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CORD BLOOD

Factors Influencing the Umbilical Cord Blood Stem Cell Industry: An Evolving Treatment Landscape

CARLA DESSELS,[a] MARCO ALESSANDRINI,[a,b] MICHAEL SEAN PEPPER [a]

Key Words. Umbilical cord blood • Umbilical cord blood banking • Haploidentical transplantation • Regenerative medicine

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is common practice today for life threatening malignant and non-malignant diseases of the blood and immune systems. Umbilical cord blood (UCB) is rich in hematopoietic stem cells (HSCs) and is an attractive alternative to harvesting HSCs from bone marrow or when mobilized into peripheral blood. One of the most appealing attributes of UCB is that it can be banked for future use and hence provides an off-the-shelf solution for patients in urgent need of a transplantation. This has led to the establishment of publicly funded and private UCB banks, as seen by the rapid growth of the UCB industry in the early part of this century. However, from about 2010, the release of UCB units for treatment purposes plateaued and started to decrease year-on-year from 2013 to 2016. Our interest has been to investigate the factors contributing to these changes. Key drivers influencing the UCB industry include the emergence of haploidentical HSCT and the increasing use of UCB units for regenerative medicine purposes. Further influencing this dynamic is the high cost associated with UCB transplantation, the economic impact of sustaining public bank operations and an active private UCB banking sector. We foresee that these factors will continue in a tug-of-war fashion to shape and finally determine the fate of the UCB industry. STEM CELLS TRANSLATIONAL MEDICINE *2018;7:643–650*

SIGNIFICANCE STATEMENT

Umbilical cord blood (UCB) has been established as a reliable source of hematopoietic stem cells for bone marrow transplantation. Emerging trends and a variety of factors are currently at play that will influence the future growth of the UCB industry. This study describes this dynamic and provides insight into the evolving UCB treatment landscape.

INTRODUCTION

The ability to successfully transplant hematopoietic stem cells (HSCs) in order to reconstitute the hematopoietic system is one of the major advances in medicine and has evolved considerably in recent years [1]. Hematopoietic stem cell transplantation (HSCT) is practiced for life threatening malignant and non-malignant diseases of the blood and immune systems [2]. These cells are procured either from the patient or a donor, and are used respectively for autologous or allogeneic transplantation. Donors for allogeneic HSCT can be either HLA-matched sibling donors (MSD) or HLA-matched unrelated donors (MUD). While MSD-HSCT generally renders better and safer outcomes, only 30% of patients have an HLA-matched sibling [2], which increases the need for MUDs. With the establishment of local and international donor registries, up to 75% of Caucasian patients are able to find a genetic match [3, 4]. This is however not the case for all patients, with less than 20% of patients from non-Caucasian groups being successful in finding an HLA-match [5]. Over and above the challenges faced in establishing a genetically diverse donor pool, registries are hampered by high donor attrition rates [6].

Although historically harvested directly from bone marrow (BM), HSCs are today mostly collected from peripheral blood, following a 4–5 days regimen with a mobilizing agent such as granulocyte colony stimulating factor. Although umbilical cord blood (UCB) is a rich source of HSCs, it is usually discarded at birth [7, 8]. HSCs from UCB offer the advantage of requiring less stringent HLA-matching criteria (six loci, rather than 10 as is the case for BM-HSCs). In addition, since these cells can be cryopreserved, this provides an off-the-shelf solution to patients in urgent need of transplantation. These factors are

[a]Institute for Cellular and Molecular Medicine, Department of Immunology, and South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [b]Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Correspondence: Michael S. Pepper, M.B.Ch.B., Ph.D., M.D., Faculty of Health Sciences, Department of Immunology, University of Pretoria, Pretoria, South Africa. Telephone: +27 (0)12 319 2179; e-mail: michael.pepper@up.ac.za

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Table 1. Overview of public private and hybrid UCB banks

	Public	Private	Hybrid
Donor/collection	Altruistic donors	Paying families	Paying families
Costs involved for collection and storage	Cost is carried by the bank	Costs covered by the paying family	Costs covered by the paying families (which subsidizes the public storage)
Owner of the UCB unit	Public bank	Paying family	One portion owned by the paying family; second portion by the public side of the bank
Recipient	Unrelated patient requiring a HSCT	Exclusively for a member of the paying family	One portion exclusively for a member of the paying family; second portion for an unrelated patient requiring a HSCT
Advantages	No financial burden to the donor All units are available to unrelated recipients via international registries Only high-quality units banked (mandatory for public banks to adhere to strict international standards) Higher probability that a stored unit will be released for treatment than units stored in private banks	Paying family can access the unit at any given time	One portion of the UCB units can be released to the paying family at any time; second portion made available to unrelated recipients via international registries Public inventory increased and activities funded by income from the private side of the bank
Disadvantages	Once stored, the donor is not free to access the unit for themselves Many units discarded if they do not meet strict storage criteria Operations rely on grant funding, government subsidies, and income from the release of UCB units	Costly for the family to store UCB units Low probability that the family will ever need the unit Privately stored units cannot be used to treat all illnesses normally treated by HSCT Not always mandatory for private banks to adhere to international standards	Low probability that a unit will be released for treatment Potential conflict of interest between private and public activities

Abbreviations: HSCT, hematopoietic stem cell transplantation; UCB, umbilical cord blood.
Sources: [13–20].

particularly advantageous for patients from non-Caucasian ethnic groups [4, 7, 9, 10], especially since this offers access to a worldwide inventory and increased the likelihood of finding a match. The safety and efficacy of UCB-HSCT has been widely studied and established for both children and adults for a variety of indications. When compared to HSCT involving stem cells harvested from BM or mobilized into peripheral blood, UCB-HSCT has a lower risk of graft-versus-host-disease (GVHD), a common and often fatal complication of HSCT [7], as well as greater protection against disease relapse in various settings [11–13]. The primary disadvantage of using UCB is the low yield of HSCs when compared to BM or peripheral blood mobilized HSCs. Use of a suboptimal HSC cell dose results in delayed hematological recovery, higher graft failure rates and risk of infection [4, 8]. This results in increased hospitalization times and a consequent increase in treatment costs. Double UCB transplantation is often employed to overcome this [14]. In addition, novel ex vivo manipulation strategies to either expand or improve the homing of UCB-derived HSCs are being explored in preclinical and clinical studies. For expansion, these include the coculture of UCB-derived HSCs with mesenchymal stem cells or small molecules such as stemregenin-1, nicotinamide and notch ligand, while to improve homing, molecules such as prostaglandin E-2, sitagliptin or fucosylation are being used [15]. The cost factor is particularly pertinent in the context of allogeneic UCB transplantation, when one considers that procurement of a single UCB unit can be in excess of USD 35,000. The costs of double UCB unit transplantation and further manipulations can therefore be prohibitively expensive. The recent licensure of UCB units by the FDA, that is, the classification of the product as a drug, is a further challenge and cost burdening factor for patients in the U.S. [16], as it requires that UCB banks demonstrate rigorous testing and qualification of their processed units in order to have their manufacturing facilities accredited.

One of the most appealing attributes of UCB is that the harvested units can be banked for future use following collection [17]. Three types of UCB banks exist, namely public, private, and hybrid (Table 1). Public banks store UCB units received altruistically from donors, which are then listed on international registries and made available for any potential recipient pending establishment of an adequate HLA match. In contrast, private banks, also referred to as family banks, store UCB for exclusive future use either by the donor or a matched relative. This limited use translates to low recall rates on UCB units. Private banks tend to overestimate the benefit of private banking. Marketing inaccuracies link the overall potential of stem cells to autologous cord blood despite the fact that indications for the use of autologous cord blood stem cells is at present limited. In addition, the industry is driven by subjective (emotional) factors. Finally, informed consent is often inadequate as it does not address these issues [18]. Hybrid banks offer combined public and private UCB storage solutions. In the first scenario, either the private bank offers a public donation or the public bank offers

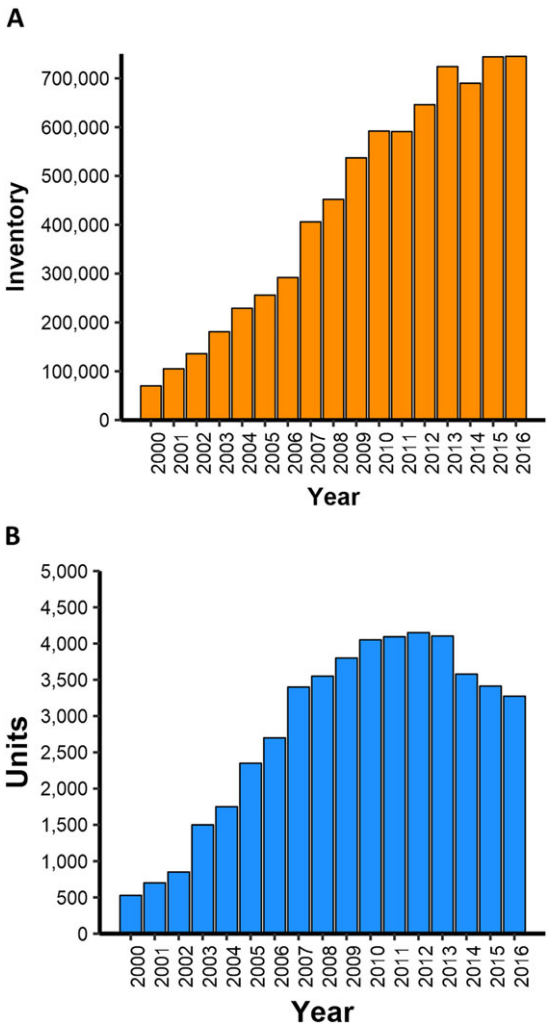

Figure 1. Number of umbilical cord blood units stored **(A)** and released **(B)** annually by public banks for allogeneic use. Data obtained from the WMDA. Data prior to 2000 was not included.

a private storage option. Alternative models include the following: (a) 25% of privately stored UCB is donated to the public system in accordance with national legislation (Turkish model); (b) UCB is stored privately but if an unrelated match is found the unit can then donated to the public (Spanish model); (c) harvested UCB units can be divided in two—one portion for exclusive use and the other for public use (Virgin model); and (d) UCB is stored for private use and at a later stage is released to the public following consent from the donor [18–21]. Either way, the public side of hybrid banks is generally cross-subsidized by income generated from its private activities.

It has been reported that more than 80 indications can be treated using UCB [9, 22, 23]. The scope of these indications has recently been extended beyond traditional applications of HSCT, and today includes several experimental strategies aimed at treating diseases such as cerebral palsy, type 1 diabetes and autism [17, 24, 25]. We have undertaken a historical analysis of the worldwide usage of UCB units in order to describe emerging trends and to provide an overview of factors shaping the UCB industry.

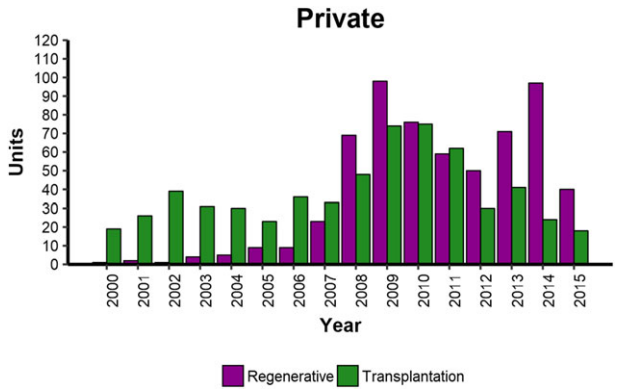

Figure 2. Units released per year by treatment category for private umbilical cord blood (UCB) banks. Indications for transplantation or regenerative purposes are listed in Table 3. Data are representative of 19 recognized UCB banks (Table 2). Data prior to the year 2000 was not included. Units released for unknown reasons were 1 (2005); 1 (2007); 1 (2009); 5 (2010); 15 (2011); 1 (2013) and 1 (2015), and are not shown on the graph.

Table 2. List of private banks from which data were obtained with the corresponding websites

Bank	Website
BioVault Family	http://biovaultfamily.com/about-us/our-experience/
Cells4Life	http://cells4life.com/cells4life-difference/cells4lifes-cord-blood-releases/
Cord Blood Centre Group	http://www.cordbloodcenter.cz/o-nas/cord-blood-center/transplantaty-cbc-pomohly
CordBlood Registry	http://www.cordblood.com/how-its-used/advancing-stem-cell-therapies/regenerative-medicine
Cordlife	https://www.cordlife.com/sg/release-track-record
CordVida	http://www.cordvida.com.br/new/por-que-cordvida/amostras-utilizadas
Criobaby	http://www.criobaby.pt/tratamentos-com-celulas-estaminais#casos-de-sucesso
CryoCell International	https://www.cryo-cell.com/cord-blood/banking-benefits/transplant-matrix
CryoSave	https://www.cryo-save.co.za/transplantations-uses-cryo-save/
Cryoviva	http://www.cryoviva.in/success-stories/cryoviva-biotech-india-transplant-outcomes/
FamiCord	http://www.nabassaite.lv/en/famicord-transplantations
FamilyCord	https://www.familycord.com/familycord-matrix-units-released-transplant/
HealthBaby	http://www.healthbaby.hk/en-hk/advantages/why-healthbaby/the-most-successful-transplants
HemaFund	http://hemafund.com/en/o-gemafond/primenenie-pupovinnoj-krovi/
Insception Lifebank	http://www.insception.com/our-transplants
LifeCell	http://www.lifecell.in/services/babycord/why-choose-Lifecell-stem-cell-banking#transplant-matrix
New England Cord Blood Bank	https://cordbloodbank.com/treatment-and-research/
Smart Cells	https://international.smartcellsbaby.com/our-transplants/
Viacord	http://www.viacord.com/why-bank/benefits-of-cord-blood/index.aspx
Vita 34	http://www.secuvita.es/trasplantes-de-exito/

Table 3. Indications for the use of umbilical cord blood-derived stem cells for transplantation and regenerative medicine purposes

Transplantation	Regenerative medicine[a]
Bone marrow failure syndromes	**Neurological disorders**
Aplastic anemia	Acquired hearing loss
Fanconi anemia	Acute disseminated encephalomyelitis
Diamond-blackfan anemia	Apraxia
Congenital dyserythropoietic anemia	Autism spectrum disorder
Dyskeratosis congenita	Brain injury
Hemoglobinopathies	Cerebellar ataxia
Thalassemia, not specified	Cerebral palsy
Beta thalassemia	Developmental delay
Alpha thalassemia	Dysgenesis of the corpus callosum
Sickle cell disease	Encephalopathy
Hemoglobinopathy, not specified	Hemiplegia
Paroxysmal nocturnal hemoglobinuria	Hydrocephalus
Histiocytosis	Hypotonia
Hemophagocytic syndrome	Hypoxia
Langerhans' cell histiocytosis	Hypoxic-ischemic encephalopathy
Hemophagocytosis	Leukodystrophy
Histiocytic disease, not specified	Krabbe disease
Immune deficiencies	Metachromatic leukodystrophy
X-linked hyper IgM syndrome	Adrenoleukodystrophy
Rare immune disorder	Pelizaeus–Merzbacher disease
Autoimmune disease, not specified	Tay-Sachs disease
Bare lymphocyte syndrome	Muscular dystrophy
CD40 ligand deficiency	Myasthenia gravis
Chediak–Higashi syndrome	Spinal cord injury
Wiskott–Aldrich syndrome	Stroke
Chronic granulomatous disease	Neurological disorders, not specified
Severe combined immunodeficiency	**Metabolic and storage diseases**
Cartilage-hair hypoplasia	Diabetes, type 1
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked	Diabetic foot[b]
Congenital immunodeficiency	Diabetes, not specified[b]
Immunodeficiency, not specified	Mucopolysaccharidosis
Common variable immunodeficiency	Osteopetrosis
Crohn's disease	Wolman disease
Disorders of the immune system, not specified	Gaucher disease
Leukocyte adhesion deficiency	Inherited disorders of metabolism
Omenn syndrome	Mucolipidosis
Primary immune deficiencies	Lesch–Nyhan syndrome
Reticular dysgenesis	Alpha mannosidosis
Thromboangitis obliterans	Neuronal ceroid lipofuscinosis
Leukemias	Sandhoff disease
Acute biphenotypic leukemia	**Other**
Acute lymphocytic leukemia	Other diseases not specified
Acute myelogenous leukemia	Wounds
Chronic lymphocytic leukemia	Hepatic cirrhosis
Chronic myelogenous leukemia	Ectodermal dysplasia
Invasive NK cell leukemia	Hepatitis C[c]
Juvenile myelomonocytic leukemia	Sepsis[d]
Leukemia, not specified	
Chronic eosinophilia leukemia	
Lymphomas	
Non-Hodgkin's lymphoma	
Hodgkin's lymphoma	
Lymphoma, not specified	
Lymphoproliferative disorders	
Myeloma	
Lymphoproliferative syndrome	
Plasma cell disorder, not otherwise specified	
Plasma cell leukemia	
Myelodysplastic/myeloproliferative diseases	
Myelodysplastic syndrome	
Myeloproliferative neoplasm	
Myelodysplastic/myeloproliferative diseases, not specified	
Essential thrombocythemia	
Polycythemia vera	
Primary myelofibrosis	
Solid tumors	
Neuroblastoma	
Medulloblastoma	
Retinoblastoma	
Cancer, not specified	
Salivary gland tumor	
Cervical cancer	
Primitive neuronal tumor	
Soft tissue cancer	
Germinal tumors	
Breast cancer	
Ewing sarcoma	
Solid tumors, not specified	
Inherited platelet abnormalities	
Congenital amegakaryocytosis	
Glanzmann thrombasthenia	
Inherited platelet abnormality not specified	

[a]Umbilical cord blood (UCB) stem cells used for regenerative medicine purposes are mainly experimental in nature with the majority of units likely to have been released for use in clinical trials.
[b]Diabetes and diabetic foot have been treated with injections or infusions of cord blood but not transplantation.
[c]Sepsis has been listed as an indication for the release of an UCB unit by Cryo-cell (Table 2; https://www.cryo-cell.com/cord-blood/banking-benefits/transplant-matrix).
[d]Hepatitis C has been listed as an indication for the release of an UCB unit by Hemafund (Table 2; http://hemafund.com/en/o-gemafond/primenenie-pupovinnoj-krovi/).

Evolving Treatment Landscape

Nearly 50,000 UCB units had been released by public banks for allogeneic transplantation purposes as of the end of 2016 (WMDA). The number of units released by private banks is unclear, but it is suggested that approximately 30 times fewer units have been released to date than from public banks [23]. From a historical perspective, UCB-HSCT started to gain momentum at the turn of the 21st century. More and more people with malignant and non-malignant hematologic disorders were being treated, and the use of UCB, particularly in the pediatric setting, was becoming well accepted. Accordingly, public, private, and hybrid UCB banks were being established globally to meet patient needs. At its peak, and during the period from 2011 to 2013, public banks held an inventory in excess of 700,000 UCB units and released approximately 4,100 UCB units per annum for allogeneic purposes (Fig. 1). Private banks in contrast have amassed nearly 4 million UCB units in inventory, but have on average released only 130 UCB units per annum for treatment [23]. When available, the data regarding the number of units released by hybrid banks is difficult to interpret. Many of the units released for private or public use are not specified under the hybrid model. Additionally, banks that offer hybrid banking are often classified as either public or private and not exclusively as a hybrid bank making it difficult to ascertain the exact number of hybrid banks.

From 2013 however, the release of UCB units decreased year-on-year, with the most recent data indicating that 3,274 units were shipped in 2016. Additionally, there has been a downturn in the number of UCB units being banked annually, resulting in a plateau in the global inventory of UCB units. Reasons for the decline are largely attributed to advances in haploidentical HSCT. In this approach, BM or peripheral blood mobilized HSPCs from a partially HLA-matched donor are used. Donors only need to be a 50% match to the recipient and are typically either the recipient's parents, siblings, or close relatives. Following transplantation, patients receive additional chemotherapy, anchored by high dose cyclophosphamide, to manage the risks of graft failure and GVHD. Given the high costs of procuring UCB units together with limitations in cell dose, and the ease with which a family member can be accessed for haploidentical transplantation, a decline in UCB-HSCT is argued to be an inevitable consequence of this procedure. An increase in haploidentical HSCT means a decrease in the need for UCB, which in turn may threaten the existence of UCB banks. This is particularly pertinent in the case of public banks, where 90% are unable to sustain themselves financially based on the sale of UCB units alone [26, 27].

The situation from a private UCB bank point of view is seemingly different. Although also impacted by the emergence of haploidentical HSCT, there has been a dramatic shift in the release of UCB units toward use for regenerative medicine purposes (Fig. 2). In fact, based on our analysis of data published by 19 of the largest private UCB banks (Table 2), over 65% of UCB units released in the last 5 years of reporting (2011–2015) have been for the treatment of non-hematological conditions. In public banks, no more than 10% of UCB units (2010–2014) were released for regenerative medicine purposes over a similar period [28–33].

These findings prompted us to investigate the scope of indications being treated with UCB. Indications were grouped into either of two treatment categories: transplantation or regenerative medicine (Table 3). Transplantation strategies included indications where UCB was used to replace or reconstitute cells of the blood and immune systems [34]. Indications are regarded as being for regenerative medicine purposes if UCB units are used to regenerate cells, tissues or organs by establishing or creating normal function after an injury or illness [34–36]. It is important to note that the use of UCB for regenerative medicine purposes is still regarded as experimental and in most cases is under investigation in clinical trials.

Our findings indicate that over 100 indications have been treated with UCB. This includes the 80 previously reported [9, 22, 23] as well as those that can be considered to be experimental in nature. We have also been able to detail the stark contrast in treatment landscapes that utilize UCB units released from public and private banks (Fig. 3). Notably, public banks have released the greater proportion of their UCB units for the treatment of leukemia (>60%), while private banks released an equivalent percentage of their inventory for neurological conditions. Conversely, public banks released no more than 7% of their units for treating neurological conditions, and private banks less than 20% for leukemia (Fig. 3). These findings are all the more striking when one considers that leukemia is the most established indication for UCB-HSCT, and although considered a valid indication, the use of UCB for neurological disease is still experimental in nature. Although many of the reported treatments exploring the use of UCB for neurological conditions have been released by public and private banks in the U.S. (Fig. 3), units have also been released from non-U.S. public banks for neurological treatment outside of the U.S. From 2010 to 2011, roughly 105 unrelated UCB units were released from CHA Medical Center Cord Blood Bank in Korea for use in a clinical trial for cerebral palsy (NCT01193660) [37], and between 2004 and 2005, eight unrelated units were used in a pilot study for cerebral palsy in Mexico [38].

Treatment of Neurological Disease with UCB

The treatment of neurological diseases and brain injury with UCB is a trend that has grown appreciably in recent years. The rationale for treating these conditions is based on arguments that UCB is able to: (a) assist in regenerating damaged brain cells; (b) reduce the inflammatory and immune responses; (c) promote cell survival; (d) induce cell migration, proliferation, and differentiation; and (e) promote angiogenesis [37, 39, 40]. UCB is a heterogeneous mixture of cells, and apart from HSCs contains mesenchymal stem cells, endothelial progenitor cells, and other stromal precursor cells [41, 42]. It has been suggested that the entire mix of hematopoietic and non-hematopoietic multipotent progenitor cells (rather than an individual sub-population) is important for improving physiological function in disease and injury of the brain [37, 42, 43]. Mechanisms other than homing and engraftment have been explored using this mixture of cells and a therapeutic benefit via paracrine signaling has been observed [44–46]. Although treating neurological conditions with UCB is still experimental, positive outcomes have been reported in children with cerebral palsy and hypoxic ischemic encephalopathy, including improved cognitive and motor function [23, 37, 39, 45–47].

There are at least 18 clinical trials investigating the use of UCB for the treatment of neurological disorders [18]. The majority are investigating the use of UCB for cerebral palsy,

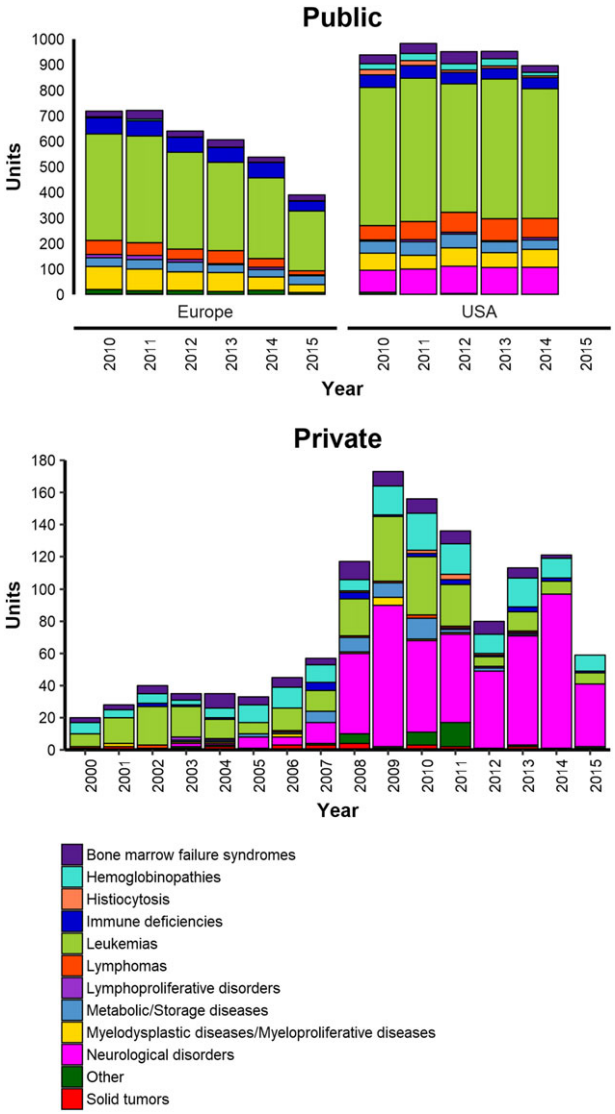

Figure 3. Indications treated with umbilical cord blood (UCB) according to disease category. Data for European public banks was obtained from a series of EBMT publications [28–32], and data for U.S. public banks from the CIBMTR ("Health Resources & Services Administration" 2016: release of 2015 data pending). Data for private banks was obtained from direct online searches of 19 private UCB banks (Table 2).

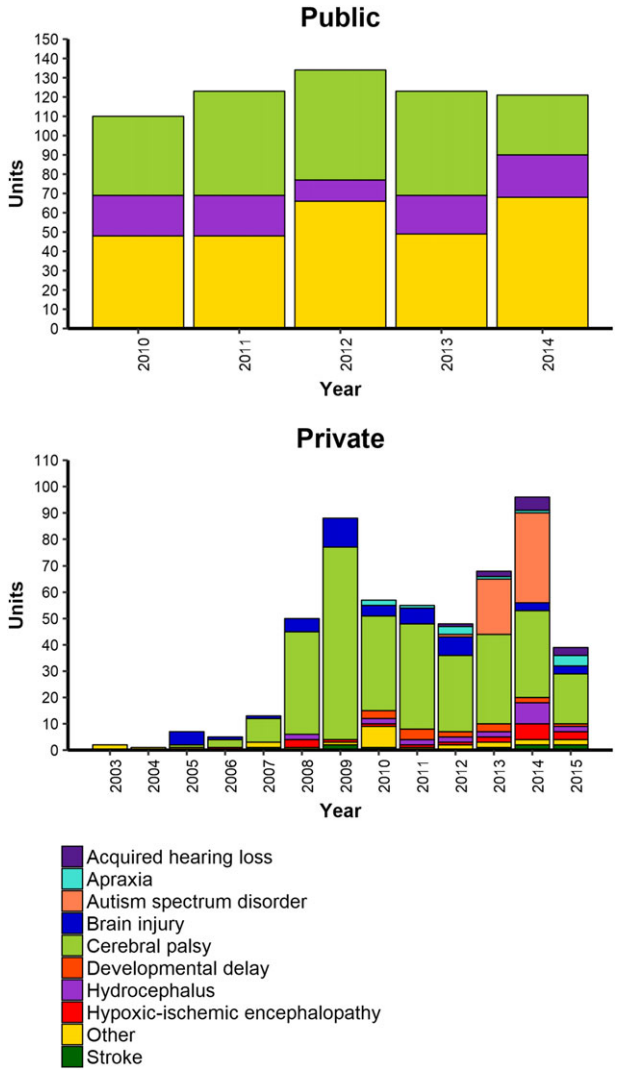

Figure 4. Umbilical cord blood units released by private and public banks for treatment of neurological conditions. Other indications including leukodystrophy and unspecified neurological disorders are not shown.

followed by hypoxic-ischemic encephalopathy and autism. As the trials draw to a close, we will gain a better understanding as to whether UCB is indeed a viable option for these patients. If favorable, the number of UCB units released for these indications will almost certainly increase [16]. Cerebral palsy makes up the greatest proportion of neurological conditions treated with UCB (Fig. 4). Approximately 30% and over 35% of UCB units were released respectively in 2013 and 2014 from private banks for autism spectrum disorder. Last, private banks have every year, since 2005, released UCB units for the treatment of hypoxic ischemic encephalopathy, brain injury, and hydrocephalus.

Summary and Outlook

The UCB industry has been influenced by a diverse range of factors. A period of rapid growth occurred as a result of the increasing acceptance of HSCT and the use of UCB as an alternative to BM-derived HSCs (harvested directly or following mobilization into peripheral blood). However, the emergence of haploidentical HSCT has resulted in a decline in the use of UCB and a plateau in global inventories. This downturn has been compensated for partially by an increase in the use of UCB for regenerative medicine purposes, albeit mostly in clinical trials. Adding to this dynamic is the question of economics. The high cost of allogeneic UCB transplantation is a challenge for many patients, which is further impacted by the FDA requirement for licensure of units in the U.S. For public banks, the cost of banking UCB units is only recovered if units are sold to HLA-matched recipients. Ongoing subsidies are thus necessary, and the fact that 90% of public banks are unable to self-sustain is clearly not conducive to growth. In contrast, private banks secure their income in advance or soon after banking UCB units, and hence sustainability is not dependent upon the sale of units. The net result is that the global inventory held by private banks exceeds four million units—nearly seven times that of public banks.

We foresee that use of haploidentical HSCT will continue to increase. This is likely to reduce UCB-HSCT and poses a significant threat to the public UCB bank industry, while the promise of regenerative medicine will remain a key driver for the growth in particular of private, but also of public UCB banks. The next decade will reveal the extent to which the use of UCB for regenerative medicine purposes will be able to turn the tide in a contracting, yet increasingly diversified treatment landscape.

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Author Contributions

C.D. and M.A.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing; M.S.P.: conception and design, fund raising, provision of study materials or patients, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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