

Regulatory Policies

Perspectives on establishing a public cord blood inventory in South Africa

Ignatius M. Viljoen, Candice Laverne Hendricks, Juanita Mellet, Michael S. Pepper

Department of Immunology and South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine, University of Pretoria, Pretoria, South Africa

*Correspondence: Michael S. Pepper, MBChB, PhD, MD, Department of Immunology and South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine, University of Pretoria, Pretoria, South Africa. Email: michael.pepper@up.ac.za

Abstract

The South African population is highly diverse, both ethnically and genetically. This diversity is particularly true for the African ancestry and various mixed ancestry population groups. These groups are under-represented in national and international bone marrow and peripheral blood donor registries, making it challenging to identify HLA-matched and mismatched unrelated donors when patients from these groups require allogeneic hematopoietic stem and progenitor cell transplantation. In most high-income countries, banked cord blood (CB) units provide an attractive source of hematopoietic progenitor cells for genetically diverse populations. SA does not have a public CB inventory, leaving many patients without access to this important treatment modality. Haploidentical transplantation provides an alternative. In recent years, the use of post-transplant cyclophosphamide has significantly reduced the incidence of graft-versus-host disease after haploidentical transplantation and has improved transplantation outcomes. However, it is difficult to identify suitable haploidentical donors in SA because of family disruption and a high prevalence of HIV. Here the authors provide a brief historical overview of the ethnic and genetic diversity of the country and region. The authors provide a southern African perspective on HLA diversity, consider the allogeneic hematopoietic stem and progenitor cell transplantation landscape and explore the need to establish a public CB bank (CBB) in SA. The health policy and regulatory frameworks that will impact on a CBB in the country SA are also explored. Finally, the authors discuss several matters we believe require attention when considering the establishment of a sustainable public CBB in the South African context.

Keywords

cord blood banking
hematopoietic stem and progenitor cell transplantation
HLA diversity
regulatory framework
South Africa
treatment access

Diversity

African and southern African genetic diversity

Modern-day South Africa (SA) is an ethnically diverse country made up of the ancient aboriginal San hunter-gatherers, more recent Khoe-speaking pastoralists (jointly Khoisan) and different Bantu agropastoralist groups that migrated from West Africa and reached southern Africa between 1500 and 500 years ago [1,2]. From 1652, Dutch traders and their south and east Asian slaves and servants set up a trading post at the Cape of Good Hope. They were followed by French Huguenot refugees, British settlers, Indian and Chinese contract laborers and gold and diamond rush opportunists from around the world. Unlike Northern Hemisphere countries, where African and mixed ancestry (MA) populations are minorities, the South African, African ancestry (AA) population group constitutes approximately 81% of the current South African population of nearly 60 million and the MA population almost 9%. There are four language family groups in the AA population, with approximately 29 million Nguni and 18 million Sotho-Tswana language family speakers comprising the largest. Within these language families, there are many linguistically and culturally distinct subgroups. However, several wars and population migrations have extended their geographic distribution into the southern African region and resulted in these groups becoming admixed. Despite segregation laws, admixture was common, resulting in at least four genetically and ethnically distinct MA subpopulations. Officially, these groups are jointly referred to as the South African colored population. A 2010 genome-wide study compared 959 MA South African colored individuals with publicly available International HapMap Consortium and Human Genome Diversity Project datasets for African Khoisan, African non-Khoisan, European, South Asian and East Asian populations. Using a subset of nearly 75 000 single nucleotide polymorphisms, maternal DNA showed mainly Khoisan (79.04%) but also south and southeast Asian (16.34%) as well as west Eurasian and European (4.62%) contributions. Paternal DNA was of sub-Saharan African (45.18%), west Eurasian and European (37.72%) and south and southeast Asian (17.11%) origin [3]. Other population groups include people of European ancestry (EA) (7.8%) and people of Indian and other Asian ancestries (2.6%) [4]. Figure 1 compares bar plots of ancestry proportions using genome-wide data and Ancestry Informative Markers (AIMs) for this study group. The genome-wide data are ordered according to proportions of African San, African non-San, European, South Asian and East Asian ancestry, whereas the AIMs ancestry proportions were estimated using 96 AIMs. Individuals appear in the same order in both bar plots [5]. Archbishop Desmond Tutu coined the phrase “Rainbow Nation” for the post-Apartheid SA population, and President Nelson Mandela aimed to unite the deeply segregated society under this rainbow banner. Figure 1 visually represents the Rainbow Nation.

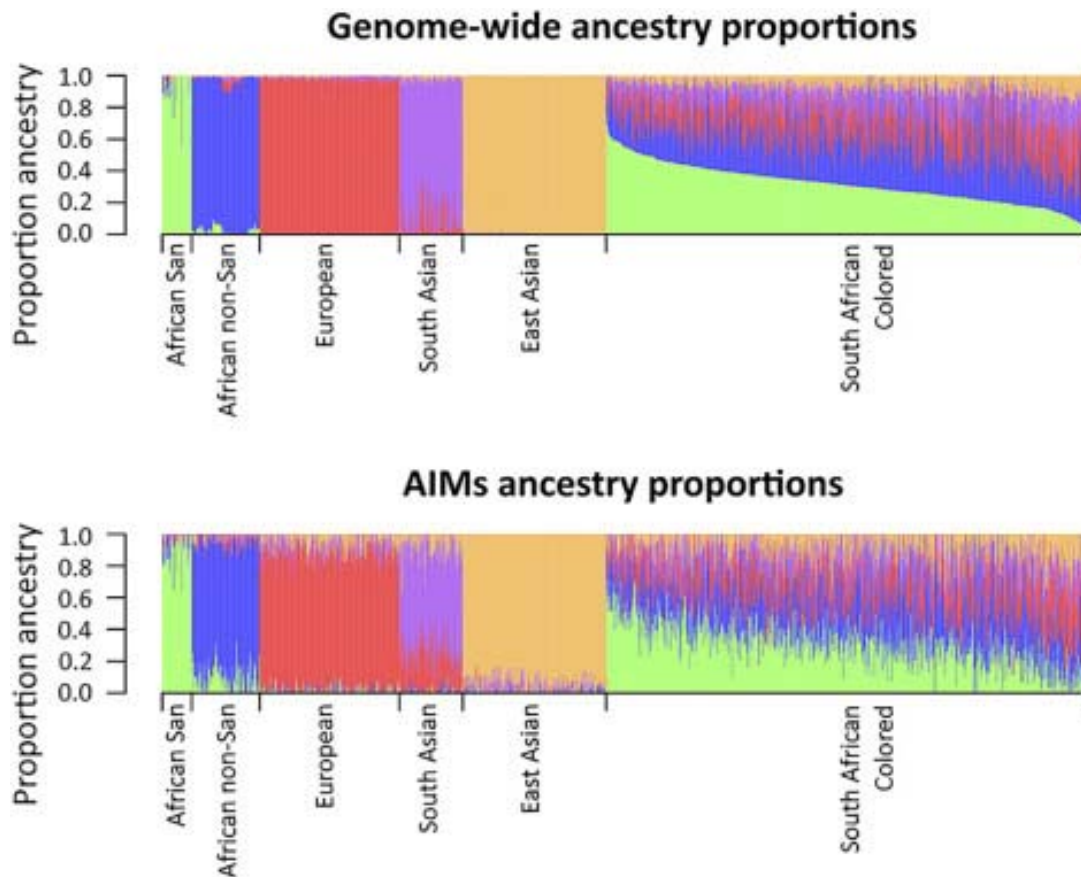


Fig. 1. Bar plots of ancestry proportions estimated using genome-wide data and AIMs. Ancestry proportions were estimated using genome-wide data. The admixed study group of 959 MA individuals (SAC) is ordered by proportions of African San, African non-San, European, South Asian and East Asian ancestry. In the second panel, ancestry proportions were estimated using 96 AIMs. Individuals appear in the same order as in the first panel. This work is licensed under the Creative Commons Attribution 2.5 Generic License. Bar plots are reproduced with permission from [5]. SAC, South African colored.

Although much work has been done on population genetics in the past 15 years, we are still at the threshold of understanding the impact of this genetic and phenotypic diversity on disease susceptibility, metabolism and treatment modalities [6]. Whole-genome sequencing on 24 AA and MA individuals in SA revealed 16 million unique variants—further testimony to the need for whole-genome sequencing to obtain an enhanced understanding of our population [7]. This is highly relevant for SA and the African continent but is also increasingly important for the rest of the world, with its growing population of people of recent African origin, including a steady increase in admixed populations. This genetic diversity extends to the HLA region and underlines the difficulty that exists in finding appropriate matches for AA and MA patients.

HLA diversity in southern Africa

The HLA region is one of the most polymorphic regions in the human genome [8]. HLA typing to match donors and recipients for transplantation has been a routine procedure for many years. Excellent clinical outcomes are observed in transplant recipients where high-

resolution matching is achieved. An increase in mismatching between individuals results in a higher risk of rejection and occurrence of graft-versus-host disease (GVHD), the process by which an immune response is mounted against the host antigens, which are seen as foreign by the donor cells [9].

Several studies during the 1980s reported HLA data in South African populations [10,11]. However, these studies used serological techniques that provided low- to medium-resolution HLA typing data. As high-resolution, sequencing-based typing methods improved, details of HLA diversity in sub-Saharan African and southern African populations began to emerge. Cumulative frequency graphs show a distinct diversity of HLA loci in South African populations (Figure 2), with curves shifting to the right indicating increased diversity since more alleles are required to cover the same combined cumulative frequency in a population. AA South Africans are more diverse at the HLA-A (Figure 2A) locus than EA South Africans, whereas MA individuals show higher diversity at all HLA-B and -C loci compared with other South African populations (Figure 2A–D). When considering the diversity identified in the aforementioned studies that included small cohorts of AA and MA individuals, one obtains a glimpse of the diversity of these populations. A recent study used previously typed HLA data from the South African National Blood Service (SANBS) and the National Health Laboratory Service. High-resolution typing data were available for 3007 individuals, and cumulative frequency graphs revealed diversity patterns similar to those seen in Figure 2. This is the largest study to date in SA, highlighting the paucity of high-resolution HLA data and our current inability to fully determine the extent of diversity within this country. It was further revealed that AA South Africans are genetically similar to other sub-Saharan populations [12]. When comparing frequency distribution of HLA-A, HLA-B and HLA-C alleles in five sub-Saharan populations, including diverse Kenyans and Ugandans, distinct HLA diversity of HLA-A and HLA-B was observed, with low population coverage and many low- to intermediate-frequency alleles [12,13].

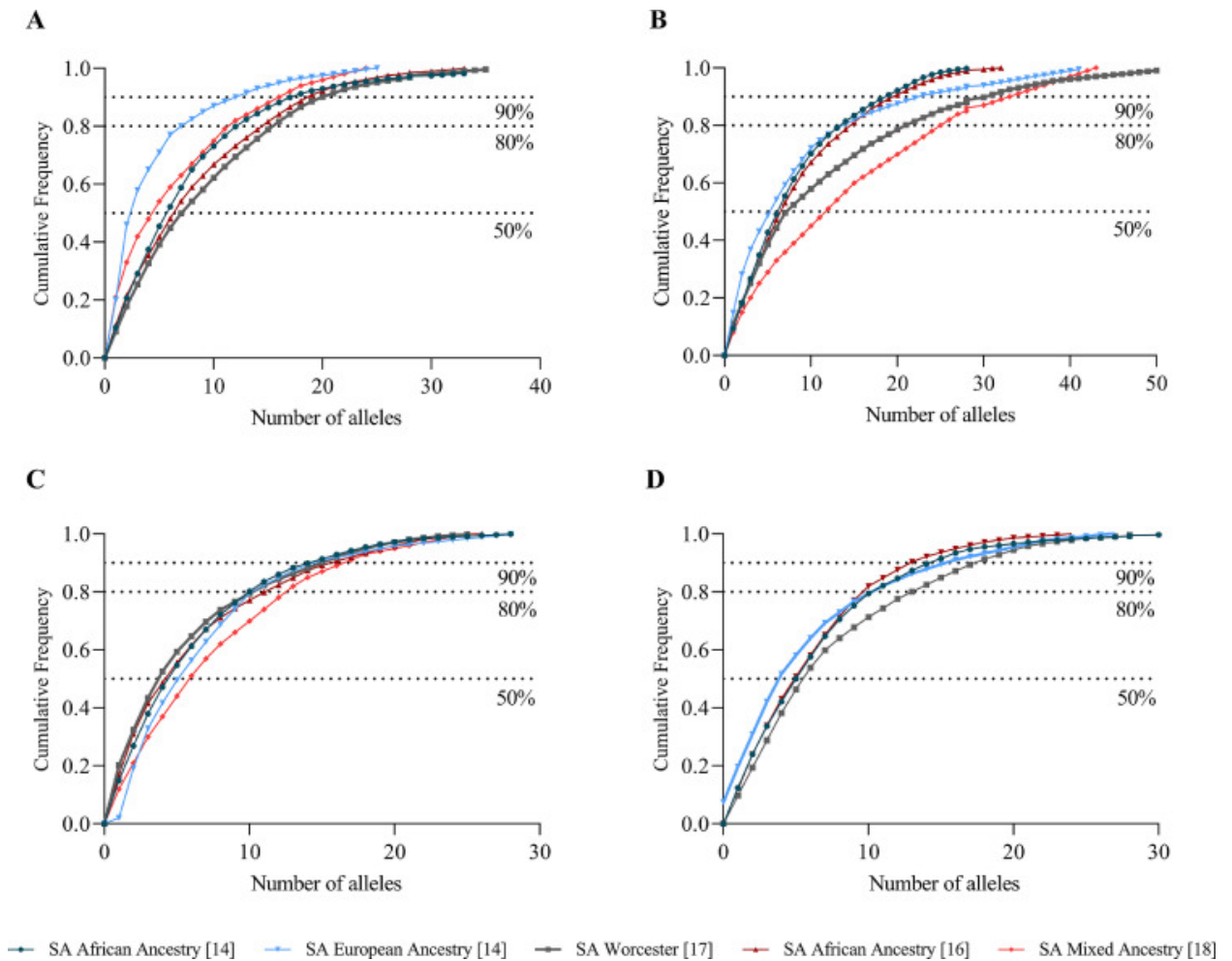


Fig. 2. Population coverage by South African HLA alleles. Cumulative frequency graphs indicating population coverage of South African (A) HLA-A, (B) HLA-B, (C) HLA-C and (D) HLA-DRB1 alleles. HLA alleles were sorted according to their allele frequencies in descending order. Cumulative frequencies were plotted according to the number of alleles. South African HLA allele frequency data were obtained from AFND [14], SA African Ancestry [13,15], SA European Ancestry [13], SA Worcester [16] and SA Mixed Ancestry [17]. AFND, Allele Frequency Net Database.

The available data remain insufficient to portray an accurate picture of the true extent of HLA diversity in AA and MA populations in SA. The South African Bone Marrow Registry (SABMR) was established in 1991 and consists of over 73 000 HLA-typed donor volunteers [18,]. However, the increased diversity and population-specific alleles, together with the under-representation of AA and MA populations in the SABMR, make it challenging to find an HLA-matched donor for these individuals. In the US, the likelihood of finding an 8/8 or 7/8 matched adult donor for EA populations is 75% and 97%, respectively. For AA individuals (African, African American, black South and Central American, black Caribbean), it is 16–19% and 66–76%, respectively [19]. By considering cord blood (CB) as a source of hematopoietic stem and progenitor cells (HSPCs), the likelihood of finding a donor ($\geq 4/6$ HLA match) for these individuals increases to 81–82% for adults (≥ 20 years of age) and 95–96% for children (< 20 years of age). In the 5 years from 2016 to 2020, SABMR conducted 1093 preliminary donor searches, of which 618 were activated and 180 resulted in transplantations. Of the preliminary donor searches, 7.8% and 2.5% resulted in

transplantations for MA and AA patients, respectively. This is compared with 29.8% for EA patients. During the past two decades, SABMR has assisted 23 patients with obtaining CB units (CBUs) from international CB banks (CBBs). Two were for AA patients, four for MA and Asian patients and 16 for EA patients. Double CBUs were sourced for one MA patient and three EA patients. North American CBBs contributed 8 units; European CBBs contributed 14 units; and CBBs in Taiwan, the Russian Federation and Australia contributed the remaining 4 units (Ingram C, Venter A, Ward J, SABMR, personal communication, December 2020).

HSPC Transplantation

A changing landscape

Haploidentical transplants

The possible establishment of a public CBB cannot be discussed without consideration of haploidentical transplant (haplo-T). According to the Center for International Blood and Marrow Transplant Research, haplo-T has overtaken CB transplantation (CBT) since 2014 [20]. Haplo-T has the advantage of rapid availability of the donor and access to multiple potential future infusions (e.g., donor lymphocyte infusion) as well as improved graft-versus-tumor effect [21]. The administration of post-transplant cyclophosphamide has also greatly reduced the incidence of GVHD. A recent systematic review and meta-analysis by Li *et al.* [22] showed comparable outcomes between the two donor sources, except for one study by Giannotti *et al.* [23], where haplo-T was found to be superior. Solomon *et al.* [24] retrospectively reviewed the outcomes of African American patients who received either haplo-T or CBT and found comparable outcomes in terms of overall survival (OS) and GVHD-free, relapse-free survival. CBT was shown to have higher non-relapse mortality (NRM); however, a higher relapse risk was found in the haplo-T group. In a prospective randomized study by Sanz *et al.* [25] using 1 CBU versus haplo-T in adults, haplo-T was superior in terms of the presence of GVHD, OS and disease-free survival. It must be noted, however, that the cohort was very small (23 CBT and 22 haplo-T). Results from a randomized phase 3 clinical trial (BMT CTN 1101) were recently published [26]. In this study, 368 patients were randomized to receive either double umbilical CB (dUCB) or haploidentical bone marrow transplant (haplo-BMT). All patients received the same conditioning regimen. Although the 2-year progression-free survival was similar in both groups (dUCB 35%, haplo-BMT 41%), the researchers concluded that haplo-BMT was superior, as NRM (dUCB 18%, haplo-BMT 11%) and OS (dUCB 46%, haplo-BMT 57%) were better in this subgroup. Importantly, a cost-effectiveness analysis was included in this study (results awaited) and will provide further guidance on these two donor sources. In pediatric patients, two approaches for haplo-T have been used. González-Llano *et al.* [27] described the use of post-transplant cyclophosphamide resulting in a high NRM rate of 36% at a median of 2.2 months, with an estimated 1-year OS rate of 50%. The researchers advocated for this approach in resource-limited settings. Superior outcomes were achieved by Locatelli *et al.* [28] and Bertaina *et al.* [29] where the haploidentical graft underwent $\alpha\beta$ T-cell and B-cell depletion. Patients had <10% cumulative incidence of NRM in both studies and a 5-year probability of chronic GVHD-free, relapse-free survival of 71% and 68%, respectively. Of note, these patients did not receive any post-transplantation GVHD prophylaxis. This study showed outcomes comparable to transplantation from matched unrelated donors and superior to mismatched unrelated donors. Should $\alpha\beta$ T-cell and B-cell depletion be considered in our setting, this would be another cost factor to consider.

Identifying suitable haploidentical donors

Kosuri *et al.* [30] reported that only 44% of African American patients had a suitable haploidentical match. Donors were mostly excluded because of underlying medical problems. SA has additional unique family structure characteristics, as families have been disrupted for many reasons during our history of enforced segregation [31]. The South African Child Gauge reports that almost a quarter of African children reside in households where neither biological parent is present [86]. Granted, at least one parent may reside elsewhere in the country; however, such a parent's availability for testing is unlikely to be immediate. SA also has the highest incidence of HIV in the world, with 7.5 million people infected [32], which may further impact donor selection.

CB as HSPC source

CB remains an important source of HSPCs that can self-renew and differentiate into all hematopoietic lineages [33]. Since its establishment as a safe source of HSPCs for transplantation in 1988.[34], [35], [36], more than 30 000 transplantations using CB stem and progenitor cells have been undertaken worldwide [37]. Unlike other donor sources, banked CBUs can provide an immediate off-the-shelf product, a significant advantage in patients who require urgent transplantation [41]. There is also no risk or discomfort associated with its collection from the umbilical vein. Most importantly, less stringent allele matching is required (six to eight alleles on the HLA-A, HLA-B and HLA-C class I loci and HLA-DRB1 in the class II region) [38,39] compared with the usual eight to 10 alleles for bone marrow- and peripheral blood-derived HSPCs, which improves the chances of obtaining a match. There is also a decreased risk of GVHD.

The high cost of CBUs and the limited number of HSPCs per CBU are the major constraints to their use. The cost of a CBU can vary between US\$29,000 and US\$45,000, with an average of around US\$36,200 [[40], [41], [42]]. The limited number of total nucleated cells (TNCs) and CD34+ cells present in a unit can lead to delayed engraftment, particularly in adults [31,41]. Two strategies used to overcome the problem of low HSPC numbers are the use of double CBU and *ex vivo* expansion. Both of these strategies have further cost implications.

Double cord transplantation

Barker *et al.* [45] showed in 2005 that when a single CBU contains an insufficient number of cells, double CBT (dCBT) can be used to treat malignant disorders. Similar to single CBT, the minimum acceptable HLA matching between either of the two CBUs and the recipient, and the two CBUs with each other, is 4/6 using low/intermediate typing (antigen) for HLA-A and HLA-B and high-resolution typing (allelic) for HLA-DRB1, [46]. Unlike single CBT, the recommended combined TNC dose in 2 units is $>3.5 \times 10^7$ cells/kg. ABO matching between patients and units is also important [47]. Although dCBT results in improved engraftment rates and survival in adults, in children, who can receive an adequate cell dose from a single CBU, there is no advantage to using 2 units [48,49]. The cost of 2 CBUs places dCBT outside the reach of many patients. When the purpose of a CBB is to serve HLA-diverse populations, banking larger CBUs will increase access by adult patients. A policy may also need to be developed to reserve CBUs with TNC counts of $>150 \times 10^7$ cells for patients over 50 kg.

***Ex vivo* HSPC expansion**

An alternative strategy for addressing low CBU TNC and CD34+ cell counts is *ex vivo* expansion. A variety of expansion strategies are being explored. These include the use of Notch ligand [50], mesenchymal stromal cell co-culture [51], nicotinamide (NiCord) [52,53], copper chelation (StemEx) [54], StemRegenin 1 [55] and the small molecule UM171 [56,57]. Under the US 21st Century Cures Act, a number of these products have received breakthrough therapy, orphan drug or regenerative medicine advanced therapy designations, which allows accelerated regulatory paths to market. It is important to note that substantially manipulated cell-based products are considered medicinal products that require medicine and health product regulatory authority approval. A challenge in the manufacture of expanded CBUs is ensuring a mixture of both short-term HSPCs to ensure rapid cell and immune recovery and long-term HSPCs to ensure sustained hematopoiesis. It can be assumed that the cost of custom prepared, *ex vivo*-expanded, cell-based products will be high. For this reason, companies are also developing larger-scale, manufactured, off-the-shelf, allogeneic products.

HSPC transplantation in South Africa

Only a small proportion of required transplantations are done in SA. Various factors contribute to this situation, including a paucity of donors; few transplantation units in the public sector, where most of the population receives health care; and underdiagnosis and under-reporting of hematological malignancies and non-malignant hematological diseases.

Transplantation statistics reveal that 1.1–4 per million allogeneic transplantations were done in SA in 2013 [58]. In comparison, 28.23 per million transplants were done in the US in 2018 [59], and 15–30 per million were performed in Western Europe and the UK (with fewer in Eastern Europe) [60]. If we use 15 per million as the benchmark and extrapolate that number according to age, we should be performing approximately 255 allogeneic transplantations in children under the age of 15 (The South African population in this age group is 17 million) every year [4] and a further 600 transplantations in patients above the age of 14. This is not taking into account autologous transplants, which usually outnumber allogeneic transplants by approximately 60:40 [60,61].

The small number of transplantations may also be due to under-reporting of leukemia cases. In 2016, The South African National Cancer Registry reported the incidence of leukemia to be 3.2 per million and 4.3 per million, respectively, for females and males under 15 years of age. For patients under 30 years of age, these numbers increased to 4.0 per million and 4.4 per million and were much lower than those reported in high-income countries [59,60]. Using global averages, we can assume over 1500 leukemia cases per year in SA in those under 30. As reporting improves, so will the need for patients to gain access to this life-saving treatment.

Establishing a Public South African CB Banking System

Considerations for establishing a South African CB banking system

A CB banking system is a complex system requiring a high level of coordination of donor recruitment, CB collection, transportation, quality-based selection, product characterization, processing, banking, data management and final distribution to transplant units. The specific

design and implementation requirements for a national public CBB fall outside the scope of this article. Figure 3 is a conceptual process flow diagram of a CB banking system.

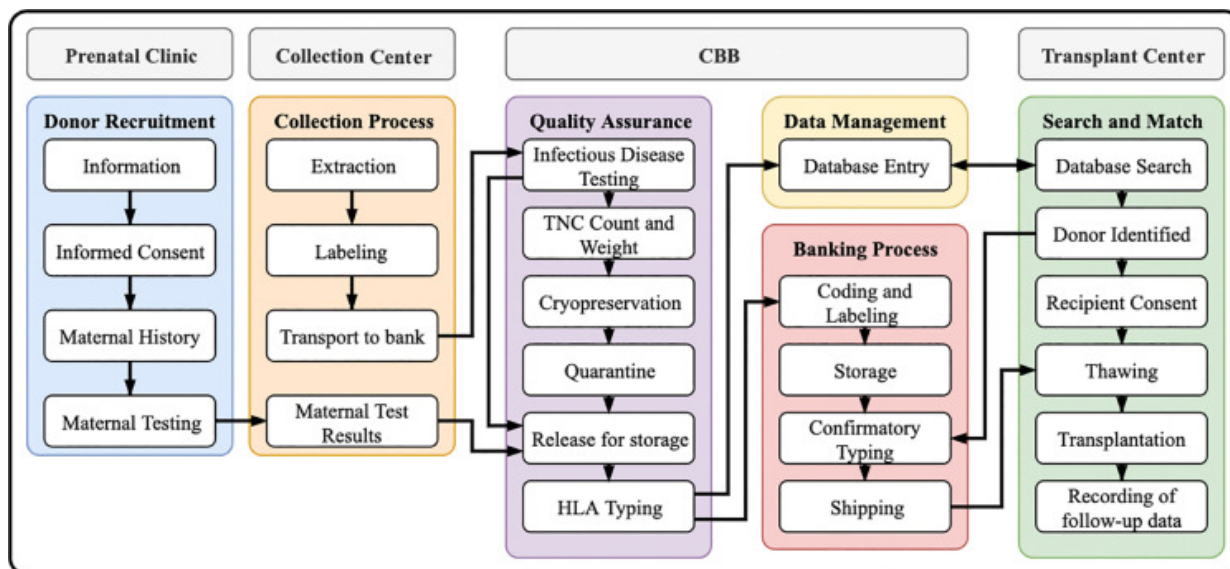


Fig. 3. Conceptual process flow diagram for a CB banking system.

The CB banking system is one component of the larger HSPC transplant (HSPCT) system, which is part of a national cancer treatment strategy within a national health policy that is informed by a legislative framework. Utilizing a public CB banking system to its full potential will require that health policy and cancer treatment strategy are aligned to maximize the benefits offered by this resource.

This section reviews the current health policy, legal and regulatory framework and how it relates to a public CBB. The authors consider different CBB models that could be applied. Finally, the authors highlight several other considerations, including sustainability, affordability and quality, with specific reference to HIV in the South African context.

Health policy, legal and regulatory framework

The South African Constitution and Bill of Rights

Section 27 of the South African Constitution [62] gives everyone the right to access health care services. From a patient's perspective, this raises expectations for access to all potential treatment options. However, from the state's perspective, the same section of the Constitution (s.27(2)) limits its responsibility to take measures “within its available resources.” Although SA is a leader in health care in sub-Saharan Africa, health care resources are nonetheless constrained. SA faces a quadruple burden of disease [63,64], including communicable diseases (HIV and tuberculosis [TB]); non-communicable diseases (obesity, diabetes, cardiovascular disease and cancer); high maternal, neonatal and child morbidity and mortality; and high levels of violence and trauma. Non-communicable diseases account for 40.0% of the total burden of disease, whereas TB and HIV accounted for 26.7% of all deaths in 2015, with TB being the leading recorded cause of death in the country. One registry that covers a rural population of just over 1 million persons found that hematological cancers (*International Classification of Diseases, Tenth Revision* codes C81–C95) constituted 3.5% of

all reported cancers [65]. In children under 14 years, leukemia and lymphoma made up 21.9% of cancers, followed by Wilms tumor and retinoblastoma. The accuracy of this data must be considered in the context of underdiagnosis, under-reporting and incorrect coding. Establishment of a public CB inventory represents an opportunity to address an unmet medical need for South African patients. However, establishing a public CBB will have to consider the cost implications in a country with many other competing health care priorities.

Sustainable development goals

In support of the United Nations Sustainable Development Goal of universal health coverage, the South African government has embarked on a National Health Insurance (NHI) program, which it aims to implement from 2025. In addition to primary and emergency health care, the 2017 white paper on the national health insurance policy [66] includes oncology and cancer treatments under hospital-based service benefits. Adult and pediatric oncology is, however, currently excluded from the district and regional hospital standard treatment guidelines and associated essential medicine list [83].

National cancer strategy

The National Cancer Strategic Framework 2017–2022 [84] identifies lung, colorectal, cervical, prostate and breast cancers as priority adult cancers. In this regard, breast and cervical cancer control policies and a palliative care policy and strategy have been developed. In addition to the five priority adult cancers, cancers of childhood/adolescence/young adulthood are also a stated national priority. This broader definition is important, especially considering that hematological malignancies, such as Hodgkin lymphoma, non-Hodgkin lymphoma and acute lymphoblastic leukemia, are important contributors to cancer cases in the 15- to 24-year-old age group. The development of a specific childhood/adolescent/young adulthood cancer control strategy should consider the role a national public CBB could play in achieving its objectives. A CBB can therefore comfortably exist within the current policy, legal and regulatory framework.

Adult patients with acute lymphoid and myeloid disorders and non-malignant disorders such as bone marrow failure, inherited disorders of metabolism and primary immune deficiencies can benefit from CB-derived HSPCT. However, the main driver for a CBB remains the treatment of childhood/adolescent/young adult cancers. A comprehensive care system should include (i) the creation of high levels of patient awareness of symptoms as well as seeking and accessing care; (ii) screening, evaluation, diagnosis and staging; (iii) treatment and supportive care; (iv) post-treatment rehabilitation and care; and (v) a solid information system. A priority should be to increase patient awareness of childhood/adolescent/young adult cancers and to put systems in place for accurate screening and clinical diagnosis. The limited number of TNCs and CD34+ cells in a CBU limits the usefulness of CB as an HSPC source, and the cost associated with dCBT and potential cost of *ex vivo* expansion will have to be considered and compared with haplo-T.

Improvement in the number of donors can only have an impact if transplantation services are simultaneously increased. Increased public awareness and training of community and primary health workers in the early detection and referral of hematopoietic and autoimmune disorders will be required, and education of hematologists and transplant physicians in the use of CBT as a treatment modality will have to form an integral part of the establishment of a public CBB.

Human biological material regulatory framework

Human biological materials (HBMs), including HSPCs, are regulated by Chapter 8 of the National Health Act [85] and its regulations. This act deals with the donation, collection, testing and distribution of fresh and preserved HBMs. Under South African legislation, compulsory tests for the absence of infectious agents that may cause transfusion-transmissible diseases include *Treponema pallidum* (syphilis), hepatitis B virus surface antigen, antibodies to the hepatitis C virus, antibodies to HIV type 1 and type 2 and p24 HIV-1 antigen. The existing private or family CBBs are established under the regulations relating to stem cell banks [82]. CBBs banked in these facilities are for autologous use, and it has been recognized globally that quality requirements may not be as stringent as those found in public banks. Health products are regulated by the South African Health Products Regulatory Authority under the Medicines and Related Substances Act [80] and its General Regulations [81]. In the US, minimally manipulated, unrelated, allogeneic placental CB intended for HSPCT needs to be licensed by the US Food and Drug Administration. CBBs note that the high cost of obtaining Food and Drug Administration licensure exacerbates the already high cost of CBBs. In the absence of an HBM agency, the South African Health Products Regulatory Authority will have to ensure that the quality and safety of CBBs are in line with international standards, such as AABB, European Directorate for the Quality of Medicines and Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee of the International Society for Cell & Gene Therapy and European Society for Blood and Marrow Transplantation, to ensure that the units can be used internationally.

CB banking models

CBBs provide an inventory of stem cell units that are particularly valuable for patients whose options for finding an HLA-matched donor are limited, such as ethnic minorities [41]. In SA's ethnically diverse society, this is of potential importance [67]. It should be noted, however, that although AA and MA groups are ethnic minorities in the "Global North," these groups constitute the majority of people present in many populations in the "Global South." In SA, these groups represent 90% of the population and an even bigger proportion in other sub-Saharan countries, which underscores the importance of catering to the diversity in these regions.

Three CBB models, private, public and hybrid, exist, with different countries adopting different models of the latter. The premise with private banks is that one would bank one's child's stem cells for autologous or family use later in life, but the evidence for recall and use of this resource is not robust [36]. Illnesses such as leukemia and other metabolic diseases cannot, in fact, be treated with autologous stem cells [35,37]. The benefits to society are limited, and this has led to this banking model losing favor for HSPCT among health care professionals in many parts of the world [35]. Kapinos *et al.* [40] and Strong *et al.* [44] found, however, that in the US, the social benefit of having a CB banking system far outweighs its costs. The changing perspective on the use of these cells for regenerative medicine purposes, where autologous stem cells would mostly be used, may change this perception [38]. Public CBBs rely on mothers making altruistic CB donations. Once collected and processed, the CBB is owned by the public bank and logged on to national and international registries [36]. Costs to maintain public banks are high and rely on a combination of government and privately sourced funding to remain economically viable. Public banking is seen as a priority in many countries, with government funding being invested in its growth. This trend is based on the increasing use of HSPCT and the need to

improve access to this resource for groups under-represented in donor registries [43]. A hybrid bank encompasses elements of both public and private banks [68]. Two main types are (i) a CBB that offers both public donation and private storage options and (ii) innovative solutions that make HLA-typed, privately stored CB available via registries for use in allogeneic transplantation [69]. This model is used by several private banks in Europe and the US. SA currently has a number of private CBBs and a recently established hybrid CBB. However, too few South African patients access the private health care sector for hybrid banking to establish a large enough inventory, both in terms of numbers and diversity. Should such a banking model be adopted, patients from the public sector would have to be included. Therefore, upon evaluation of the three banking models, it would appear that a public CBB is a natural choice for SA. If a public CBB model is adopted, financial sustainability would be a major concern. Income from units sold would be factored in, and partnerships with private CBBs might need to be considered.

Other considerations

Sustainability

Internationally, CBBs are under financial pressure, resulting in bankruptcy and closure of some CBBs and merging of others. Magalon *et al.* [41] elegantly state that the current challenge for CBBs is “not only to provide—but rather to afford to provide compatible units for everyone.” It is thus important for CBBs to be sustainable and remain economically viable, especially for the benefit of ethnic groups under-represented in donor registries [70]. To ensure CBB sustainability, the design of the banking system would need to include (i) establishing an optimized inventory, (ii) maximizing utilization and (iii) minimizing operating expenses. These three aspects are closely interconnected and can only be addressed by ensuring product quality, diversity and affordability.

Quality

Quality aspects of CBUs include purity of the cell product and number of CD34+ stem and progenitor cells.

Purity

In 2017, HIV prevalence among women who attended antenatal clinics in SA was 30.7% [71]. The introduction of anti-retrovirals has decreased the mother-to-child-transmission rate from around 50% to 1.1% [72]. With the country's high HIV prevalence, it is imperative to confidently screen for HIV in donated CB [73]. Screening of CB for HIV RNA has been validated for sensitivity and specificity by Meissner-Roloff *et al.* [72] using the Ultrio Plus, a qualitative *in vitro* nucleic acid test for the detection of HIV RNA (in addition to hepatitis B DNA and hepatitis C RNA). Regular testing of mothers up to 12 months post-delivery would, however, be a requirement, and CBUs would have to be placed in quarantine until this was done to ensure that the window period of infection was taken into account.

In addition to compulsory tests for communicable agents, the cytomegalovirus status of CBUs would have to be confirmed because of the high prevalence of cytomegalovirus in the country.

TNC and CD34+ cell counts

Good clinical outcomes depend on CBU TNC and CD34+ cell counts. A CBB in SA would also be required to provide for the needs of adult patients. Considering a minimum dose of 2.5×10^7 TNCs/kg body weight, 60-kg and 75-kg adults require CBUs with TNC counts of at least 150 and 188×10^7 cells, respectively. Bart *et al.* [42] found that CBUs with TNC counts $\geq 150 \times 10^7$ cells constituted only 13% of the banked units in Swiss and US CB registries but comprised 65% of the distributed units. Most CBUs in these banks will never be used. Transplant physicians often favor larger CBUs over better matched but smaller units. This group proposed that the cutoff for banking should be a minimum of 125×10^7 TNCs and possibly even 150×10^7 TNCs. Magalon *et al.* [42] derived a CBU utilization score based on a retrospective analysis of 9396 CBUs registered in Bone Marrow Donors Worldwide between January 1, 2009, and December 31, 2011. They found that TNC counts had a larger influence on CBU selection for transplant than CD34 counts. The Canadian Blood Service CBB set TNC count cutoffs of 150×10^7 cells and 130×10^7 cells for Caucasian donors and non-Caucasian donors, respectively [74]. Various banks report smaller collection volumes and TNC counts from African and MA donor cords compared with European donor cords. Collection volumes and TNC counts for AA and MA South African donors have not been determined. The application of early recruitment criteria in terms of the mother's and baby's health status, including early indicators of low birth weight, can be used to maximize collection volumes. Obstetric staff must be trained to optimally collect umbilical CB and to make a pre-shipment quality assessment on volume as proxy for TNC count.

Diversity

A major challenge in the design and collection strategy of CBB in SA would be determining the optimum inventory size and population group composition. The paucity of high-resolution typed HLA data for the AA and MA population groups makes it impossible to pre-determine how many CBUs would be required to satisfy a given percentage of HLA haplotypes. Pedigree data from typing mother and CBU combined with patient typing data will have to be systematically analyzed for cumulative haplotype frequencies. The target number of CBUs will be a moving target informed by the evolving data set [74]. An aspirational annual banking target can be set. Based on the stringency of the TNC count cutoff or minimum collection volume, the number of CBUs collected may be higher by a factor of 10 compared with the number of CBUs banked. To rapidly build the HLA haplotype data set, there may be a decision to also do HLA typing on collected but unbanked units. Reported ethnic group identity data may lead to further stratified subgroup collection targets [74]. Although the primary purpose of the CBB would be to address the needs of population groups with limited access to donors, the exclusion of other groups could be considered discriminatory. An initial strategy may consider collection based on population proportions and, as cumulative HLA frequencies become available, adjust the collection strategy to focus on under-represented haplotypes.

Affordability

Cost-effectiveness thresholds are useful for deciding whether a given health intervention should be considered or maintained. Cost is often expressed in terms of disability-adjusted life years. Previously, the World Health Organization recommended a cost-effectiveness threshold of one to three times the per capita gross domestic product (GDP) but withdrew its recommendation in 2016. In 2015, the South African government established a health

opportunity costs threshold of ZAR38,456 (US\$2,575). This was equivalent to 53% of the GDP per capita at the time. For 2019, SA GDP per capita was US\$7,346, which is approximately ZAR107,912 (US\$1 = ZAR14.93 in mid-March 2021).

According to the general household survey, 17.2% of the South African population was covered by some form of private health insurance in 2019. The level of care can vary greatly between packages, but all medical insurers must guarantee a prescribed minimum benefit package of treatments. The remaining 48 million South Africans rely on tax-funded public health care services. The South African government intends to start implementing NHI by 2025. At the time of writing, there is no indication of the cost-effectiveness thresholds that will be applied [75]. There are still many issues related to the implementation of NHI that remain contentious; one is the level of service that will be, or can be, provided considering the limited resources available. The design of a sustainable CB banking system will need to be considered in the context of a resource-constrained society.

The average shipping price of CBUs is around US\$36,000, which limits the utilization of CBUs and may favor haplo-T in resource-poor settings. There is, however, no relationship between the true acquisition cost and selling price of a given unit. The high price is the result of an accounting practice that allocates the total inventory cost, including that of non-moving CBUs, to shipped units, which disincentivizes their use in certain settings.

Jaime-Pérez *et al.* [76] reported a banking efficiency of 57.5%. Factors that impacted on this efficiency included (i) units that had to be discarded because they did not meet the selection criterion of being processed within 48 h of collection; (ii) a minimum collection volume of 80 mL; (iii) a TNC cutoff of 80×10^7 cells; and (iv) a minimum CD34+ cell count cutoff of 2×10^6 cells. Based on data from the US National Marrow Donor Program and Swiss Blood Stem Cells CB registries, Bart *et al.* [42] reported a 33% efficiency at a TNC cutoff of 90×10^7 TNCs. This means that for every 3 units collected, 1 unit can be processed and banked. If we assume a cost of US\$200 per collected unit and a processing cost of US\$900 per selected unit, the cost to recruit, process and bank an 80×10^7 TNC unit would be US\$1,500. Including overhead and distribution costs, the total cost would be less than US\$3,000 [41,42,40]. Collection cost could be reduced by better using pre-selection criteria, reducing transport losses and using trained volunteers and obstetric personnel rather than paid collection staff. A further analysis of the National Marrow Donor Program data reported by Bart *et al.* shows that a TNC cutoff of 125×10^7 cells will require 6.5 collected units for 1 banked unit, resulting in a unit cost of US\$2,200 (excluding overhead and distribution costs). A 150×10^7 TNC cutoff will require 12.1 units at a cost of US\$3,320, and a 175×10^7 TNC cutoff will require 22.8 units at a cost of US\$5,460 (excluding overhead and distribution costs). [42] As stated earlier, the quality of the CBU impacts on its utilization. An important strategic decision for the establishment of a CBB in SA would be the trade-off between HLA and haplotype diversity and CBU quality.

Synergies

In 2001, the country's blood services, except the Western Cape Blood Transfusion Service, were consolidated into the SANBS. SANBS is well placed to add CB banking to its service offering. As the service has a well-established national logistics network and testing laboratories that already provide apheresis collection services and high-resolution HLA typing, CB banking could be a logical product extension that could benefit from the various synergies. In addition, at the time of writing, SANBS is in the process of obtaining Joint

Accreditation Committee of the International Society for Cell & Gene Therapy and European Society for Blood and Marrow Transplantation accreditation (Poole C, SANBS personal communication, December 2020).

New uses

Beyond being a donor source for HSPCs, CB has other unique advantages. Among these include the provision of a source of regulatory T cells that can be infused to reduce immunoreactivity in the pathogenesis of GVHD as well as virus-specific T cells [77]. Furthermore, a CBB provides a unique advantage through ensuring the availability of an off-the-shelf product that can serve the field of cellular therapies, such as chimeric antigen receptor natural killer cell therapies [78]. It also serves as a source of induced pluripotent stem cells for use in regenerative medicine [77]. Whether using autologous or allogeneic CB cells, trials exploring induced pluripotent stem cell use in neurological disorders, type 1 diabetes and cardiovascular disorders are underway [78]. A rise in the use of CB has been noted during the coronavirus disease 2019 pandemic, during which haplotype donor travel has been restricted (Allan D, personal communication, November 17, 2020). This must be considered in the continuing coronavirus disease 2019 climate and for possible future pandemics. Advocacy for the implementation of a CBB should therefore be seen in addition to, and not in conflict with, the need to pursue haplo-T. The two cannot be mutually exclusive in a society in which as many donor sources as possible are required to meet a large transplantation need.

Expanded geography

A public CBB based in SA would be a valuable resource for South, southern and sub-Saharan Africa as well as countries with minority populations of African origin.

Cost focus

The diverse population of SA is spread over a large geographic area. Collecting and transporting CBUs to a central processing and banking facility will add complexity. Gauteng province, which includes Johannesburg and Pretoria, is home to 26% of the country's population, or 15.5 million people. It also contains the most ethnically diverse population. In the period 2006–2020, nearly 5 million people migrated internally into the province. Approximately 12% of the country's population, or 7 million people, live in the Western Cape province, with 4.6 million in the Cape Town metropolitan area. The Western Cape has received approximately 1.4 million internal migrants. Health care infrastructure and logistics in these two areas are well developed, and an initial recruitment focus on these two metropolitan areas could provide a foundation on which to expand.

Discussion

There are over 53 million AA and MA South Africans [4]. These people are under-represented in HSPC donor registries, making it challenging to find suitable donors when HSPCT is indicated. This situation can be addressed by increasing representation in donor registries and doing haplo-T and unrelated CBT. There is, however, no public CB inventory in SA. Establishing a public CBB would increase access to this life-saving treatment for people living in SA as well as sub-Saharan African people and people of African origin across the world. The authors are cognizant that building a public CBB in the resource-

constrained South African health system would be a significant challenge. Nevertheless, the authors believe that it is vital to establish a national feasibility steering group to study this in detail and to report to the National Department of Health on all aspects related to the establishment of a South African national umbilical CBB.

Many of these aspects have been the subject of research previously undertaken at the Institute for Cellular and Molecular Medicine, University of Pretoria, South Africa. The research that has been conducted has addressed public acceptability [67], the testing of CB for HIV [73], flow cytometric analysis of CB-derived HSPCs, factors determining the composition of the bank (including mapping of HLA genotypes/alleles) [79] and economic feasibility (initial set-up and long-term sustainability). The authors acknowledge the need for more prevalence and transplantation data and an extensive analysis of a variety of factors, including the relative frequency of haplotypes in each population group and subgroup and CB collection volume and TNC and CD34+ count standards, as these factors will ultimately dictate the CB collection strategy and CBU banking policy. Considering the current paucity of data in the South African context, a “modern” CBB will have to rely on data science tools, such as artificial intelligence and machine learning, to consolidate the various data sets that will inform feasibility, sustainability, etc. It is essential to consolidate the research into a single policy/strategic document and to identify gaps in the body of research that should be addressed.

Funding

This study was funded by the South African Medical Research Council (Extramural Unit, Stem Cell Research and Therapy) and the University of Pretoria (Institute for Cellular and Molecular Medicine).

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: IMV and CLH. Drafting or revising the manuscript: All authors. All authors have approved the final article.

Acknowledgments

The authors thank Drs C. Ingram, A. Venter and J. Ward of the South African Bone Marrow Registry for the data provided. The authors also thank Dr C. Poole of the South African National Blood Service for the insights provided.

References

[1] Tishkoff SA, Reed FA, Friedlaender FR, et al. The genetic structure and history of Africans and African Americans. *Science* 2009;324(5930):1035–44.

- [2] Lambert CA, Tishkoff SA. Genetic structure in African populations: implications for human demographic history. *Cold Spring Harb Symp Quant Biol* 2009;74:395–402.
- [3] Quintana-Murci L, Harmant C, Quach H, et al. Strong Maternal Khoisan Contribution to the South African Coloured Population: A Case of Gender-Biased Admixture. *Am J Hum Genet* 2010;86(4):611–20.
- [4] Statistics South Africa. Mid-Year Population Estimates 2020. Pretoria 2020 (P0302):1–35. Mid-Year Population Estimates 2020. Accessed March 25, 2021.
- [5] Daya M, Van der Merwe L, Galal U, et al. A panel of ancestry informative markers for the complex five-way admixed South African Coloured population. *PLoS One* 2013;8(12):e82224.
- [6] Cambell MC, Tishkoff SA. African Genetic Diversity: Implications for Human Demographic History, Modern Human Origins, and Complex Disease Mapping. *Annu Rev Genomics Hum Genet* 2008;9:403–33.
- [7] Choudhury A, Ramsay M, Hazelhurst S, et al. Whole-genome sequencing for an enhanced understanding of genetic variation among South Africans. *Nat Commun* 2017;8(1):2062.
- [8] Major E, Rigó K, Hague T, Bérces A, Juhos S. HLA Typing from 1000 Genomes Whole Genome and Whole Exome Illumina Data. Seo J-S, ed. *PLoS One* 2013;8 (11):e78410.
- [9] Edinur HA, Manaf SM, Mat NFC. Genetic barriers in transplantation medicine. *World J Transplant* 2016;6(3):532–42.
- [10] Du Toit ED. In: Mayr WR, ed. *Advances in Forensic Haemogenetics*. *Advances in Forensic Haemogenetics*, 2, Berlin: Springer; 1988:42–51.
- [11] Du Toit ED, MacGregor KJ, Taljaard DG, Oudshoorn M. HLA-A, B, C, DR and DQ polymorphisms in three South African population groups: South African Negroes, Cape Coloureds and South African Caucasoids. *Tissue Antigens* 1988;31(3): 109–25.
- [12] Tshabalala M, Mellet J, Vather K, et al. Mixed Resolution HLA~A, ~B, ~C, ~DRB1, ~DQA1, ~DQB1 and ~DPB1 Diversity in South African Populations. Unpublished manuscript. Submitted 2021
- [13] Paximadis M, Mathebula TY, Gentle NL, et al. Human leukocyte antigen class I (A, B, C) and II (DRB1) diversity in the black and Caucasian South African population. *Hum Immunol* 2012;73(1):80–92.
- [14] Gonzalez-Galarza FF, McCabe A, dos Santos EJM, et al. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. *Nucleic Acids Res* 2019;48(D1):D783–8. <https://doi.org/10.1093/nar/gkz1029>.
- [15] Loubser S, Paximadis M, Gentle NL, Puren A, Tiemessen CT. Human leukocyte antigen class I (A, B, C) and class II (DPB1, DQB1, DRB1) allele and haplotype variation in Black South African individuals. *Hum Immunol* 2020;81(1):6–7.

- [16] Grifoni A, Sidney J, Carpenter C, et al. Sequence-based HLA-A, B, C, DP, DQ, and DR typing of 159 individuals from the Worcester region of the Western Cape province of South Africa. *Hum Immunol* 2018;79(3):143–4.
- [17] Loubser S, Paximadis M, Gentle NL, Puren A, Tiemessen CT. Human leukocyte antigen class I (A, B, C) and class II (DPB1, DQB1, DRB1) allele and haplotype variation in Black South African individuals. *Hum Immunol* 2020;81(1):6–7.
- [18] Du Toit ED, Schlaphoff T, Borrill V. The South African Bone Marrow Registry—role in providing unrelated donors for allogeneic stem cell transplantation. *Contin Med Educ J* 2012;30(8):293–4.
- [19] Gragert L, Eapen M, Williams E, et al. HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry. *N Engl J Med* 2014;371(4):339–48.
- [20] Kindwall-Keller TL, Ballen KK. Umbilical cord blood: The promise and the uncertainty. *Stem Cells Transl Med* 2020;9(10):1153–62.
- [21] Mo X-D, Tang B-L, Zhang X-H, et al. Comparison of outcomes after umbilical cord blood and unmanipulated haploidentical hematopoietic stem cell transplantation in children with high-risk acute lymphoblastic leukemia. *Int J Cancer* 2016;139 (9):2106–15.
- [22] Li D, Li X, Liao L, Li N. Unrelated cord blood transplantation versus haploidentical transplantation in adult and pediatric patients with hematological malignancies—a meta-analysis and systematic review. *Am J Blood Res* 2020;10(1):1–10.
- [23] Giannotti F, Labopin M, Shouval R, et al. Haploidentical transplantation is associated with better overall survival when compared to single cord blood transplantation: an EBMT-Eurocord study of acute leukemia patients conditioned with thiotepa, busulfan, and fludarabine. *J Hematol Oncol* 2018;11(1):1–10.
- [24] Solomon SR, Martin AS, Zhang MJ, et al. Optimal Donor for African Americans with Hematologic Malignancy: HLA-Haploidentical Relative or Umbilical Cord Blood Transplant. *Biol Blood Marrow Transplant* 2020;000:1–7.
- [25] Sanz J, Montoro J, Solano C, et al. Prospective Randomized Study Comparing Myeloablative Unrelated Umbilical Cord Blood Transplantation versus HLA-Haploidentical Related Stem Cell Transplantation for Adults with Hematologic Malignancies. *Biol Blood Marrow Transplant* 2020;26(2):358–66.
- [26] Fuchs EJ, O'Donnell P V, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood* 2021;137(3):420–8.
- [27] González-Llano O, González-López EE, Ramírez-Cázares AC, Marcos-Ramírez ER, Ruiz-Argüelles GJ, Gómez-Almaguer D. Haploidentical peripheral blood stem cell transplantation with posttransplant cyclophosphamide in children and adolescents with hematological malignancies. *Pediatr Blood Cancer* 2016;63(11):2033–7.

- [28] Locatelli F, Merli P, Pagliara D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after ab T-cell and B-cell depletion. *Blood* 2017;130(5):677–86.
- [29] Bertaina A, Zecca M, Buldini B, et al. Unrelated donor vs HLA-haploidentical α/β T-cell- and B-cell-depleted HSCT in children with acute leukemia. *Blood* 2018;132(24):2594–607.
- [30] Kosuri S, Wolff T, Devlin SM, et al. Prospective Evaluation of Unrelated Donor Cord Blood and Haploidentical Donor Access Reveals Graft Availability Varies by Patient Ancestry: Practical Implications for Donor Selection. *Biol Blood Marrow Transplant* 2017;23(6):965–70.
- [31] Hall K, Posel D. Fragmenting the Family? The Complexity of Household Migration Strategies in Post-Apartheid South Africa. *IZA J Dev Migr* 2019;10(2):1–20.
- [32] UNAIDS. Country factsheets South Africa | 2019 [Internet]. 2019. p. 1-10. Available from <https://www.unaids.org/en/regionscountries/countries/southafrica>. Accessed 25 March 2021.
- [33] Sachdeva A, Gunasekaran V, Malhotra P, et al. Umbilical Cord Blood Banking: Consensus Statement of the Indian Academy of Pediatrics. *Indian Pediatr* 2018;55 (6):489–94.
- [34] Shahrokhi S, Mena F, Alimoghaddam K, McGuckin C, Ebtekar M. Insights and Hopes in Umbilical Cord Blood Stem Cell Transplantations. *J Biomed Biotechnol* 2012;2012:1–11.
- [35] Haw J. From waste to (fool's) gold : promissory and profit values of cord blood. *Monash Bioeth Rev* 2015;33(4):325–39.
- [36] Gluckman E, Ruggeri A, Rocha V, et al. Family-directed umbilical cord blood banking. *Haematologica* 2011;96(11):1700–7.
- [37] Shearer WT, Lubin BH, Cairo MS NL. Cord Blood Banking for Potential Future Transplantation: Subject Review. *Pediatrics* 2017;104(5):116–8.
- [38] Dessels C, Alessandrini M, Pepper MS. Factors Influencing the Umbilical Cord Blood Stem Cell Industry: An Evolving Treatment Landscape. *Stem Cells Transl Med* 2018;7(9):643–50.
- [39] Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood* 2019;134(12):924–34.
- [40] Kapinos K, Briscoe B, Gracner T, et al. Challenges to the Sustainability of the U. S. Public Cord Blood System. Santa Monica, Calif.: RAND Corporation; 2017.
- [41] Magalon J, Maiers M, Kurtzberg J, et al. Banking or Bankrupting : Strategies for Sustaining the Economic Future of Public Cord Blood Banks. *PLoS One* 2015;10 (12):1–12.

- [42] Bart T, Boo M, Balabanova S, et al. Impact of Selection of Cord Blood Units from the United States and Swiss Registries on the Cost of Banking Operations. *Transfus Med Hemotherapy* 2013;40(1):14–20.
- [43] Bart T. Cost effectiveness of cord blood versus bone marrow and peripheral blood stem cells. *Clin Outcomes Res* 2010;2(1):141–7.
- [44] Strong A, Gračner T, Chen P, Kapinos K. On the Value of the Umbilical Cord Blood Supply. *Value Heal* 2018;21(9):1077–82.
- [45] Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood* 2005;105(3):1343–7.
- [46] Brunstein CG, Petersdorf EW, DeFor TE, et al. Impact of Allele-Level HLA Mismatch on Outcomes in Recipients of Double Umbilical Cord Blood Transplantation. *Biol Blood Marrow Transplant* 2016;22(3):487–92.
- [47] Kurtzberg J. A History of Cord Blood Banking and Transplantation. *Stem Cells Transl Med* 2017;6(5):1309–11.
- [48] Wagner JE, Eapen M, Carter S, et al. One-Unit versus Two-Unit Cord-Blood Transplantation for Hematologic Cancers. *N Engl J Med* 2014;371(18):1685–94.
- [49] Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. *Blood* 2016;127(26):3450–7.
- [50] Delaney C. Notch Mediated Expansion of human CB progenitor cells capable of rapid myeloid reconstitution. *J Intern Med* 2010;266(2):141–53.
- [51] Mehta RS, Saliba RM, Cao K, et al. Ex Vivo Mesenchymal Precursor Cell-Expanded Cord Blood Transplantation after Reduced-Intensity Conditioning Regimens Improves Time to Neutrophil Recovery. *Biol Blood Marrow Transplant* 2017;23 (8):1359–66.
- [52] Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. *J Clin Invest* 2014;124 (7):3121–8.
- [53] Horwitz ME, Wease S, Blackwell B, et al. Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide. *J Clin Oncol* 2019;37(5):367–74.
- [54] Stiff PJ, Montesinos P, Peled T, et al. Cohort-Controlled Comparison of Umbilical Cord Blood Transplantation Using Carlecortemcel-L, a Single Progenitor-Enriched Cord Blood, to Double Cord Blood Unit Transplantation. *Biol Blood Marrow Transplant* 2018;24(7):1463–70.

- [55] Wagner JE, Brunstein CG, Boitano AE, et al. Phase I/II Trial of StemRegenin-1 Expanded Umbilical Cord Blood Hematopoietic Stem Cells Supports Testing as a Stand-Alone Graft. *Cell Stem Cell* 2016;18(1):144–55.
- [56] Fares I, Chagraoui J, Lehnertz B, et al. EPCR expression marks UM171-expanded CD34+ cord blood stem cells. *Blood* 2017;129(25):3344–51.
- [57] Fares I, Chagraoui J, Gareau Y, et al. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal. *Science* 2014;345(6203):1509–12.
- [58] Baldomero H, Aljurf M, Zaidi SZA, et al. Narrowing the gap for hematopoietic stem cell transplantation in the East-Mediterranean/African region: comparison with global HSCT indications and trends. *Bone Marrow Transplant* 2019;54 (3):402–17.
- [59] Health Resources and Services Administration. Donation and Transplantation Statistics. <https://bloodstemcell.hrsa.gov/about/faqs>. Accessed September 23, 2020.
- [60] Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: More than 40 000 transplants annually. *Bone Marrow Transplant* 2016;51(6):786–92.
- [61] Grobbelaar S, Mercier AE, Verburgh E, Brittain D. Haematopoietic stem cell transplantation in South Africa: current limitations and future perspectives. *SAMJ* 2019;109(8):47–53.
- [62] Hall K, Sambu W. Demography of South Africa’s children. *South African Child Gauge* 2015;2016:106–10.
- [63] Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. *Lancet* 2009;374(9693):934–47.
- [64] Pillay-van Wyk V, Msemburi W, Laubscher R, et al. Mortality trends and differentials in South Africa from 1997 to 2012: Second National Burden of Disease Study. *Lancet Glob Heal* 2016;4(9):e642–53.
- [65] Somdyala NIM, Parkin MD, Sithole N, Bradshaw D. Cancer incidence in selected municipalities of the Eastern Cape Province, 2008–2012. Eastern Cape Province Cancer Registry Technical Report. Cape Town: South African Medical Research Council; 2015. p. 1–38 Eastern Cape Province Cancer Registry Technical Report. Accessed March 25, 2021.
- [66] National Department of Health. White Paper: National Health Insurance Policy-Towards Universal Health Coverage. *Government Notice* 2017;40955(627):1–67
- [67] Meissner-Roloff M, Pepper MS. Establishing a public umbilical cord blood stem cell bank for South Africa: an enquiry into public acceptability. *Stem Cell Rev Reports* 2013;9(6):752–63.
- [68] Chang HC. The third way of umbilical cord blood banking. *Nat Biotechnol* 2014;32(4):318–9.

- [69] CELVI. CELVI_Join the Movement! <https://mdaltd.org.au/>. Published 2019. Accessed August 19, 2020.
- [70] Pupella S, Bianchi M, Ceccarelli A, et al. A cost analysis of public cord blood banks belonging to the Italian Cord Blood network. *Blood Transfus* 2018;16:313–20.
- [71] Woldesenbet SA, Kufa T, Lombard C, et al. National Department of Health. The 2017 National Antenatal Sentinel HIV Survey Key Findings. Pretoria 2019;27:1–97. 2017 National Antenatal Sentinel HIV Survey. 2011 Accessed March 25, 2021.
- [72] Goga A, Chirinda W, Ngandu NK, et al. Closing the gaps to eliminate mother-to-child transmission of HIV (MTCT) in South Africa: understanding MTCT case rates, factors that hinder the monitoring and attainment of targets, and potential game changers. *South African Med J* 2018;108:17–24.
- [73] Meissner-Roloff M, Gaggia L, Vermeulen M, et al. Strategies for screening cord blood for a public cord blood bank in high HIV prevalence regions. *Glob Heal Epidemiol Genomics* 2018;3:e9.
- [74] Allan D, Kiernan J, Gragert L, et al. Reducing ethnic disparity in access to high-quality HLA-matched cord blood units for transplantation: analysis of the Canadian Blood Services' Cord Blood Bank inventory. *Transfusion* 2019;59(7):2382–8.
- [75] Edoaka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. *Health Policy Plan* 2020;35(5):546–55.
- [76] Jaime-Pérez JC, Monreal-Robles R, Rodríguez-Romo LN, Mancías-Guerra C, Herrera-Garza JL, Gómez-Almaguer D. Evaluation of Volume and Total Nucleated Cell Count as Cord Blood Selection Parameters. *Am J Clin Pathol* 2011;136 (5):721–6.
- [77] Gupta AO, Wagner JE. Umbilical Cord Blood Transplants: Current Status and Evolving Therapies. *Front Pediatr*. 2020;8:1-11.
- [78] Kindwall-Keller TL, Ballen KK. Umbilical cord blood: The promise and the uncertainty. *Stem Cells Transl Med* 2020;9(10):1153–62.
- [79] Mellet J, Alessandrini M, Steel HC, Pepper MS. Constituting a public umbilical cord blood bank in South Africa. *Bone Marrow Transplant* 2015;50(4):615–6.
- [80] South African Parliament. Medicines and Related Substances Act No. 101 of 1965 as amended. *Government Gazette* 1965;1171(1002):1–70 Medicines and Related Substances Act No. 101 of 1965. Accessed March 25, 2021.
- [81] Minister of Health, South Africa. General Regulations to the Medicines and Related Substances Act 101 of 1965 (as amended to August 2017). *South African Government Gazette* 2017(GN 859):1–90 General Regulations to the Medicines and Related Substances Act. Accessed March 25, 2021.

[82] South Africa National Department of Health. Regulations Relating to Stem Cell Banks. South African Government Gazette 2012;35099(GN R183):1–14 Regulations Relating to Stem Cell Banks. 2012 Accessed March 25, 2021.

[83] South African National Department of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital Level. p 1, 3rd Pretoria, South Africa: The National Department of Health; 2012. p. 1–424 Standard Treatment Guidelines and Essential Medicines List for South Africa. 32012 Accessed March 25, 2021.

[84] The Ministerial Advisory Committee on Cancer Prevention and Control. National Cancer Strategic Framework for South Africa 2017—2022. Pretoria, South Africa: The National Department of Health; 2020. p. 1–56 National Cancer Strategic Framework for South Africa. 12020 Accessed March 25, 2021.

[85] South African Parliament. National Health Act No. 61 of 2003. South African Government Gazette 2003;26595(GN 869):1–89 National Health Act No. 61 of 2003 as ammended. 2013 Accessed March 25, 2021.

[86] Children’s Institute, University of Cape Town. Demography of South Africa’s children. In: Shung-King M, Lake L, Sanders D, Hendricks M, eds. South African Child Gauge 2019 - Child and adolescent health - Leave no one behind, Cape Town, South Africa: Children’s Institute, University of Cape Town; 2019:216–20 South African ChildGauge 2019. 2019. Accessed March 25, 2021.