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Worldwide Network for Blood and Marrow Transplantation Recommendations for Establishing a Hematopoietic Stem Cell Transplantation Program in Countries with Limited Resources, Part II: Clinical, Technical, and Socioeconomic Considerations

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A B S T R A C T
The development of hematopoietic stem cell transplantation (HSCT) programs can face significant challenges in most developing countries because such endeavors must compete with other government health care priorities, including the delivery of basic services. Although this is may be a limiting factor, these countries should prioritize development of the needed expertise to offer state-of-the-art treatments, including transplantation, by providing financial, technological, legal, ethical, and other needed support. This would prove beneficial in providing successful programs customized to the needs of their population and potentially provide long-term cost savings by circumventing the need for their citizens to seek care abroad. The costs of establishing an HSCT program and the costs of the HSCT procedure itself can be substantial barriers in developing countries. In addition, socioeconomic factors intrinsic to specific countries can influence access to HSCT, patient eligibility for HSCT, and timely utilization of HSCT center capabilities. This report describes recommendations from the Worldwide Network for Blood and Marrow Transplantation for establishing HSCT programs, with a specific focus on developing countries, and identifies challenges and opportunities for providing this specialized procedure in resource-constrained settings.

INTRODUCTION

The establishment of hematopoietic stem cell transplantation (HSCT) programs in developing countries can enhance and improve tertiary care health services. There are various positive attributes that favor the establishment of such a high-profile venture; however, there are also significant obstacles to be addressed.

Because the obvious issue in most economies is cost distribution and budget allocations for healthcare, public health measures take precedence over noncommunicable chronic diseases. However, over time, there has been an increasing focus on chronic diseases, particularly cancers, which have become the leading cause of mortality in both developing and developed nations. There has been an exponential growth in both the prevalence and incidence of diseases that can be cured by HSCT, including sickle cell anemia, thalassemia, leukemia, myeloma, lymphoma, immunodeficiencies, and metabolic disorders. As a result, many new HSCT centers have been opening in developing nations.

In most developing countries, a HSCT program must compete for allocation of limited funds with other priorities for basic health care services, such as food, sanitation, immunization, population control, and communicable disease prevention. Nonetheless, developing countries should have the expertise to offer state-of-the-art treatments, including HSCT, to enable treatment locally at a much lower cost than abroad.

The most important step in this effort is providing financial, technological, legal, ethical, and other support for local individuals and institutions to proactively establish new HSCT programs. The goals include to develop a customized local experience tailored to each developing country and also to allow local dissemination of this experience as it evolves [1].

When establishing a HSCT program in a developing country, financial, technological, logistic, and social challenges, as well as the availability of skilled manpower, are all potential difficulties that should be taken into consideration. Given the exponential growth in both the number of HSCTs performed worldwide and the establishment of new HSCT centers in both high- and low-income countries, the Worldwide Network for Blood and Marrow Transplantation (WBMT) has recognized the need to provide guidance to institutions and individuals considering opening a new HSCT center. Part I of this report describes the absolute minimum, minimum, preferred, and ideal requirements for the establishment of a new HSCT program. Here in Part II, we address clinical, technical, and financial considerations for establishing an HSCT program in the resource-constrained setting typical in developing countries.

Financial Issues and Costs of Establishing an HSCT Program

HSCT remains a highly specialized, complex, resource-intensive, and costly medical procedure. A 2009 report from the US Agency for Healthcare Research and Quality identified HSCT as among the top 10 procedures with the greatest increase in hospital costs from 2004 to 2007. Total US national costs of HSCT hospitalization increased from $694 million to $1.3 billion over this period [2].

Thus, establishment of a dedicated center for this costly procedure requires a comprehensive understanding of economic indicators and challenges. There are 4 main economic evaluations that provide information to guide decision making on the basis of the value for money: cost minimization, cost benefit, cost effectiveness, and cost utility.

Cost minimization is commonly practiced in HSCT whenever a lower-cost, equally effective treatment is chosen over more expensive treatments. A cost-benefit analysis is rarely used in procedures like transplantation because it requires assignment of monetary costs to measure clinical benefits, which are difficult to assign in this complex setting with potential for long-term cure for a proportion of recipients.

Cost utility analysis is a specific type of cost-effectiveness analysis in which outcomes are adjusted to consider health-related quality of life, so that a cure without treatment sequelae is considered more valuable than a cure resulting in continuing health disabilities [3].

In this article, we emphasize HSCT interventions that focus primarily on cost-effectiveness or cost utility. To develop a cost containment program, proof of both clinical and economic effectiveness is preferred before widespread adoption of new technologies [4].

It is critical to identify the exact drivers of cost before considering initiation of a HSCT program. Little data are available for evaluating the exact drivers of HSCT costs in developing countries. A recent study of establishment of a cancer center in Rwanda, a developing country, identified $556,105 as the necessary startup funding to implement the cancer program [5]. The annual operating cost of the program was calculated as $957,203. Radiotherapy, labor, and chemotherapy were the most significant cost drivers; however, radiotherapy required sending patients out of the country because of the absence of radiation units in Rwanda. Labor accounted for 21% of the cost, and chemotherapy, supportive medications, and consumables together accounted for 15%. Although radiation therapy is not routinely performed for HSCT, it is a

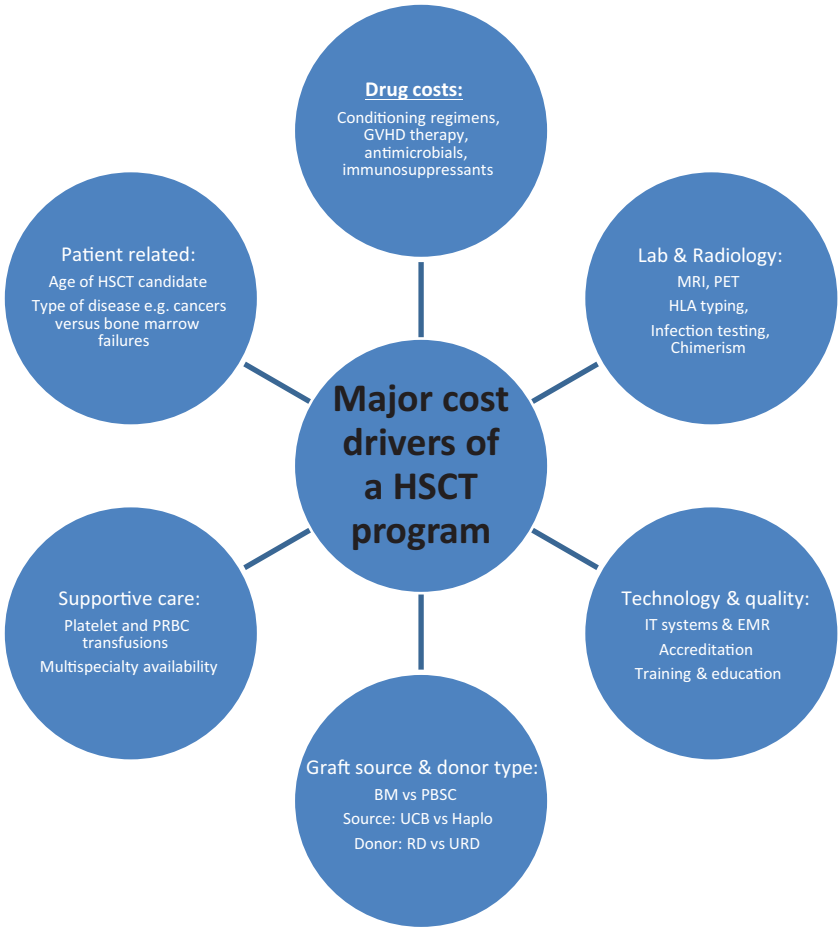

Figure 1. Major determinants of costs in establishment of an HSCT program. MRI indicates magnetic resonance imaging; PET, positron emission tomography; IT, information technology; EMR, electronic medical record; BM, bone marrow; PRBCs, packed red blood cells; UCB, umbilical cord blood; haplo, haploidentical; RD, related donor

necessary part of certain preparative regimens, and thus the establishment of a radiation therapy unit is likely to significantly increase costs.

The high costs of HSCT can be attributed to various factors, as discussed below (Figure 1).

Patient-Related Factors

When designing a national program for HSCT in a developing country, few patient-related factors can be assessed for opportunities for cost reduction. Although there are no consistent correlations between costs and patient age, sex, performance status, or disease risk, in some more recent studies, advanced risk disease was a significant predictor of higher costs [6-10].

In view of the limited resources in developing countries, health authorities should allocate available resources to the priority areas where low cost inputs yield high dividends. However, there are no clear recommendations, and each country needs to adopt the policies that best address the needs of its populations.

Considering the young median patient age in many developing countries, it would be prudent to initially make HSCT available to younger patients with curable diagnoses and longer lifespan benefits. Subsequently, expanding the eligibility for HSCT to older patients and patients with advanced disease may be appropriate as the program develops.

Transplantation Center Experience

Cost reduction and clinical outcomes have been shown to improve with increasing institutional experience [11]. However, this economic advantage may be offset as the complexity of treated patients increases and more aggressive supportive interventions are applied, resulting in a plateau in the improvement curve [11-13]. Growing local expertise and adopting cost-effective practices can limit total costs and improve transplantation outcomes.

Human Resources and Continuous Training

The availability of sufficient well-trained staff at the various steps of transplantation with continuous training to advance their knowledge is a cornerstone of any successful transplantation program. Migration of health care professionals from developing to developed countries deprives the developing world of valuable and essential human resources [14]. Countries should strengthen health system requirements, including physical infrastructure and skilled human resources, to meet the multidisciplinary requirements of HSCT, aiming for high quality and safety as fundamental principles. International cooperation and twinning with other institutions in developed countries could facilitate exchange of expertise across the globe. Adequate attention for neutropenic and hygienic precautions and any other measures to reduce infection should be considered.

Donor Selection and HLA Typing

With the advances in immunogenetics and transplantation immunology, particularly in the structure and function of the HLA system in the 1990s, new and efficient technologies for HLA typing have emerged and progressed [15,16].

According to the guidelines of World Marrow Donor Association and European Federation for Immunogenetics, high-resolution HLA typing should be performed for both HSCT recipients and donors. HLA typing should also include the HLA-C locus owing to the recognized role of this locus in graft rejection [17,18].

The technology for HLA typing has evolved from the serologic level to the cellular level and more recently to the molecular level. Serotyping was the mainstream method for HLA typing and played a critical role in organ transplantation before the 1990s. However, most HLA antisera are polyclonal with lower specificity and variable sensitivity, and thus molecular methods to type HLA at the DNA level have replaced serologic and cellular typing.

Commonly used DNA-based HLA typing methods include PCR-based sequence-specific primers (PCR-SSP), PCR-based restriction fragment length polymorphism (PCR-RFLP), PCR-based single-strand conformation polymorphism (PCR-SSCP), PCR-based sequence-specific oligonucleotide (PCR-SSO), and PCR-based single nucleotide polymorphism (PCR-SNP). PCR-SSP genotyping is commonly used for HLA typing in clinical laboratories worldwide. PCR-SSP and PCR-SSO are associated with high cost and prolonged operation time and thus are rarely used for HLA typing at present.

PCR-SNP is a simple and fast method with high resolution that will become more popular as the technology continues to improve. At present, PCR sequence-based typing (PCR-SBT) technology has significant advantages over other HLA typing methods in terms of accuracy, efficiency, and automation. In addition, the operational costs are greatly reduced [15]. It is recommended that new programs in developing countries with limited resources should start by performing matched sibling transplantation, in which high-resolution typing might not be necessary and some risks are reduced.

Outsourcing HLA typing can be a cost-effective alternative in developing countries where laboratories with immunogenetic capabilities and expertise are not yet available. Many companies in developed countries offer molecular-based HLA typing at competitive prices, particularly for bulk contracts.

Conditioning Intensity

Both the intensity and the duration of conditioning affect the cost of HSCT. Large studies have confirmed the lower costs associated with reduced-intensity regimens, with fewer median hospital days within the first year after transplantation compared with high-dose and myeloablative regimens [8].

Myeloablative allogeneic HSCT is associated with a higher frequency and severity not only of short-term toxicities, but also of late complications such as infertility, growth retardation in children, and new primary malignancies. It also may be associated with increases in the use of blood products, risk of infections, transplantation-related mortality, and length of hospital stay. Despite their advantages, lower-intensity regimens must be adapted for important patient- and disease-related variables, given a recent multicenter trial showing a clear advantage in reducing AML relapse with the use of myeloablative regimens in younger, fit patients [19].

Several recent studies have suggested that intermediate-intensity regimens with a 20% to 30% reduction in dose intensity could reduce toxicity without causing significant increases in the risk of relapse or overall worse transplantation outcomes [20-22].

The cost and limited availability of radiation therapy in many developing countries should not be a major obstacle, because non-radiation-based conditioning regimens are available for nearly all diseases or conditions in which HSCT is indicated.

Blood Product Support

In adult recipients of autologous HSCT, 2 randomized trials reported similar rates of bleeding with the use of a therapeutic rather than a prophylactic strategy for platelet transfusion [23,24]. Both American Society of Clinical Oncology and the British Society of Haematology recommend the use of a therapeutic platelet transfusion strategy in the autologous HSCT setting, which results in less platelet use and substantial cost savings [25,26]. In allogenic HSCT, a randomized study subgroup analysis found similar rates of bleeding at low platelet doses (1.1×10^{11}) compared with medium (2.2×10^{11}) and high (4.4×10^{11}) doses. This led to a decreased number of platelets transfused per patient at doses between 1.1×10^{11} and 4.4×10^{11} platelets/m^2 with similar bleeding events [27]. Irradiated blood products should be used according to international guidelines.

Performing Autologous HSCT without Stem Cell Cryopreservation

Cryopreservation of stem cells requires a relatively advanced stem cell processing laboratory with mechanical, controlled-rate freezers. Several reports have described the feasibility of noncryopreserved G-CSF-mobilized whole blood or autologous bone marrow (with or without previous administration of G-CSF). Stem cell graft containing blood units or bone marrow can be stored briefly in a standard blood bank refrigerator at +4 °C until infusion [28-30].

Several centers have recently reported outcomes of autologous HSCT for multiple myeloma using noncryopreserved stem cells without G-CSF support [31-34]. The success of this technique depends on abbreviated conditioning, with 1 day of high-dose melphalan for patients with multiple myeloma and short-duration conditioning for patients with lymphoma. This technique precludes the need for costly cryopreservation and avoids the possible side effects from infusion of DMSO for cryopreservation. These autologous transplantation techniques were reported to yield early engraftment and reduced hospital length of stay, with significant cost savings. Outcomes were comparable to those from conventional conditioning with cryopreserved stem cells in patients with multiple myeloma [31-34]. Two recent studies of noncryopreserved autografts from developing countries using post-HSCT G-CSF also indicate comparable engraftment rates to cryopreserved autografts [35,36].

Thus, given the evident safety and efficacy of using noncryopreserved stem cells, a new HSCT center might not need mechanical freezers in place for autograft cryopreservation.

Graft Source

Peripheral blood stem cells (PBSCs) are known to offer more rapid neutrophil and platelet recovery compared with bone marrow grafts, with an early cost reduction of approximately 30% compared with bone marrow in some studies [37-39]. The use of PBSCs can lead to specific resource savings in hospitalization, platelet transfusions, and use of growth factors [40,41].

Unlike in autologous HSCT, chronic GVHD is a serious late complication of allogeneic HSCT that results in serious morbidity and mortality. Most studies have reported a higher incidence of chronic GVHD with the use of allogeneic PBSCs, which may potentially offset the early cost savings. Appropriate selection of cases and developing well-informed indications for the use of PBSCs could reflect favorably on procedural costs and transplantation outcomes [42].

In a recent study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the use of PBSCs resulted in an acceptable alternative for transplanting patients with aplastic anemia in developing countries, as PBSC grafts were associated with faster engraftment, lower frequency of infections, and a lower likelihood of graft rejection in heavily pretransfused patients [43].

However, in autologous HSCT there is strong evidence of clinical benefit and cost savings using PBSCs which has been consistently reported [44-47].

Alternative Donors and Graft Manipulation

The use of alternative donors, specifically HLA-compatible unrelated donors (URD), has emerged as a significant driver of costs, even beyond the costs of stem cell procurement [8,48,49]. Among the various sources of alternative donors, myeloablative umbilical cord blood transplantation is associated with the highest costs, followed by matched URD. Accordingly, these donor sources should not be considered a priority in developing countries for a new HSCT program.

The preferred and most cost-effective alternate donor transplantation modality in developing countries may be a related (family-member) haploidentical transplantation using post-transplant cyclophosphamide (PTCy) for GVHD prevention. The posttransplant course, however, might require more experience as conventional, URD HSCT.

Alternatives to PTCy for haploidentical transplantation use different methods of T-cell depletion (TCD) of the donor graft or other cellular manipulations, which are complex and require advanced and costly stem cell processing technology [50].

Cost of Supportive Care Medications

Pharmacy costs range from 8% to 39% of the total expenditures related to HSCT. Hematopoietic growth factors, GVHD prophylactic agents, and antimicrobials are the major contributors to pharmacy costs [51-53]. Several generic forms are now available for fluconazole and more recently for voriconazole as well [54]. This could help offset some costs, provided that these alternative products demonstrate similar efficacy. Pharmacy costs are expected to continuously rise given the changes in HSCT practice, with increasing use of newer immunosuppressive regimens and the higher cost of new anti-infective agents [52]. The long-term excess pharmacy costs for patients with chronic GVHD who may require prolonged immunosuppressive treatment are unpredictable and may be large [52].

A biosimilar drug is a similar copy of an approved injectable original biologic substance that may be available after the original patent protection has expired [55]. Because drugs are produced by cultured cells, small biological differences between original and biosimilars may exist. Nonetheless, provided that they are demonstrably as safe and efficacious as the originator product, the use of well-established biosimilars should be considered to aid in cost containment and to increase the availability of drugs needed for HSCT. If these biosimilars are properly evaluated and their clinical effectiveness is proven, their generally reduced costs may contribute to the long-term financial sustainability of HSCT programs [55-57]. Several biosimilars of G-CSF are less expensive alternatives to the original brand product. The European Medicines Agency has recently approved several biosimilar versions after the patent of the original G-CSF brand expired in Europe in 2006 [55].

Several G-CSF biosimilars have been evaluated in the setting of stem cell mobilization for autologous HSCT. Results show similar mobilization yields with comparable safety profiles as the originator G-CSF. Moreover, both myeloid and platelet recovery times are similar to those of the originator G-CSF product [56-62]. This noninferiority model could be extrapolated to other medications, ultimately leading to significant cost savings. Highly reputable pharmaceutical companies are already involved in the manufacturing process of several biosimilar medications essential for HSCT [63]. Table 1 presents several currently approved biosimilars used in the HSCT arena. The use of these biosimilars should be explored in developing countries once local approvals are in place.

Beyond the costs of certain drugs, another major problem is reliable availability. The experience in different countries and

Table 1
Some Biosimilars Approved in the United States and European Union Pertaining to HSCT*

Generic/Molecule	Biosimilar	Year Approved	Use in HSCT
Filgrastim	Tevagrastim Ratiograstim Filgrastim Hexal Zarzio Accofil Zarxio	2008 (EMA) 2008 (EMA) 2009 (EMA) 2009 (EMA) 2014 (EMA) 2015 (FDA)	Mobilization of peripheral stem cells for autologous HSCT
Rituximab	Truxima Rixathon Ritemvia	2017 (EMA) 2017 (EMA) 2017 (EMA)	Treatment of chronic GVHD
Infliximab	Inflectra Flixabi	2013 (EMA); 2016 (FDA) 2016 (EMA)	Treatment of acute GVHD
Etanercept	Benepali Erelzi	2016 (EMA) 2016 (FDA); 2017 (EMA)	Treatment of acute GVHD Treatment of BOS; treatment of IPS
Enoxaparin	Inhixa Thorinane	2016 (EMA) 2016 (EMA)	DVT prophylaxis DVT treatment

* The table lists only some of the approved biosimilars and is not intended to be inclusive of all approved biosimilars. The WBMT is working on a separate publication that will contain a complete list of approved biosimilars.EMA indicates European Medicines Agency; FDA, US Food and Drug Administration; BOS, bronchiolitis obliterans syndrome; IPS, idiopathic pulmonary syndrome; DVT, deep venous thrombosis.

continents underscores the need to check the availability and approval of the essential drugs needed to perform HSCT. In some countries, cyclosporine is only available orally but not intravenously, busulfan may not be available at all, and importing needed drugs is sometimes very difficult. The WBMT has prepared a list of essential drugs that should be available for a successful program. Licensing of drugs in a country may depend on the demand, and some drugs needed for HSCT may be used only for HSCT. Sometimes availability of drug needed for HSCT will also improve the treatment of the underling disease before HSCT. Close interaction with national health authorities is recommended to guide informed policies for specific drug availabilities.

Post-Transplantation Factors

Several post-transplantation factors may greatly increase costs. Prolonged hospitalization and late complications are the most significant drivers of costs. Designing programs for post-transplantation care, including home health services and outpatient follow-up systems allowing safe follow-up either at home or at a hostel where a well-trained and qualified nurse can monitor patients who need less aggressive interventions, have been found to reduce post-transplantation costs [64].

Socioeconomic and Other Factors

In many developing countries, many patients with acute leukemia die before referral to a national or regional HSCT center. This indirectly leads to a relatively larger proportion of HSCTs performed for non-neoplastic indications, such as bone marrow failure and hemoglobinopathies, diseases more permissive of delays to HSCT. The time from diagnosis to HSCT is likely to be longer in developing countries, with the resulting unintended consequences of having sicker candidates present for HSCT owing to advanced disease, poor performance status, more infections, or transfusion alloimmunization. The consequences of delay may be higher costs and poorer outcomes of HSCT. Efforts to shorten the time from diagnosis to HSCT should be considered a priority in developing countries. Increasing public awareness and patient education about essential hygienic and infection control measures, as well as utilization of social services, may also help educate patients and caregivers about recommendations that will increase HSCT success in developing countries.

The Human Development Index (HDI) is used by the United Nations to evaluate a country's socioeconomic achievements based on 3 parameters: longevity, knowledge, and standard of living [65]. The number of transplantations performed per unit population, as well as early and long-term outcomes, are directly related to the HDI [66-70].

Information Technology and Quality Benchmarks

The most effective way to improve HSCT outcomes is to establish and maintain good quality programs in transplantation centers. Established databases define benchmarks for error reduction and improvement of outcomes. It is desirable for each HSCT center to have an internal database with experienced data managers and staff who can maintain the database and report the data to global registries (eg, European Society for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research). Developments in artificial intelligence (AI) for some aspects of tertiary care center management is predicted to lower costs. These may include machine learning algorithms in medical billing, supply chain management, scheduling efficiencies, virtual radiology (for image interpretation), and prevention of readmissions [71-77]. Because many AI companies are currently originating in developing countries, it may be valuable to explore the application of AI systems at HSCT startup with the goal of cost reduction.

Telemedicine in Developing Countries

Currently available techniques allow intensive cooperation with experienced centers. Pilot programs are currently active worldwide. This approach is particularly valuable in settings where a highly experienced HSCT program director is not available. Important guidelines for success involve training of local senior physicians, suitable facilities and laboratory capabilities, and regular communication with outside consultants.

CONCLUSION

Establishing an HSCT center in countries with limited resources is a multistep endeavor requiring extensive financial, social, technical, and human resources and the involvement of physicians, health authorities, politicians, nurses, and scientific societies. In some countries, the main obstacle remains constrained resources and inexperience, which may lead to high operating and maintenance costs and also may complicate the initial organization of a program. The WBMT has outlined the major drivers of costs for a HSCT program and has provided general recommendations to help limit initial program costs. New cost-effectiveness studies from developing countries for each aspect of HSCT—conditioning type, GVHD management, information technology systems implementation, graft source and donor choice, laboratory testing, drug costs (and biosimilar use), blood bank utilization (defined thresholds for packed red blood cell and platelet transfusion)—may be of particular value in improving the safety and affordability of HSCT.

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REFERENCES

1. Thorsteinsdóttir H, Quach U, Martin DK, Daar AS, Singer PA. Introduction: promoting global health through biotechnology. *Nat Biotechnol*. 2004;22 (suppl):DC3–DC7.
2. Stranges E, Russo CA, Friedman B, Healthcare Cost and Utilization Project (HCUP). *Procedures with the most rapidly increasing hospital costs, 2004-2007: Statistical Brief 82*. Rockville, MD: Agency for Healthcare Research and Quality; 2009.
3. Khera N, Zeliadt SB, Lee SJ. Economics of hematopoietic cell transplantation. *Blood*. 2012;120:1545–1551.
4. Welch HG. Valuing clinical strategies early in their development. *Ann Intern Med*. 1992;116:263–264.
5. Neal C, Rusangwa C, Borg R, et al. Cost of providing quality cancer care at the Butaro Cancer Center of Excellence in Rwanda. *J Glob Oncol*. 2018;4: 1–7.
6. Lee SJ, Klar N, Weeks JC, Antin JH. Predicting costs of stem-cell transplantation. *J Clin Oncol*. 2000;18:64–71.
7. Lin YF, Lairson DR, Chan W, et al. The costs and cost-effectiveness of allogeneic peripheral blood stem cell transplantation versus bone marrow transplantation in pediatric patients with acute leukemia. *Biol Blood Marrow Transplant*. 2010;16:1272–1281.
8. Saito AM, Zahrieh D, Cutler C, et al. Lower costs associated with hematopoietic cell transplantation using reduced intensity vs high-dose regimens for hematological malignancy. *Bone Marrow Transplant*. 2007;40: 209–217.
9. Saito AM, Cutler C, Zahrieh D, et al. Costs of allogeneic hematopoietic cell transplantation with high-dose regimens. *Biol Blood Marrow Transplant*. 2008;14:197–207.
10. Rizzo JD, Vogelsang GB, Krumm S, Frink B, Mock V, Bass EB. Outpatient-based bone marrow transplantation for hematologic malignancies: cost saving or cost shifting? *J Clin Oncol*. 1999;17:2811–2818.
11. Griffiths RI, Bass EB, Powe NR, Anderson GF, Goodman S, Wingard JR. Factors influencing third-party payer costs for allogeneic BMT. *Bone Marrow Transplant*. 1993;12:43–48.
12. Bennett CL, Armitage JL, Armitage GO, et al. Costs of care and outcomes for high-dose therapy and autologous transplantation for lymphoid

malignancies: results from the University of Nebraska 1987 through 1991. *J Clin Oncol*. 1995;13:969–973.
13. Majhail NS, Mothukuri JM, Macmillan ML, et al. Costs of pediatric allogeneic hematopoietic cell transplantation. *Pediatr Blood Cancer*. 2010;54:138–143.
14. Taylor AL, Hwenda L, Larsen BI, Daulaire N. Stemming the brain drain—a WHO global code of practice on international recruitment of health personnel. *N Engl J Med*. 2011;365:2348–2351.
15. De Santis D, Dinauer D, Duke J, et al. 16(th) IHIW: review of HLA typing by NGS. *Int J Immunogenet*. 2013;40:72–76.
16. Yuying S, Yongzhi X. The advanced HLA typing strategies for hematopoietic stem cell transplantation. In: Demirer T, ed. *Innovations in Stem Cell Transplantation*. IntechOpen; 2013. Available at: https://www.intechopen.com/books/innovations-in-stem-cell-transplantation/the-advanced-hla-typing-strategies-for-hematopoietic-stem-cell-transplantation. Accessed 13 December 2018 .
17. World Marrow Donor Association. WMDA standards. 2017. Available at: https://www.wmda.info/professionals/quality-and-accreditation/wmda-standards/. Accessed 9 November 2018.
18. European Federation for Immunogenetics. Standards for histocompatibility and immunogenetics Testing 2019. Available at: https://www.efi-web.org/fileadmin/user_upload/Website_documenten/EFI_Committees/Standards_Committee/Standardv6.3.pdf. Accessed 7 January 2019.
19. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.
20. Suh KJ, Kim I, Lim J, et al. Total costs and clinical outcome of hematopoietic stem cell transplantation in adults with leukemia: comparison between reduced-intensity and myeloablative conditioning. *Clin Transplant*. 2015;29:124–133.
21. Chen YB, Coughlin E, Kennedy KF, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2013;19:981–987.
22. Eom KS, Shin SH, Yoon JH, et al. Comparable long-term outcomes after reduced-intensity conditioning versus myeloablative conditioning allogeneic stem cell transplantation for adult high-risk acute lymphoblastic leukemia in complete remission. *Am J Hematol*. 2013;88:634–641.
23. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med*. 2013;368:1771–1780.
24. Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet*. 2012;380:1309–1316.
25. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2018;36:283–299.
26. Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. *Br J Haematol*. 2017;176:365–394.
27. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med*. 2010;362:600–613.
28. Hechler G, Weide R, Heymanns J, Köppler H, Havemann K. Storage of noncryopreserved peripheral blood stem cells for transplantation. *Ann Hematol*. 1996;72:303–306.
29. López-Otero A, Ruiz-Delgado GJ, Ruiz-Argüelles GJ. A simplified method for stem cell autografting in multiple myeloma: a single institution experience. *Bone Marrow Transplant*. 2009;44:715–719.
30. Ramzi M, Zakerinia M, Nourani H, Dehghani M, Vojdani R, Haghighinejad H. Non-cryopreserved hematopoietic stem cell transplantation in multiple myeloma, a single center experience. *Clin Transplant*. 2012;26:117–122.
31. Carey PJ, Proctor SJ, Taylor P, Hamilton PJ. Autologous bone marrow transplantation for high-grade lymphoid malignancy using melphalan/irradiation conditioning without marrow purging or cryopreservation. The Northern Regional Bone Marrow Transplant Group. *Blood*. 1991;77:1593–1598.
32. Gómez-Almaguer D. The simplification of the SCT procedures in developing countries has resulted in cost-lowering and availability to more patients. *Int J Hematol*. 2002;76(suppl 1):380–382.
33. Wannesson L, Panzarella T, Mikhael J, Keating A. Feasibility and safety of autotransplants with noncryopreserved marrow or peripheral blood stem cells: a systematic review. *Ann Oncol*. 2007;18:623–632.
34. Bekadja MA, Brahimi M, Osmani S, et al. A simplified method for autologous stem cell transplantation in multiple myeloma. *Hematol Oncol Stem Cell Ther*. 2012;5:49–53.
35. Kardduss-Urueta A, Gale RP, Gutierrez-Aguirre CH, et al. Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas. *Bone Marrow Transplant*. 2018;53:457–460.
36. Naithani R, Dayal N, Pathak S, Rai R. Hematopoietic stem cell transplantation using non-cryopreserved peripheral blood stem cells graft is effective in multiple myeloma and lymphoma. *Bone Marrow Transplant*. 2018;53:1198–1200.
37. Pavletic ZS, Bishop MR, Tarantolo SR, et al. Hematopoietic recovery after allogeneic blood stem cell transplantation compared with bone marrow transplantation in patients with hematologic malignancies. *J Clin Oncol*. 1997;15:1608–1616.
38. Faucher C, Fortanier C, Viens P, et al. Clinical and economic comparison of lenograstim-primed blood cells (BC) and bone marrow (BM) allogeneic transplantation. *Bone Marrow Transplant*. 1998;21(suppl 3):S92–S98.
39. Körbling M, Przepiorka D, Huh YO, et al. Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: potential advantage of blood over marrow allografts. *Blood*. 1995;85:1659–1665.
40. Bennett C, Waters T, Stinson T, et al. Valuing clinical strategies early in development: a cost analysis of allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 1999;24:555–560.
41. Kline RM, Meiman S, Tarantino MD, Herzig RH, Bertolone Jr SJ. A detailed analysis of charges for hematopoietic stem cell transplantation at a children's hospital. *Bone Marrow Transplant*. 1998;21:195–203.
42. Storek J, Gooley T, Siadak M, et al. Allogeneic peripheral blood stem cell transplantation may be associated with a high risk of chronic graft-versus-host disease. *Blood*. 1997;90:4705–4709.
43. Kumar R, Kimura F, Ahn KW, et al. Comparing outcomes with bone marrow or peripheral blood stem cells as graft source for matched sibling transplants in severe aplastic anemia across different economic regions. *Biol Blood Marrow Transplant*. 2016;22:932–940.
44. Vicent MG, Madero L, Chamorro L, Madero R, Diaz MA. Comparative cost analysis of autologous peripheral blood progenitor cell and bone marrow transplantation in pediatric patients with malignancies. *Haematologica*. 2001;86:1087–1094.
45. Vellenga E, van Agthoven M, Croockewit AJ, et al. Autologous peripheral blood stem cell transplantation in patients with relapsed lymphoma results in accelerated haematopoietic reconstitution, improved quality of life and cost reduction compared with bone marrow transplantation: the Hovon 22 study. *Br J Haematol*. 2001;114:319–326.
46. Woronoff-Lemsi MC, Arveux P, Limat S, Deconinck E, Morel P, Cahn JY. Cost comparative study of autologous peripheral blood progenitor cells (PBPC) and bone marrow (ABM) transplantations for non-Hodgkin's lymphoma patients. *Bone Marrow Transplant*. 1997;20:975–982.
47. Kucharski AJ, Ghalie R, Greenstein S, Matuszewski K. The clinical effectiveness and financial impact of utilizing peripheral blood progenitor cells as rescue therapy following autologous bone marrow transplant. *Int J Tech Assess Health Care*. 1996;12:172–179.
48. Majhail NS, Mothukuri JM, Brunstein CG, Weisdorf DJ. Costs of hematopoietic cell transplantation: comparison of umbilical cord blood and matched related donor transplantation and the impact of posttransplant complications. *Biol Blood Marrow Transplant*. 2009;15:564–573.
49. Kanate AS, Szabo A, Raj R, et al. Comparison of graft-acquisition and early direct charges of haploidentical related donor transplantation versus umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2019;25:1456–1464.
50. Roth JA, Bensink ME, O'Donnell PV, Fuchs EJ, Eapen M, Ramsey SD. Design of a cost-effectiveness analysis alongside a randomized trial of transplantation using umbilical cord blood versus HLA-haploidentical related bone marrow in advanced hematologic cancer. *J Comp Eff Res*. 2014;3:135–144.
51. Pechlivanoglou P, De Vries R, Daenen SM, Postma MJ. Cost benefit and cost effectiveness of antifungal prophylaxis in immunocompromised patients treated for haematological malignancies: reviewing the available evidence. *Pharmacoeconomics*. 2011;29:737–751.
52. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus host disease. *Blood*. 2004;104:3501–3506.
53. Yalniz FF, Murad MH, Lee SJ, et al. Steroid-refractory chronic graft-versus-host disease: cost-effectiveness analysis. *Biol Blood Marrow Transplant*. 2018;24:1920–1927.
54. Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother*. 2016;71:3599–3606.
55. European Medicines Agency. Guideline on similar biological medicinal products. 2013. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf. Accessed 19 November 2019.
56. Abraham I, Tharmarajah S, MacDonald K. Clinical safety of biosimilar recombinant human granulocyte colony-stimulating factors. *Expert Opin Drug Saf*. 2013;12:235–246.
57. Dylst P, Vulto A, Godman B, Simoens S. Generic medicines: solutions for a sustainable drug market? *Appl Health Econ Health Policy*. 2013;11:437–443.
58. Gascon P. Presently available biosimilars in hematology-oncology: G-CSF. *Target Oncol*. 2012;7(suppl 1):S29–S34.
59. Shaw BE, Confer DL, Hwang WY, Pamphilon DH, Pulsipher MA. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association. *Haematologica*. 2011;96:942–947.
60. Lefrère F, Brignier AC, Elie C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. *Adv Ther*. 2011;28:304–310.
61. Publicover A, Richardson DS, Davies A, et al. Use of a biosimilar granulocyte colony-stimulating factor for peripheral blood stem cell mobilization: an analysis of mobilization and engraftment. *Br J Haematol*. 2013;162:107–111.

62. Cesaro S, Tridello G, Prete A, et al. Biosimilar granulocyte colony-stimulating factor for mobilization of autologous peripheral blood stem cells in pediatric hematology-oncology patients. *Transfusion*. 2015;55:246–252.
63. Roger SD. Biosimilars: current status and future directions. *Expert Opin Biol Ther*. 2010;10:1011–1018.
64. Svahn BM, Remberger M, Myrbäck KE, et al. Home care during the pancytopenic phase after allogeneic hematopoietic stem cell transplantation is advantageous compared with hospital care. *Blood*. 2002;100:4317–4324.
65. Human United Nations Development Programme: Human Development Reports. Human Development Index. Available at: http://hdr.undp.org/en/2018-update. Accessed 9 February 2019.
66. Giebel S, Labopin M, Ehninger G, Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia. *Blood*. 2010;116:122–128.
67. McWhirter WR, Smith H, McWhirter KM. Social class as a prognostic variable in acute lymphoblastic leukaemia. *Med J Aust*. 1983;2:319–321.
68. Coebergh JW, van der Does-van den Berg A, Hop WC, et al. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. *Eur J Cancer*. 1996;32A:286–289.
69. Pollock BH, DeBaun MR, Camitta BM, et al. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group study. *J Clin Oncol*. 2000;18:813–823.
70. Bhatia S, Sather HN, Heerema NA, Trigg ME, Gaynon PS, Robison LL. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. *Blood*. 2002;100:1957–1964.
71. Dai W, Brisimi TS, Adams WG, Mela T, Saligrama V, Paschalidis IC. Prediction of hospitalization due to heart diseases by supervised learning methods. *Int J Med Inform*. 2015;84:189–197.
72. Bates DW, Saria S, Ohno-Machado L, Shah A, Escobar G. Big data in health care: using analytics to identify and manage high-risk and high-cost patients. *Health Aff (Millwood)*. 2014;33:1123–1131.
73. Warner JL, Zhang P, Liu J, Alterovitz G. Classification of hospital-acquired complications using temporal clinical information from a large electronic health record. *J Biomed Inform*. 2016;59:209–217.
74. Mortazavi A, Khamseh AA, Azimi P. Designing of an intelligent self-adaptive model for supply chain ordering management system. *Eng Appl Artif Intell*. 2015;37:207–220.
75. Vemulapalli V, Qu J, Garren JM, et al. Non-obvious correlations to disease management unraveled by Bayesian artificial intelligence analyses of CMS data. *Artif Intell Med*. 2016;74:1–8.
76. Srinivas S, Ravindran AR. Optimizing outpatient appointment system using machine learning algorithms and scheduling rules: a prescriptive analytics framework. *Expert Syst Appl*. 2018;102:245–261.
77. Wang J, Yang X, Cai H, Tan W, Jin C, Li L. Discrimination of breast cancer with microcalcifications on mammography by deep learning. *Sci Rep*. 2016;6:27327.