception. Because of the potential for false-positive results in nontreponemal testing, if a specific treponemal confirmatory test is negative, the donor will be deemed eligible from syphilis standpoint. A donor who tests positive or reactive for CMV is not necessarily ineligible to donate human cells, tissues, and cellular- and tissue-based products. A positive or reactive (past or recent exposure (IgG or IgM)) CMV test result should also be communicated to the physician responsible for accepting the human cells, tissues, and cellular- and tissue-based products. In case of a positive IgM CMV, it is best to exclude CMV seroconversion.

After completion of donor eligibility screening history, physical examination, and laboratory tests, written donor eligibility determination is required for all human cells, tissues, and cellular- and tissue-based products donors, except for autologous use. All human cells, tissues, and cellular- and tissue-based products must not be transplanted, infused, or transferred until the donor has been determined to be eligible, unless (1) there is no other appropriate donor and the proposed donor poses less risk to the recipient than not using the donor and (2) approval is obtained from

the recipient to proceed with transplantation using these cells. This often poses concern because information about donor health is strictly confidential and can only been released with explicit permission from the donor. If HPC collection proceeds with an ineligible donor, written justification is needed and shall be documented.

The results of these RCDAD screening tests must be reviewed prior to initiating preparative conditioning therapy in the recipient. If the time between initial donor evaluation and collection is delayed, repeat testing may be necessary. In the event of missing or incomplete screening test results at the time of HPC collection, the product should be labeled clearly by the collection center that the product has not been evaluated for infectious disease markers. Donors are declared as ineligible, with processing centers having policies and procedures in place for the storage and release of "ineligible donor" products.

4.3.2 Donor Suitability

All donors must be medically evaluated to detect conditions that might significantly increase donor risk to unacceptable levels and to ensure their safety to donate. Peripheral blood hematopoietic progenitor cell (HPC) donation typically involves the administration of 4 or 5 daily injections of granulocyte-colony stimulating factor (G-CSF) and/or other mobilizing agent followed by apheresis collection. For autologous patients, mobilization commonly includes G-CSF +/− plerixafor or chemotherapy. Side effects of HPC mobilization with G-CSF or other mobilization agent(s) and apheresis collection should be taken into consideration when assessing donor suitability. The designated physician (or appropriately licensed supervised advanced practitioner) performs a medical history and physical examination according to standard medical practice. Medical records should also be reviewed as part of the assessment. The history not only provides an additional opportunity to review/affirm questions provided on donor screening health questionnaire but looks to evaluate current health. Typical questions to be covered during history taking are seen in Table 4.4. The physical examination will also include assessment of signs/stigmata of RCDADs (Appendix 4.2). Vital sign testing, height, weight, noting Karnofsky- or Lansky- performance scores, and assessment of venous access are an essential part of the physical examination. Laboratory testing and other investigations are also required to evaluate a donor's suitability (Table 4.5).

The NMDP has developed several tools or lists of clinical disorders/diseases to assess an URD donor's health and RCDAD risk (National Marrow Donor Program (NMDP) n.d.-a). Several centers often use these tools as guidance for their RDs. Donors with atypical responses to screening questions, history, and physical examination must be evaluated on a case-by-case basis to determine the donor's eligibility and suitability. The individual performing or evaluating the health screening, history, and PE should be knowledgeable by training or experience to accept or defer donors. In general, donors with moderate or severe organ impairment should be deferred; this includes donors with coronary artery disease and renal or hepatic impairment. Occasionally, a medical condition is identified that does not warrant

Table 4.4 Typical questions asked on taking a donor history

History of heparin allergy, heparin intolerance, heparin-induced thrombocytopenia
History of requirement for therapeutic anticoagulation
Immunization history
Blood product transfusions and donation(s)
Allergies
Current medication (prescription and nonprescription)
Previous exposure to anesthetics and family history of problems to anesthesia
Infectious disease risk including recent upper and lower respiratory tract infections within the last 30 days, risk of tuberculosis exposure
Pulmonary and upper airway disease
Cardiovascular disease including treatment
Diabetes mellitus
Arthritis including back problems
Autoimmune diseases
Abnormalities of the spine
Possibility of pregnancy for all biological female donors with reproductive potential
Travel history
Cancer
Inherited disease(s)

Table 4.5 Typical laboratory and other investigations performed in donor evaluation

Complete blood count (CBC) with differential and reticulocyte count
Electrolytes (Na, K, CO_2, chloride), blood urea nitrogen (BUN) and creatinine, alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, SGPT), glucose, serum total protein plus albumin, or serum protein electrophoresis
ABO, Rh typing, antibody screening
Infectious disease markers (IDMs) (see above)
CMV antibody screening (see text)
Serum beta-HCG pregnancy (if female of child-bearing potential)
Malarial testing if donors travelled to malaria endemic areas
Screening for hemoglobinopathy (e.g., SickleDex or equivalent)
If donating for Thalassemia patient, thalassemia screening for hemoglobin A, A2, and F
urinalysis
Tuberculosis testing as clinically indicated
Oxygen saturation
Chest X-ray and EKG as clinically indicated. Chest X-ray and EKG are not routinely required However, they may be performed at the discretion of the examining medical professional or the collection facility/donor center physicians based on medical assessment Criteria for whom to perform an EKG may include • History of diabetes mellitus (DM) • History of cardiovascular disease (CVD) • Treatment with digoxin or diuretics • Pulmonary disease (room air $O_2 < 90\%$) • Smoking >20 pack years • Age over 40 (males) and over 50 (females) • If a delay in donor collection of more than 30 days repeat EKG may be required in certain cases such as history of DM, CVD, and treatment with digoxin or diuretics. Otherwise for other donors this can be repeated if more than 6 months since the last EKG Criteria for who to perform a chest X-ray may include • History of pulmonary disease • Oxygen saturation <90%

immediate deferral, but may require further investigation. Any referral to a specialist or additional workup required should be expedited and the recipients team should be informed as soon as possible so that the transplant clinicians can determine whether or not the donor, if found to be suitable, would be available in a timely manner.

If a donor is deemed unsuitable but a decision is made that there is no other suitable donor available and the donor is prepared to take a reasonable risk, a justification must be documented.

In the event that the transplant procedure is delayed, collection or transplant facilities may require repeat donor assessment within a specified time. The NMDP requires that donor assessment is always current to within 12 weeks (3 months) of the proposed collection date. This includes a repeat administration of a screening questionnaire with additional tests to ensure continuing medical suitability based on updated information provided. There are no mandatory tests and NMDP does not require any extended testing when less than 6 months have passed since the original physical examination date. Laboratory markers for RCDADs however will need to be repeated within 30 days from collection of HPCs (Table 4.2).

Additional risks for recipient safety following donation, other than infectious diseases, that need to be assessed during evaluation of the donor include autoimmune diseases (ADs), inherited diseases, and malignancy. The development of an AI disorder from a donor with the same condition has been reported and includes thyroid disease (Olivares et al. 2002; Thomson et al. 1995), diabetes mellitus (Lampeter et al. 1998), psoriasis (Snowden and Heaton 1997), and vitiligo (Campbell-Fontaine et al. 2005). Inherited diseases within the hematopoietic system that will be transmitted include hemoglobinopathies such as sickle cell disease, thalassemia, congenital platelet disorders, and inherited bone marrow failure syndromes.

Transmissions of malignant diseases from donors to patients have been reported in the past, most of them inadvertently from subclinical malignant disease or diseases not recognized by the current screening methods. The risk for transmission of tumors is assumed to be of a very low incidence. These rates do not include secondary malignancies of donor cell origin arising in the recipient after allo-HCT.

In addition, patients with a history of heparin allergy, heparin intolerance, or heparin-induced thrombocytopenia are at increased risk for complications with infusion of heparin-containing products. This is essentially important if heparin is used as part of the anticoagulant during the apheresis collection process. Donor evaluation provides an ideal opportunity to get full informed consent. The donor would require a comprehensive discussion of potential risks and "theoretical donor safety" issues. The donor should be aware that they are not obliged to donate, even if for a family member. There should be no coercion and it is essential that allogeneic donor suitability should be evaluated by a physician who is not the physician of the recipient. If the donor consents to donation and then chooses to pull out of their decision after the recipient has started conditioning treatment, the potential risks to the recipient should be discussed fully with the donor.

4.4 Children as Donors

The most suitable donor for younger patients who undergo allo-HCT is often a minor sibling. In rare cases, children may also be considered as potential donors for an adult sibling, parent, or other family member. Worldwide data indicate that more than 30% of children undergoing HCT receive allografts from siblings under the age of 18 (Miano et al. 2007). The use of minors as HPC donors is considered medically safe (Pulsipher et al. 2005) and legally accepted given that no alternative approach of comparable effectiveness exists; however, donation of HPCs is not without risk (Pulsipher et al. 2013; Styczynski et al. 2012; Grupp et al. 2006) and appropriate medical evaluation of the donor is essential.

The source of the graft (peripheral blood vs. bone marrow) has the greatest influence on the type of adverse events that may present. It is important to note that in children majority of grafts are of bone marrow origin. Side effects include pain, either from G-CSF treatment, placement of central venous catheter (CVC), or the puncture wounds made when harvesting bone marrow. Most young donors will require a CVC for apheresis, thus, exposing them to potential risks such as bleeding, infection, pneumothorax, and complications of sedation or general anesthesia (Pulsipher et al. 2005; Styczynski et al. 2012). Collection of peripheral blood graft 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 HPCs via apheresis continues to be studied in ongoing investigations, but to date, no convincing evidence has shown significant health risks (Pulsipher et al. 2006). The worldwide network for blood and marrow transplantation (WBMT) recommends G-CSF is used with caution and only when needed and emphasize the need for long-term follow-up for these donors (Halter et al. 2013). Several published findings suggest that pediatric donors may experience psychosocial issues around the time of and following donation including higher anxiety and lower self-esteem than non-donors (Packman et al. 2008), moderate levels of post-traumatic stress, depression, behavioral problems, identity problems, guilt, and resentment (Packman et al. 1997, 2008; Wiener et al. 2007). Young donors may also fear the medical aspects and pain involved in donation and experience anxiety and ambivalence about donation (Kinrade 1987; MacLeod et al. 2003).

Although parents for the majority consent to medical interventions on behalf of their children, respecting a child's autonomy and obtaining a child's assent or appropriately regarding his or her dissent or refusal—is generally thought to be of paramount ethical importance. Decision makers are burdened with great responsibility: their choice will have life-and-death consequences for another vulnerable child.

Recognizing that HPC donation has no physical benefit to these young donors and its associated with potential risks, the American Academy of Pediatrics Committee on Bioethics (AAPCOB) (Committee on Bioethics 2010) has published guidelines specifying when minors may ethically serve as HPC donors. The AAPCOB has deemed that children may ethically serve as hematopoietic stem cell donors if five criteria are fulfilled (Table 4.6).

Table 4.6 The 5 AAPCOB criteria for minors to ethically serve as hematopoietic progenitor cell donors (Committee on Bioethics 2010)

1. There is no medically equivalent histocompatible adult relative who is willing and able to donate
2. There is a strong personal and emotionally positive relationship between the donor and recipient
3. There is a reasonable likelihood that the recipient will benefit
4. The clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient
5. Parental permission and, where appropriate, child assent have been obtained

A donor advocate with expertise in pediatric development (second physician or a child life specialist) should be appointed for all children who have not reached the age of majority (age at which a person is recognized by state law to be an adult) and who are being evaluated as hematopoietic graft donors. The donor advocate must be independent of the team responsible for direct care of the recipient to ensure that the AAPCOB recommendations are met. He or she should ideally be involved from the onset, starting with the decision about whether the minor should undergo HLA testing so that potential family or sibling donors with medical or psychological reasons not to donate would not be HLA typed. Donors with medical conditions should be carefully examined by skilled professionals, and if their risks of complications with collection are increased, they should be deferred.

In the advancement of the effectiveness of different hematopoietic stem cell transplants, research is often needed to be performed on donors and/or recipients. When the donor is a minor, the research must conform to the federal regulations governing pediatric subjects. This may require national review when the research imposes more than minimal risk without prospect of direct benefit to donor subjects. Several publications have addressed this area and should be considered before donors are evaluated for research (Wendler et al. 2016; Shah et al. 2015).

4.5 Older Adults as Donors

With the increased availability of NMA conditioning over the last two decades (Pingali and Champlin 2015; Alyea et al. 2005), and improvement in supportive care, the ability of many older patients to tolerate allo-HCT has now become apparent. For older patients, an HLA-matched sibling is often a donor. Unlike URD registries, there are no strict age limits recommended for related allogeneic donors. There is experience available in the literature for donors up to the age of 75 years.

Many health disorders are more prevalent with increasing chronological age, including cardiovascular, cerebrovascular and peripheral vascular disease, chronic airways diseases, diabetes mellitus, malignancies, etc., and must be taken into consideration by any provider assessing the suitability of an older individual to donate. In some reports, HPC collection by apheresis seems to be a safe procedure for donors ≥60 including those with significant comorbidities (Ghada et al. 2006). However, certain complications are more frequent in the older donors and have demonstrated more procedure related complications than younger donors (Lysák et al. 2011). For example, one study demonstrated higher complications associated

with hypocalcemia, thrombocytopenia, and problems with venous access in donors ≥55 years of age compared with younger donors (29% vs. 15%, $P = 0.0096$). Venous access complications were also more frequently present in donors with circulatory system diseases (arterial hypertension, chronic venous insufficiency) compared with the donors without this medical history (11% vs. 3%, $P = 0.006$) (Lysák et al. 2011). A recent related-donor safety study, looking at health-related quality of life issues among older related HCT donors (>60 years) compared to younger adult counterparts, showed very few differences in indicators in physical and mental health donation-related experiences (Switzer et al. 2017). This may suggest that older sibling donors do not experience the donation process as significantly more physically or psychologically impactful than their younger counterparts and, in some aspects, their experiences were more positive—for example, less donation-related pain and less anxiety about donation. There was less conclusive evidence supporting the procedure in sibling donors as old as mid-70s (Switzer et al. 2017).

Regarding graft composition, some authors have found that in older donors may be different from that obtained in younger donors (Al-Ali et al. 2011; Richa et al. 2009; Miller 1996) with $CD34^+$ cells in the peripheral blood and apheresis yield being lower in older donors (Richa et al. 2009; Suzuya et al. 2005). One study noted the failure of mobilization (collection of less than $2 \times 10^6 CD34^+$cells/kg of recipient body weight) rate at 7% in the older donor group (≥55 years) versus 0.8% in the younger donor group. It was noted, however, that in donors younger than 50 years, the relationship is not statistically significant and is no longer an independent prognostic factor, also seen by other studies (Ings et al. 2006). Several studies have however reported contradictory results regarding donor-predicting factors for mobilization and yield and cannot confirm an independent influence of age on mobilization (Bagnara et al. 2000; Miflin et al. 1996; Rinaldi et al. 2012). There is some suggestion that the conflicting results are likely due to often small sample sizes and heterogeneous treatment with mobilizing regimens (Lysák et al. 2011).

In autologous transplantation, elderly patients can have a high risk of poor mobilization (Goker et al. 2015). Some studies reported that $CD34^+$ cell mobilization in patients of advanced age (70 years and older) with multiple myeloma was poor but still possible (Morris et al. 2003). This is contrary to that reported suggesting no differences in the mobilization kinetics between younger (<65 years) and older (≥65 years) myeloma patients (Jantunen et al. 2006). Other investigations into whether age affects mobilization in autologous transplantation has also been contradictory in donors <70 years old (Bensinger et al. 1994, 1995). Therefore, age can be a confounding factor in autologous stem cell mobilization. Several donor factors predict outcome after allo-HCT and age is one of the important non-HLA factors affecting the survival rates after transplantation (Kollman et al. 2001). Clinical practice often prefers "HLA-matched siblings" as first-line donors for transplantation despite donor's age; however, the survival rates for unrelated donor transplants with young fully HLA compatible donors are similar to those using older sibling donors (Kollman et al. 2016). Allo-HCT from older adults have been associated with higher nonrelapse mortality (NRM) but donor age was not associated with relapse (Kollman et al. 2016). Observed higher rates of grade II to IV acute GvHD after transplantation of grafts from older donors may be explained by replacement of naïve T-cells with memory T-cells as the immune system ages in the older donors (Miller 1996).

4.6 Donors with Psychological/Psychiatric Disorders

On occasion, the only matched related donor identified may be an individual who has a known psychological/psychiatric disorder, and the decision for any physician to deem this prospective donor suitable may be very difficult indeed. In 2013, the WBMT standing committee on donor issues held an international workshop to develop a consensus document with recommendations of suitability criteria for final donor workup in family donors and included donors with psychological-psychiatric disorders (Worel et al. 2015). These recommendations as well as recruitment assessment tools such as those used by NMDP registries may be helpful for physicians who have concerns about suitability in these donors (National Marrow Donor Program (NMDP) n.d.-a, n.d.-b).

Donors with a history of substance abuse may not be automatically deferred, but require a careful history and medical assessment. Donors should be assessed for risk factors for infectious diseases or underlying psychiatric disorders. Compulsive dependence on a chemical can cause various physical ailments such as liver damage secondary to alcohol abuse. In the case of infrequent substance abuse with marijuana alone, individuals are mostly suitable but may require cessation of use before donation or initiating G-CSF. Donors with a previous history (and not currently using) of cocaine, crack, and methamphetamine (intranasal/oral) abuse might also be suitable; however, the use of these drugs has been associated with an increased risk of cardiovascular disorders, and careful assessment of the donor is required. In intravenous drug abusers, donation is generally not recommended due to the increased risk of communicable diseases such as HIV, hepatitis B, and hepatitis C with contaminated needles. Individuals who are on a substitution program but otherwise healthy may be suitable.

Donors with eating disorders (anorexia and/or bulimia) are suitable only if their disease is stable under appropriate treatment and their BMI is >16.0 in adults (Worel et al. 2015). These potential donors should be deferred if their overall physical status (including body size, demeanor, skin color, etc.) indicates serious health concerns.

HPC donation in individuals with multiple personality disorders and psychosis is generally not recommended. Subjects with obsessive-compulsive, attention deficit, or attention-deficit hyperactivity disorders are suitable if their disease is well controlled. However, the donor's capacity to follow through the donation process may be affected.

In donors with underlying psychiatric disorders such as anxiety, depression, and bipolar disorders or in donors where there is concern that donors may not follow-through with donation, bone marrow harvest procedures may be questionable and apheresis collection and cryopreservation should be considered in advance before the conditioning regimen is started.

4.7 Medication

Certain medication may potentially defer a donation or render a donor ineligible (Table 4.7) due to concern for potential RCDAD transmitted by transfusions and HCT. Donors would be declared ineligible but may be able to donate dependent on institutional practice.

For the majority of potential donors, it is not usually the medication that they are taking that is likely to be a concern, but rather the underlying medical condition for which that treatment was prescribed, that may make a donor unsuitable to donate. Certain medications would potentially increase donor or recipient risk, but these are often also required to treat a medical condition that would likely defer the donor as well (Table 4.8). For certain medication for which the donor's medical conditions are well controlled, the donor may be suitable to proceed with donation (Table 4.8). For donors on lithium, due to its interaction with GCSF, HPC collection using apheresis is generally not allowed and these donors may be considered and evaluated for marrow donation.

If a donor or a recipient has a past allergic reaction to heparin or a history of heparin-induced thrombocytopenia (HIT), the donor may donate by apheresis; however, the anticoagulant use for both circuit and product should be with ACD-A (i.e., citrate) alone.

Table 4.7 Medication rendering donor ineligibility (AABB Medication Deferral List n.d.)

• Human growth hormone. Concern for Creutzfeldt-Jakob disease (CJD)
• Donors with diabetes previously receiving bovine insulin. Concern for new variant CJD the same agent responsible for bovine spongiform encephalopathy (BSE) or "Mad Cow Disease"
• Hepatitis B immune globulin (HBIG) used to prevent infection following an exposure to HBV. HBIG does not prevent HBV infection in every case and if a donor has taken it in the last 12 months HBV can still be transmitted
• Unlicensed vaccine is usually associated with a research protocol and the effect with regard to stem cell recipients is unknown

Table 4.8 Recommendations for suitability to donate based on medication (National Marrow Donor Program (NMDP) 2016)

Accept	Evaluate for suitability	Defer related donor (author's practice)	Defers unrelated donor (NMDP practice)
Oral contraceptives	Short term oral steroids (taking <3 months) such as prednisone, hydrocortisone, cortisone	Uncontrolled diabetes	Insulin
Medications that have fetal risk (i.e. category X), such as isotretinoin, etretinate, finasteride, dutasteride, if underlying condition is acceptable	Anti-inflammatory or pain medications taken on daily/ frequent basis to control chronic pain such as ibuprofen, indomethacin, meperidine, celecoxib, hydrocodone	Chemotherapy including tamoxifen unless taking for cancer prevention	Chemotherapy including tamoxifen unless taking for cancer prevention

(continued)

Table 4.8 (continued)

Accept	Evaluate for suitability	Defer related donor (author's practice)	Defers unrelated donor (NMDP practice)
Thyroid hormone replacement medication (not for cancer), if well-controlled	Oral diabetic medications including chlorpropamide, tolbutamide, tolazamide, glipizide, glyburide, glimepiride	Patient on cardiac medications for angina or uncompensated CHF	Cardiac medications such as nitrates, nitroglycerin and digoxin
Prescription eye drops, if underlying condition is acceptable	Injected non-insulin medication such as exenatide or lyraglutide for treatment of diabetes	Immunosuppressive medication such as azathioprine, tacrolimus, MMF, cyclosporine, cyclophosphamide and methotrexate	Immunosuppressive medication such as azathioprine, tacrolimus, MMF, cyclosporine, cyclophosphamide and methotrexate
Topical medications (i.e., for acne) including topical steroids	Medications used as part of a clinical trial or investigation[a]	TNF Blockers	TNF Blockers
Allergy medications such as antihistamines or allergy shots		Long-term oral steroids (>3 months) such as prednisone, hydrocortisone, cortisone	Long-term oral steroids (>3 months) such as prednisone, hydrocortisone, cortisone
Antibiotic or antiviral, if treating current infection that is resolving or for treatment of acne		Treatment of a condition requiring antiplatelet agents for TIA or unmanaged cardiac disease. Treatment with anticoagulation for venous thromboembolism	Treatment of a condition requiring anticoagulant or antiplatelet medication
Anti-anxiety and anti-depression medications, such as diazepam and fluoxetine (selective serotonin reuptake inhibitors), if underlying condition is well-controlled		Lithium (Defer PB HPC donation, can collect donor by bone marrow harvest)	Lithium (Defer PB HPC donation, can collect donor by bone marrow harvest)
Hypertension medications, if blood pressure is well-controlled and there is no underlying cardiac disease			

Table 4.8 (continued)

Accept	Evaluate for suitability	Defer related donor (author's practice)	Defers unrelated donor (NMDP practice)
Over-the-counter vitamins, mineral, and herbal products			
Antacid or acid reflux medications such as proton pump inhibitors (PPIs), H2 receptor antagonists, if underlying condition is well controlled			

[a]Accept if participation in an investigational study that does not involve receipt of an experimental medication

4.8 Zika Virus

Zika virus (ZIKV) became a notifiable condition in the United States in January 2016 (Centers for Disease Control and Prevention 2016) and, by February of the same year, was declared a Public Health Emergency of International Concern by the World Health Organization (WHO 2005). Although infections are frequently asymptomatic or mildly symptomatic, deaths have been reported. Associations with severe neurologic complications in infants born to mothers infected with ZIKV during pregnancy as well as neurologic complications in adults (e.g., Guillain-Barre Syndrome) have made ZIKV a high-priority pathogen. There are currently no licensed vaccines or therapeutics against ZIKV (Food and Drug Administration 2017); however, there are numerous vaccine candidates currently in development. As of February 2016, local mosquito-borne transmission had not been reported in the continental United States, but only multiple travel-associated cases had been reported. In July 2016, Florida was added to the list of areas of risk of ZIKV transmission (Table 4.9). By February 2017, up to 200 documented cases of mosquito-borne transmission of ZIKV to a human had occurred in the continental United States in southern Florida and the Brownsville, Texas, area.

The FDA identified ZIKV as a RCDAD. The potential risk of transmission of ZIKV by HCT/Ps was supported by evidence that ZIKV has been detected in tissues such as semen and placenta. In March 2016, no FDA-cleared diagnostic tests for ZIKV were available and the FDA provided donor screening recommendations to reduce the risk of transmission of ZIKV by HCT/Ps (Food and Drug Administration 2016). All donors of HCT/Ps should be considered ineligible if they have had a medical diagnosis of ZIKV infection in the past 6 months and resided in, or travelled to, an area with active ZIKV transmission within the past 6 months. Donors were also declared ineligible if they had sex within the past 6 months with a male who was known to have either of the risk factors.

Table 4.9 List of areas with risk of ZIKV transmission (Centers for Disease Control and Prevention 2017)

Americas		
Anguilla	Dominican Republic	Panama
Antigua	Ecuador	Paraguay
Argentina	El Salvador	Peru
Aruba	Florida, state of*	Saba
Barbados	French Guiana	Saint Barthélemy
Belize	Grenada	Saint Lucia
Bolivia	Guadeloupe	Saint Martin
Bonaire	Guatemala	Saint Vincent and the
Brazil	Guyana	Grenadines
Colombia	Haiti	Saint Eustatius
Commonwealth of Puerto	Honduras	Saint Maarten
Rico, US territory	Jamaica	Suriname
Costa Rica	Martinique	Trinidad and Tobago
Cuba	Monserat	Turks and Caicos Islands
Curacao	Mexico	U.S Virgin Islands
Dominica	Nicaragua	Venezuela
Oceana/Pacific Islands	**Africa**	
American Samoa	Angola	Guinea-Bissau
Fiji	Benin	Kenya
Kosrae, Federated States of	Burkina-Faso	Liberia
Micronesia	Burundi	Mali
Marshall Islands	Cameroon	Niger
New Caledonia	Cape Verde	Nigeria
Palau	Central African Republic Chad	Rwanda
Papua New Guinea	Congo (Congo-Brazzaville)	Senegal
Samoa	Côte d'Ivoire Democratic	Sierra Leone
Solomon Islands	Republic of the Congo	South Sudan
Tonga	(Congo-Kinshasa)	Sudan
Asia	Equatorial Guinea Gabon	Tanzania
Bangladesh	Gambia	Togo
Burma (Myanmar)	Ghana	Uganda
Cambodia	Guinea	
India		
Indonesia		
Laos		
Malaysia		
Maldives		
Pakistan		
Philippines		
Singapore		
Thailand		
Timor-Leste (East Timor)		
Vietnam		

The first few blood transfusion transmissions that have been reported were in Brazil, where four transmissions occurred from three donors. On August 26, 2016, FDA issued revised guidance, recommending that blood centers in all states and the United States territories screen individual units of donated whole blood and blood components with a blood-screening test authorized for use by FDA under an investigational new drug (IND) application, or with a licensed test when available. In late 2016, blood centers began implementing investigational blood tests with nucleic acid testing (Goodnough and Marques 2017).

As of April 2017, there remained no commercially available diagnostic test cleared by FDA for the detection of ZIKV. Current tests with IND include serologic tests (to assess whether individuals who may have recently been exposed to ZIKV were actually infected) and PCR or NAT tests (to diagnose acute/active ZIKV infection).

There is currently no mandate to perform laboratory testing for ZIKV in HCT/Ps; however, several centers are currently using IND serological or NAT tests available to them. In the event that laboratory testing is performed, attention should be given to the following:

1. Results must be included in the donor's relevant medical records.
2. A reactive/positive test is considered a risk factor, even if an investigational test was used.
3. A nonreactive/negative test does not override any risk factors identified in the March 2016 ZIKV guidance (Food and Drug Administration 2016).

4.8.1 Expert Point of View

The donation of HPC is a well-recognized and regulated procedure that is performed on thousands of patients and donors throughout the world annually. Donation of autologous HPC is part of a treatment plan with high-dose therapy in these patients aiming for potential cure or at least prolonged remission from their underlying malignancy. The aim of their donated HPCs is to "rescue" the patients' marrows from the myeloablative chemotherapy received at the time of transplant for which a patient needs to be reasonably medically fit to receive. In these patients, suitability for HPC collection is often determined at the time of deeming the patient a suitable candidate for auto-HCT. The majority of severe complications are often associated with the pancytopenia accompanying chemomobilization. As a result of this as well as the predictability of cytokine only mobilized collections, several centers now collect autologous donor HPCs from using G-CSF with/without plerixafor as mobilization agent(s) only. These patients need to be assessed for suitability to donate; however, as the HPCs infused are their own, there is less concern for transmission of communicable diseases and eligibility to donate is not needed (Food and Drug Administration 2005).

Allogeneic HPC donation is a safe procedure with very low rates of serious adverse events. The side effects commonly faced during donation are transient for the majority of both related and unrelated donors. However, there have been several donation-related deaths (Halter et al. 2009), mostly in the related donor setting. As the majority of fatal and serious adverse events have occurred in donors with preexisting medical issues, it is suspected that robust donor assessment procedures will reduce fatal

complications. Therefore, all donors must be carefully evaluated and fully informed prior to HPC donation by clinicians with good understanding of the potential physical and psychological complications and factors that may increase risk. As discussed, donors must also be able to provide informed consent without coercion or pressure and for this the medical evaluation of any allogeneic donor should never be conducted by a physician in the same transplant team caring for the recipient.

In addition to suitability determination, donor eligibility determination is also essential and physicians evaluating allogeneic donors should be up to date with regulations and laws governing screening requirements for RCDADs. These are important particularly with the emergence of new diseases such as that seen with WNV, SARS, and ZIKV.

Several regulatory agencies, registries, and accreditation bodies ensure steps taken to improve donor and patient safety alike. National and international registries continue to provide updated recommendations for the safe selection of unrelated donors and provide tools and recent guidance that could be extrapolated and used in the related donor setting (Sacchi et al. 2008; Lown et al. 2014; Worel et al. 2015). Donor and collection centers should be encouraged to enroll in accreditation bodies, such as FACT/JACIE and AABB, to enable potential improvements in the standard of donor evaluation and collection as well as to ensure continuous improvements in their own quality management system.

4.8.2 Future Directions

Despite 3–5-year survival rates being nearly similar between matched URD and sibling RD HCT (Horowitz 2012), the higher incidence of GvHD often assumes a matched sibling as the transplant physician's first choice for the majority of transplant indications. In light of this as well as the notable increase in the use of related HLA-haploidentical transplants (Center for International Blood and Marrow Transplant Research (CIBMTR) 2016), RD will continue to need appropriate evaluations as to their medical suitability to donate. There continues to be concern about the heterogeneity in the care of related HPC donors (O'Donnell et al. 2010). Changes to FACT standards (The Foundation for the Accreditation of Cellular Therapy (FACT) 2017) addressed some of these issues and there has since been some improvement in the practice of adult related-donor care (Anthias et al. 2016a, b). However, there still appears to be particular concerns including counseling and assessment of donors before HLA typing, with the use of unlicensed mobilization agents, and the absence of long-term donor follow-up (O'Donnell et al. 2010).

The World Marrow Donor Association (WMDA) brings forward a compelling argument for the management of RD to be performed by donor registries by offering an established structure for donor care, and extensive experience in the medical evaluation of donors. In particular, they suggest there should be significant consideration for registry provision of centralized donor follow-up (Anthias et al. 2015). Donor long-term follow-up is an important aspect of donor evaluation and further development of follow up of donors should be an integral part of a donor program to allow vigilance and surveillance of donations and improve knowledge of the risks of donation.

At the end of 2011, a US appeals court ruled that it was now legal to pay apheresis donors for their HPC (Medpage Today 2012). Unlike bone marrow tissue, it was felt that peripheral blood HPC are no different from other body fluids like semen and plasma where national organ transplant act (NOTA) does not prohibit paid donors. In a concession to the spirit of NOTA, it was deemed that the compensation could not be in the form of cash but rather a voucher that can be applied to things such as scholarships, education, housing, or donation to a charity. In 2011, the WMDA put out a position statement why HPC donors should not be paid (Boo et al. 2011). Reasons included ethical concerns raised by remuneration, potential to damage the public will to act altruistically, the potential for coercion and exploitation of donors, increased risk to patients, and harm to local transplantation programs and international stem cell exchange, and the povssibility of benefiting some patients while disadvantaging others.

Appendix 4.1: Example of Donor History Questionnaire[a]

Donor history questionnaire-HPC, apheresis and HPC, marrow	**Yes**	**No**	
Are you			
1. Currently taking an antibiotic?			
2. Currently taking any other medication for an infection?			
Please read the Medication Deferral List			
3. Are you now taking or have you ever taken any medications on the Medication List?			
4. Have you read the educational materials?			
In the past **12 weeks** have you			
5. Had any vaccinations or other shots?			
6. Had contact with someone who had a smallpox vaccination?			
In the past **12 months** have you			
7. Been told by a healthcare professional that you have West Nile Virus infection or any positive test for West Nile Virus?			
8. Had a blood transfusion?			
9. Come into contact with someone else's blood?			
10. Had an accidental needle-stick?			
11. Had a transplant or graft from someone other than yourself, such as organ, bone marrow, stem cell, cornea, sclera, bone, skin or other tissue?			
12. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?			
13. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?			
14. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything *not* prescribed by their doctor?			
15. Female donors: Had sexual contact with a male who has ever had sexual contact with another male? (Males: check "I am male.")			I am male ☐

16. Had sexual contact with a person who has hepatitis?			
17. Lived with a person who has hepatitis?			
18. Had a tattoo?			
19. Had ear or body piercing?			
20. Had or been treated for syphilis or other sexually transmitted infections?			
21. Been in juvenile detention, lockup, jail, or prison for more than 72 h?			
In the past **3 years** have you			
22. Been outside the United States or Canada?			
In the past **5 years**, have you			
23. Received money, drugs, or other payment for sex?			
24. Male donors: Had sexual contact with another male, even once? (Females: check "I am female.")			I am female ☐
25. Used needles to take drugs, steroids, or anything *not* prescribed by your doctor?			
From **1980 through 1996**			
26. Did you spend time that adds up to three (Center for International Blood and Marrow Transplant Research (CIBMTR) 2016) months or more in the United Kingdom? (Review list of countries in the UK)			
27. Were you a member of the U.S. military, a civilian military employee, or a dependent of either a member of the U.S. military or civilian military employee?			
From **1980 to the present**, did you			
28. Spend time that adds up to five (Schmidt et al. 2017) years or more in Europe? (Review list of countries in Europe.)			
29. Receive a transfusion of blood or blood components in the United Kingdom or France? (Review list of countries in the UK.)			
Have you **EVER**			
30. Had a positive test for the HIV/AIDS virus?			
31. Had hepatitis or any positive test for hepatitis?			
32. Had malaria?			
33. Had Chagas disease and/or a positive test for *T. cruzi*?			
34. Had babesiosis?			
35. Tested positive for HTLV, had adult T-cell leukemia, or had unexplained paraparesis (partial paralysis affecting the lower limbs)?			
36. Received a dura mater (or brain covering) graft?			
37. Had sexual contact with anyone who was born in or lived in Africa?			
38. Been in Africa?			
39. Been diagnosed with any neurological disease?			
40. Had a transplant or other medical procedure that involved being exposed to live cells, tissues, or organs from an animal?			
41. Has your sexual partner or a member of your household ever had a transplant or other medical procedure that involved being exposed to live cells, tissues, or organs from an animal?			
42. Have any of your relatives had Creutzfeldt-Jakob disease?			

Additional Questions	Yes	No
March 2016 Final Guidance "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products"		
In the past **6 months** have you		
Zika Additional Question: 1. **For Living Donors**—Had a Zika virus infection?		
Zika Additional Question: 2. **For Living Donors**—Lived in or traveled to an area with active Zika virus transmission? (Review the list of ZIKA virus areas of transmission)		
Zika Additional Question: 3. **For Living Donors**—Had sexual contact with a man, who in the **6 months prior to sexual contact**, has had a Zika virus infection or lived in or traveled to an area with active Zika virus transmission?		
May omit question number 4 if this type of donation is not applicable to your program		
Zika Additional Question: 4. **For Non-Heart-Beating (Cadaveric) Donors**—In the past **6 months** has the donor had a medical diagnosis of a Zika virus infection?		

[a]AABB HPC, Apheresis and HPC, Marrow DHQ Version 1.6, December 2016—with permission

Appendix 4.2: Example of Physical Examination Supplemental Checklist

Areas to be evaluated and documented during history and physical examination (H&P) of potential allogeneic/syngeneic donors of peripheral blood stem cells or marrow. Note in Comments location, severity, and/or physical findings.

Yes **No**

[ ] [ ] Physical evidence of non-medical percutaneous drug use such as needle tracks, including examination of tattoos, which may be covering needle tracks
Comments:

[ ] [ ] Physical evidence of recent tattooing, ear piercing, or body piercing
Comments:

[ ] [ ] Disseminated lymphadenopathy
Comments:

[ ] [ ] Oral thrush
Comments:

[ ] [ ] Blue or purple spots consistent with Kaposi's sarcoma
Comments:

[ ] [ ] Unexplained jaundice, hepatomegaly, or icterus
Comments:

[ ] [ ] Physical evidence of sepsis, such as unexplained generalized rash
Comments:

[ ] [ ] Large scab consistent with recent smallpox immunization
Comments:

[ ] [ ] Eczema vaccinatum
Comments:

[ ] [ ] Generalized vesicular rash (generalized vaccina)
Comments:

[ ] [ ] Severely necrotic lesion consistent with vaccina necrosum
Comments:

[ ] [ ] Corneal scarring consistent with vaccinial keratitis
Comments:

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