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Early Release Paper

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Transcriptional silencing of Ets-1 oncogene contributes to human granulocytic differentiation

by Valentina Lulli, Paolo Romania, Roberta Riccioni, Alessandra Boe, Francesco Lo-Coco, Ugo Testa, and Giovanna Marziali

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Family-directed umbilical cord blood banking

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Abstract

Umbilical cord blood transplantation from HLA-identical siblings provides good results in children. These results support targeted efforts to bank family cord blood units that can be used for a sibling diagnosed with a disease curable by allogeneic hematopoietic stem cell transplantation or for research that investigates the use of allogeneic or autologous cord blood cells. Over 500 patients transplanted with related cord blood units have been reported to the Eurocord registry with a 4- year overall survival of 91% for patients with non-malignant diseases and 56% for patients with malignant diseases. Main hematological indications in children are leukemia, hemoglobinopathies or inherited hematological, immunological or metabolic disorders. However, family-directed cord blood banking is not widely promoted, many cord blood units used in sibling transplantation have been obtained in private banks that do not meet the necessary criteria needed to store these units. Marketing by private banks who predominantly store autologous cord blood units leads to public confusion. There are very few current validated indications for autologous storage but some new indications might appear in the future. Little effort is devoted to provide unbiased information and education to allow for the distinction between the different types of banking, economic models and standards involved by such programs. In order to provide a better service for families in need, directed-family cord blood banking activities should be encouraged and closely monitored with common standards and better information on current and future indications.

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Introduction

Since 1988, umbilical cord blood (CB) has been successfully used as a source of stem cells for hematopoietic reconstitution in allogeneic hematopoietic stem cell transplantation (HSCT). The first transplant using CB was performed in a 5-year-old boy with Fanconi anemia, an inherited bone marrow failure syndrome, which can only be cured by allogeneic HSCT[1]. The mother was pregnant with a girl who was known, before birth, to be HLA-identical to her brother and not a carrier of the same genetic defect. The CB was collected and cryopreserved at birth and transplanted to the patient. More than 22 years later, the patient is alive and well with a normal hematological and immunological reconstitution provided by his donor cells.

In 1991, the first public CB bank (CBB) was established at the New-York Blood Center[2] and, in 1993, the first unrelated CB transplant (CBT) was performed in a 4-year-old child with leukemia[3]. Since then, more than 100 public CBBs have collected over 500,000 CB units (CBUs) from altruistic, free and anonymous donations that resulted in over 25,000 unrelated CBT worldwide. Most banks cooperate through international registries that list publicly banked CBUs in searchable databases such as Bone Marrow **Donors Worldwide** (BMDW), the Netcord Foundation, the National Marrow Donor Program (NMDP) and other national registries, in order to provide access to all patients in need. International accrediting bodies and governmental regulatory requirements are in place to assure that publicly available CBs meet strict rules for quality[4, 5]. Outcome data are routinely collected and available for analysis through international data registries that allow good monitoring and analysis of CBT activity and outcomes. The activity of these international registries, such as Eurocord (Figure 1), and the Center for International Blood and Marrow Transplant Research (CIBMTR) contribute to the knowledge of the use of unrelated CBT.

In contrast with the well developed public banking systems, few countries have a centralized program for family-directed CB collection and storage, which requires different procedures for the procurement of high-quality products. This approach is clinically indicated and validated in families where the mother is pregnant and has an existing child or has a known risk of having a child affected by a disease curable by allogeneic HSCT[1, 6-9]. While in public banking most pregnant woman would be qualified to donate, family-directed banking requires a more focused approach to identify the few candidates that would benefit from collection. As a result, the practice of collecting CBUs from family members specifically stored for the potential benefit of another family member with a disease curable by HSCT is not widespread. This is in spite of the fact that family-directed CBT has several advantages over unrelated CBT, including greater likelihood of survival, decreased graft-versus-host disease (GVHD) and the opportunity to re-collect bone marrow cells from the same donor in case of relapse or rejection[8, 9]. Today, CB banking for family use is mostly an indirect result of autologous banking, marketed by the private sector, to families for private CB collection and storage without any current therapeutic purpose and for potential use by the donor later in life. A CB banked in this manner may occasionally benefit a sibling. Whereas family-directed banking for allogeneic purposes does not raise ethical concerns, autologous CB banking in an *a-priori* healthy family is controversial because its value is not entirely supported by clinical evidence, despite which this has developed into a private industry predominantly used by economically advantaged families [10,11]. Discussion about the development of hybrid CBB models that could combine efforts to support all banking activities is the subject of intense controversy because of ethical, scientific, regulatory, economic and social concerns[12,13].

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The current situation of family-directed CB transplantation and banking

The Eurocord registry has identified 596 patients transplanted with related CB from 1988 to 2010 but, in contrast to unrelated CBT, the number of related CBTs has not increased year after year. Most recipients were children, and all but 29 were HLA-matched. The major characteristics of the patients and transplants are listed in Tables 1 and 2. 4- year overall survival was 91% for patients with non-malignant diseases and 56% for patients with malignant diseases (Table 3 and Figure 2). The cumulative incidence (CI) of neutrophil engraftment was 91±3% in a median of 22 days (range 12-80 days). The incidence of acute and chronic GVHD at day 100 and at 4 year was 12±3% and 13±2%, respectively (Eurocord unpublished data). In another Eurocord study, on long-term outcomes of 147 HLA-identical sibling CBT recipients with hematological malignancies, the 5-year disease-free survival was 44%[14]. Compared with HLA-identical BMT, HLA-identical sibling CBTs displayed delayed granulocyte and platelet engraftment and reduced incidence of acute and chronic GVHD, but survival was similar[15]. Although the mechanism of such GVHD reduction is not fully understood, the immunological immaturity of the newborn and the enrichment of CB in T reg cells may account for at least part of it. Though generated from family-related CBTs such clinical data, which indicated that GVHD was reduced when CB was used instead of bone marrow, were the basis for advocating HLA-mismatched CBTs and for developing unrelated CBBs and programs for HLA-mismatched transplants[16-19].

A number of studies have reported on efforts to systematically identify, collect and store CBs for family-directed use (table 4). Reed et al.[20] were the first to document the value of a focused program to collect and bank family-directed CBs from donors in families with children who have disorders curable by HSCT. CB was collected in remote sites with a kit provided by the bank. Participation was voluntary and unremunerated; 540 families from 42 different states were enrolled;. Despite the lack of experience and the heterogeneity of collection centers, the median number of cells was satisfactory, with more than 93% of the banked CBs containing enough cells for transplanting the sibling. Seventeen units (3,4%) had been transplanted. The same group published data on sibling donor cord blood transplantation in patients with thalassemia major. Thirty-two of 96 donor-recipient pairs were HLA identical and 14 (44%) received a CBT. Eleven of the 14 survived free of thalassemia after transplantation. [21]

Smythe et al.[22] have reported the 10-year experience of family-directed CB banking in the National Blood Service in England. Informed consent, CB testing, processing and storage followed the same procedures as for unrelated public CB banking. A total of 268 CBs were collected from 244 mothers. Diagnoses were hematological malignancies in 114 cases, non malignant hematological disorders in 68 cases, immunodeficiency in 44 cases and enzyme deficiency in 9 cases. . Of the matched units, 13 were transplanted. In a study limited to children with malignant diseases , Goussetis et al., in Greece, have reported a low usage rate of banked sibling CB: 48 [23]. CBs were successfully collected, but only 1 out 4 children who needed HSCT was successfully transplanted . The same authors reported their experience in 50 families with beta-thalassemia major[24]. Eight out of 12 HLA matched collections were released for CBT. All patients survived, 7/8 thalassemia free. The authors conclude that the development of directed CBB programs necessitates a policy to limit long-term storage for banked CBs with a low probability of usage. For example, CBs that are not HLA-matched to the patient or that are HLA-matched to a patient who has achieved long-term remission are unlikely to be used while banking for hemoglobinopathies increases the probability of usage to 16%. **In Italy, the family-directed cord blood banking is supported by a national program (Decreto 18 November 2009). The**

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Centro Nazionale Sangue (CNS) reported 2176 CB banked (242 were banked in the year 2010) by the Italian public bank network up to 31 December 2010, of these 129 were used for transplantation. In France, two CBBs (Hospitals Saint-Louis in Paris and Henri Mondor in Creteil) have collected 548 family-directed CBUs (unpublished data). The first banked all CBUs as requested by the patients' physicians (number collected for 437 patients: 216 leukemia, 118 hemoglobinopathies, 23 aplastic anemia, 17 immune deficiencies, 10 Fanconi anemia, 6 metabolic diseases, 5 solid tumors and 42 with unreported diagnoses), the second banked 111 CBUs mostly from siblings of patients with sickle cell disease (89 collections, i.e. 80%). Twenty-four CBTs were performed from HLA-identical sibling donors, 13 from the first bank and 11 from the second bank. Outcome was excellent: the 5-year overall survival was 83%, and 100% when considering hemoglobinopathies only. These data indicate that hemoglobinopathies are rather worthwhile indications of family-directed disease-oriented CB banking.

These studies should be contrasted with the, as yet seldom, reported experience in the use of private banking as the source of CB for either autologous or sibling use. Thornley et al. have presented data from a 2004 cross-sectional survey of 152 pediatric HSCT physicians from 57 centers in the United States and Canada[25]. The respondents reported 9 autologous and 41 allogeneic transplants using privately banked CB. In 36 of 40 allogeneic cases , the CB had been collected because of a known indication in the recipient. The indications for allogeneic CBTs were acute leukemia (20 cases), hemoglobinopathies (7 cases), Fanconi anemia (7 cases) and others (7 cases). The 9 autologous CBTs were performed in severe aplastic anemia (4 cases), neuroblastoma (1 case), retinoblastoma (1 case), Schwachman-Diamond syndrome (1 case), brain tumor (1 case) and 1 with unreported diagnosis. Few respondents stated they would choose autologous CB over alternative stem cell sources for treating acute leukemia in second remission, whereas 55% said they would choose autologous CB to treat high-risk neuroblastoma or aplastic anemia in the absence of an available donor. No respondent would recommend banking of autologous CB for a newborn when both parents are of northern European descent, 11% would recommend such banking when parents are of different minority ethnicities. Indeed, the probability of using family-directed CB for allogeneic HSCT is very low when patients have frequent, highly represented haplotypes in the large unrelated bone marrow or CB inventories, whereas the situation is quite different in families with parents of different ethnic minorities and for whom the chance of finding a suitable unrelated donor is limited. However, current results of HLA matched sibling CBT are better than when an unrelated bone marrow or CB donor is used. More recently, Rosenthal et al. have reported the successful use of banked autologous CB to treat severe aplastic anemia in 3 patients[26]. However, they note that the probability of being able to use an autologous CB is very low (4/million).

Cost-benefit analysis

The potential cost of family-directed banking can be estimated by looking at matched rates found in the published studies and estimating the average cost of CBUs banked using the data published by the Institute of Medicine (IOM) in 2004, where the costs of collecting, processing and banking for public banking are estimated. There, these costs were estimated to be approximately $1,500 per unit plus $50 annually for storage. The IOM estimates reflect costs of collecting, but not of processing units determined to be unsuitable for collection prior to any processing and the costs of HLA typing for all banked units. Family-directed banking would likely incur lower per-unit banking costs as units of smaller size would be acceptable for banking and HLA testing would only be done at the time of

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potential need. The estimated costs per unit used are consistent with graft acquisition costs for unrelated donors when costs of donor screening, testing and selection are taken into account.

According to Rosenthal et al.'s 2011 study[26], the cost for the first year private storage, including collection, shipping and storage fees, varies in the United States from $1993 to $2195 plus an annual storage fee of $125. Of more than 355,000 CBUs stored in two large private banks, 77 were used for allogeneic HSCT and 32 for autologous HSCT, the average cost of the CBU used would then be over 100 times that of an unrelated bone marrow or CB product.

Kaimal et al.[27] have investigated the cost-effectiveness of private CB banking relative to no banking. They conclude that private banking is not cost-effective because it costs an additional $1,374,246 per life-year gained. In sensitivity analysis, if the cost of CB banking is less than $262 or the likelihood of a child needing a HSCT is greater than 1 in 110, private banking becomes cost-effective. They conclude, thus, that private CB banking is cost-effective only in families with children with a very high likelihood of needing a HSCT.

Indications of family-directed CB banking is now limited to children with hematological malignancies, genetic disorders or acquired aplastic anemia. If a genetic disease is the indication for HSCT, the chances of a sibling being a non-carrier and HLA match range from 1:8 to 1:16 depending on the inheritance of the genetic condition. In some diseases (e.g., hemoglobinopathies) matched carrier siblings are appropriate donors, but in others (e.g., inherited metabolic disorders) they cannot be utilized. In the United States, the annual incidence of ALL in children aged 0-19 years is estimated at 30.6/million for Caucasians and 15.9/million for Afro-Americans. The annual incidence of severe aplastic anemia is estimated at 3/million and that of high-risk neuroblastoma which can be treated by autologous transplant at 3 to 5/million[25]. Moreover, parents considering family banking in the absence of a patent indication should be informed of the remote likelihood that a CB will be used for the donor child or another family member. It should however be noted that these considerations are based on current hematological indications without taking into account the potential use of CB in non-hematological diseases. Indeed, several studies are exploring the possibility to treat infants with cerebral palsy or type 1 diabetes using autologous CBTs[28] (www.**clinicaltrials**.gov). If current clinical trials are successful, directed CB banking may become more and more cost efficient as new indications appear.

Discussion

Efforts to expand family-directed banking have to take into account alternatives to sibling CBT as well, especially in non-malignant settings when HSCT could be delayed, one being the use of a sibling bone marrow. This approach is less expensive than a CBT and has shown good clinical results; however the process of graft acquisition, although safe, is not harmless in a very young donor. Moreover, the delay of the transplant and the potential for other complications or the possibility that the sibling donor may not otherwise be fit to donate when needed should also be considered. CB collection is harmless for the baby and the mother and does not raise any ethical concern[11], while one should consider the possible side effects of bone marrow or peripheral blood collection for mobilized hematopoietic stem cells in young children, which to our knowledge have not yet been evaluated. Moreover, in some cases, the patient cannot wait long enough for the donor's bone marrow to be safely collected, e.g. when HSCT is indicated for leukemia, aplastic anemia or a hereditary disorder such as severe combined immunodeficiency, osteopetrosis or mucopolysaccharidosis. In all these cases, the current alternative options, in the absence of a matched related or unrelated donor, are to propose a haploidentical family hematopoietic stem cell

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bone marrow or peripheral blood transplant or a mismatched unrelated cord blood transplant whose results are clearly less favorable than an HLA matched sibling cord blood transplant.

Family-directed CB banking may have other advantages . For instance, CB usage may be the only practical option available in developing countries where infant mortality is high and the risks associated with bone marrow collection and/or insertion of central venous access for obtaining mobilized hematopoietic stem cells in the peripheral blood are a concern. Where the risk of acquired infectious diseases such as hepatitis or HIV infection is present, collection of the CB may also be the best way to limit or prevent the risk of transmission of infectious diseases since testing of the CBU for these diseases can then be done to assure no transmission. **However, it is important to be aware that in this context, a transplant program would only be feasible if the necessary basic healthcare infrastructure (e.g. vaccination, air, water quality, nutrition, etc) and education is well established to ensure quality and safety.** Hemoglobinopathies are indeed the main indications of CBT in many developing countries and, even though data on the cost of CB banking and transplantation in these countries is unknown, and could vary from country to country, one can speculate that the cost of CB HSCT might be acceptable compared with life-long complications, iron chelation or the cost of bone marrow procurement. If a cost-effective way can be found to identify a matched CB, this could permit to extend use of this therapy to such countries. Costs might even be decreased by the development of dedicated centers for treatment of hemoglobinopathies in developing countries where the cost of labor is lower than in developed countries. The use of reduced intensity conditioning regimens and protocols of supportive care adapted to the local situation might decrease the cost even further.

Further effort should be made to determine whether a national high-quality program of sibling CB banking can be maintained at relatively low cost despite logistical difficulties of organizing collections from many hospitals and issuing CBs for transplantation to diversely located transplant centers Growing recognition of the benefits of family-directed banking has resulted in programs to more systematically test the cost and benefit of this approach. These include a pilot program currently underway in the United States, sponsored by the Department of Health and Human Services and administered through NMDP, which involves the development of promotional materials and campaigns to create awareness of the value of directed donation banking. Five public banks and one family bank participate under agreements to collect, store and bank units that meet the program criteria. The processes applied to these CBs are almost identical to those applied to public units. Many private banks also offer this service for free for families in need. These should be encouraged but only if they are pursued consistent with the goal of banking high quality units[29]. Most private banking is not subject to the same regulatory oversight that public banks are required to meet. For instance, in the United States, autologous banks are not required to be licensed. Voluntary accreditation may address the lack of regulatory oversight but many autologous banks do not seek accreditation through Fact-Netcord, the standard for public banks that has been adopted in many European countries as well as in Australia and Canada. Specific criteria for family-directed banking have been established by Fact-Netcord but few existing private banks are Fact-accredited. Accreditation is also available through the American Association of Blood Banks (AABB) or other national accreditation bodies.

In order to find a compromise, public-private hybrid banks models are currently extensively discussed[10-13]. One driver for these models is to improve the financial viability of the CBBs. A number of models for combined banking have been developed including joint marketing of separate banking

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operations, opportunities to split units for private and public use, and the offer to bank units as either public or private initially, but with the potential of converting their status at a later date or event. To be useful to families, these new approaches will need to more rigorously adopt and apply accreditation standards, improve the accuracy of their informed consent, share benefits to help research on CB cells and offer free sibling banking when there is a clear indication for allogeneic HSCT. In order to be able to transfer some private units to the public inventory a WMDA policy statement on the combined private and public banking of CB and other related products has been established (www.worldmarrow.org). Many families with children affected by hematological malignant disease or a hereditary disorder have subsequent children. However, births are scattered among hospitals that may lack the infrastructure required to collect or bank locally and may often be collected in hospitals that are not accredited for collection, unlike CBUs collected by accredited maternity units[26]. Efforts to improve the quality of collections will, thus, be an important part of any program to collect family-directed units . Optimal policies, procedures and indications are not clearly established for use in these routine birthing center. Information should state clearly that banking CB does not guarantee that the cells will provide a cure or be applicable for every situation. [29]. Medical treatments using family banked cord tissue are in early research and are not available today; there is no guarantee that therapies will be developed in the future. Gene and cellular therapies for various disorders including thalassemia or severe combined immunodeficiency syndrome show promising results[30, 31]. In the future, prenatal diagnosis may identify patients who may benefit from gene therapy using their own CB. In this case, gene-modified CB cells could be infused early in life avoiding the treatments and complications related to these diseases. Pre-implantation genetic testing has been approved in many countries to ensure that a pregnancy will result in a child free from a serious inherited disorder and HLA-identical to his sibling, candidate for an allogeneic HSCT. This practice will increase the probability of finding an HLA-identical sibling donor and so the number of sibling CB collections is likely to increase[32]. The potential scope of medically indicated family-directed CB banking is considerable (Table 5). **Another important factor using family-directed CBU is that the unit could be combined with different sources of stem cell such as BM from the same donor, in case it is needed. Up to date there are over 100 transplants reported to Eurocord, using related CB in combination with BM for malignant and non malignant diseases.** In the future, some non-hematological diseases might be treated with allogeneic or autologous cells[33]. Continuing academic research and help from the industry for the development of new products and for the implementation of worldwide regulation rules will regulate and guarantee the quality, safety and potency of the CB market on the basis of new scientific and clinical protocols and rigorous clinical trials.

Conclusion

The use of CBUs for allogeneic HSCT has saved many lives all-over the world and hold great promise to benefit many more. The current practice and approach to CBB, both public and private, are overlooking an important opportunity to provide an optimal cell source for families where there is a possibility to collect CB for a sibling with a known condition that would benefit from a related CBT. For this purpose private banks should meet the same standards, quality control and accreditation requirements as those required for public cord blood banking. Outcomes can be improved and more lives saved through a more organized approach to identify and collect CB for family-directed uses.

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Authorship and disclosure

Conflict of interest statements (see COI)

Pr Eliane Gluckman and Pr Joanne Kurtzberg are member of the scientific committee of Cord-use.

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Authors contribution

Eliane Gluckman is the corresponding author, she is president of Eurocord, member of the Board of Netcord and President of WMDA, she had access to all the data, wrote the manuscript, submitted and got approval from the coauthors and wrote the final version of the manuscript after collecting co authors comments.

Annalisa Ruggeri is member of Eurocord, she collected and analyzed the data of related cord blood transplants collected by Eurocord and help for the writing and editing of the manuscript

Vanderson Rocha is the medical Director of Eurocord, he helped analyzing the data and write the manuscript and gave his final approval

Etienne Baudoux is President of Netcord Foundation, he helped for the design of the study, the writing and gave the final approval

Michel Boo is member of NMDP and WMDA, he helped for the design of the study, the writing and gave the final approval

Joanne Kurtzberg is member of Netcord, WMDA and NMDP, she helped for the design of the study, the writing and gave final approval

Kathy Welte is member of NMDP, chair of the cord blood working group of WMDA, she helped for the design of the study, the writing and gave final approval

Cristina Navarrete is member of the Board of Netcord, Co-chair of the cord blood working group of WMDA, she helped for the design of the study, the writing and gave final approval

Suzanna M van Walraven is chair of the ethics committee of WMDA, she helped for the design of the study, the writing and gave final approval

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List of tables and figures

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Table 1. Disease and transplant characteristics of patients treated with family CB transplants (n=596) (Eurocord unpublished data)

Characteristics	**Median or N**	**Min – Max or %**
Male gender	331	56%
Age, in years	6	1 – 50
Weight, in kg	19	3-86
Previous transplant	34	6%
Malignant diseases	**255**	
-Acute leukemia	187	31.5%
-ALL	*140*	
-AML	*47*	
-Myelodysplastic syndrome	26	4.5%
-Chronic myeloid leukemia	21	3.5%
-Lymphoproliferative disorders	11	2%
-Non Hodgkin lymphoma	*9*	
-Hodgkin lymphoma	*2*	
-Solid tumour	10	2%
Non-malignant diseases	**341**	
-Aplastic anemia	92	15.5%
-Fanconi anemia	*36*	
-Haemoglobinopathies	193	32.5%
-Thalassemia	*145*	
-Sickle cell disease	*48*	
-SCID	36	6%
-Metabolic diseases	15	2.5%
-Other	5	1.5%
Type of transplant		
-Single CB unit	474	79.5%
-Single CB unit + bone marrow (same donor)	110	18.5%
- Single CB unit+ other SC source	12	2%

Abbreviations: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; SCID: severe combined immunodeficiency; SC: stem cells

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Table 2: Donor and **transplant** characteristics of patients treated with family CB transplants (Eurocord unpublished data)

Characteristics	**Median or N**	**Min – Max or %**
Storage time of the CB unit, in months	7	0 – 162
Total nucleated cells at infusion (10^7/kg)	3.9	1-20
Total CD34+ at infusion (10^5/kg)	1.5	1-30
ABO compatibility		
-compatible	262	66%
-minor incompatibility	50	13%
-major incompatibility	83	21%
Sex-matched (CB/patient)	292	51%
Conditioning regimen		
-reduced intensity	59	12%
-myeloablative	422	88%
-with TBI	*132*	
-with busulfan (or treosulfan)	*290*	
Use of anti-thymocyte globulin	175	38%
GVHD prophylaxis		
-none	8	2%
-CsA alone	275	55%
-CsA + steroids	62	12%
-CsA + MTX ± steroids	111	22%
-Other	45	9%

Abbreviations: TBI: total body irradiation, CsA: cyclosporine A, MTX: methotrexate

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Table 3. Outcomes after family CB transplant (n=519) (Eurocord unpublished data)

Outcomes	**N or %**
Follow-up in months, median (range)	48 (3-248)
Neutrophil recovery	477/519
Time in days, median (range)	22 (12-80)
Cumulative Incidence at day 60 (%)	91±2%
Acute GvHD	71/519
Grade 0-1	448 (86%)
Grade II	52 (10%)
Grade III	15 (3%)
Grade IV	4 (1%)
Cumulative incidence at day 100 (%)	12±2%
Chronic GVHD	46/451
Limited	38
Extensive	8
Cumulative incidence at 4 years (%)	13±2%
Overall Survival at 4 years (%)	75±2%
Malignant diseases	56±4%, n=188/218
Non-malignant diseases	91±2%, n=259/301
Non relapse mortality at 4 years (%)	8±2%
Cause of death	111
Relapse	62
Transplant-related cause	44
Unknown	5

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Table 4.Number **of family directed cord blood units stored and transplanted**

Ref	Units banked	Units used	Diagnosis
Reed[20]	540	17	Data not reported
Smythe[22]	268	13	Thalassemia, n=7 Acute lymphoblastic leukemia, n=3 Bone marrow failure syndromes, n=3
Goussetis[23]	48	1	Acute Leukemia, n=1
Goussetis[24]	50	8	Thalassemia, n=8
Italy (CNS data)	2176	129	Data not reported
France (unpublished data) Hospital Saint Louis	437	13	Acute leukemia, n=4 Immune deficiency, n=3 Thalassemia, n=2 Chronic leukemia, n=1 Fanconi anemia, n=1 Metabolic disease, n=1 Unknown, n=1
France (unpublished data) Hospital Henri Mondor	111	11	Sickle cell disease, n=9 Thalassemia, n=2

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Table 5. **Indication of family-directed cord blood use in developed countries**

Indication	Validated	Investigational
Diseases	Hematological: -Acute Leukemia -Lymphoma -MDS/MPD -Inherited and acquired bone marrow failure syndrome -Hemoglobinopathies -Immune deficiency -Metabolic diseases -Solid Tumors	• Non Hematological -Cerebral palsy -Diabetes -Hearing loss • Immunotherapy for infectious disease or against tumors • Gene therapy
Source	Cord Blood	Cord Blood Umbilical Cord Placenta
Type of cells	HSC	HSC Lymphocytes MSC IPSc
Quality and safety	Supposed good quality if in **experienced** local hospitals	Unknown

Abbreviation: MDS/MPD: myelodysplastic syndrome; myeloproliferative disordes; HSC: Hematopoietic stem cells; MSC: mesenchymal stromal cells; IPS: induced pluripotent stem cell.

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Figure 1. Number of related and unrelated cord blood units provided per year, n= 6805 (Eurocord data)

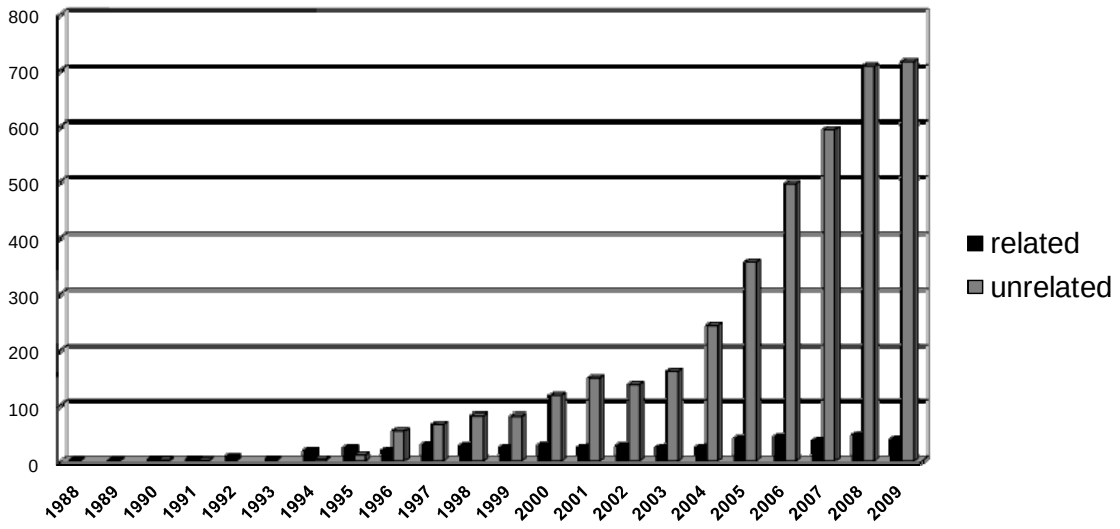

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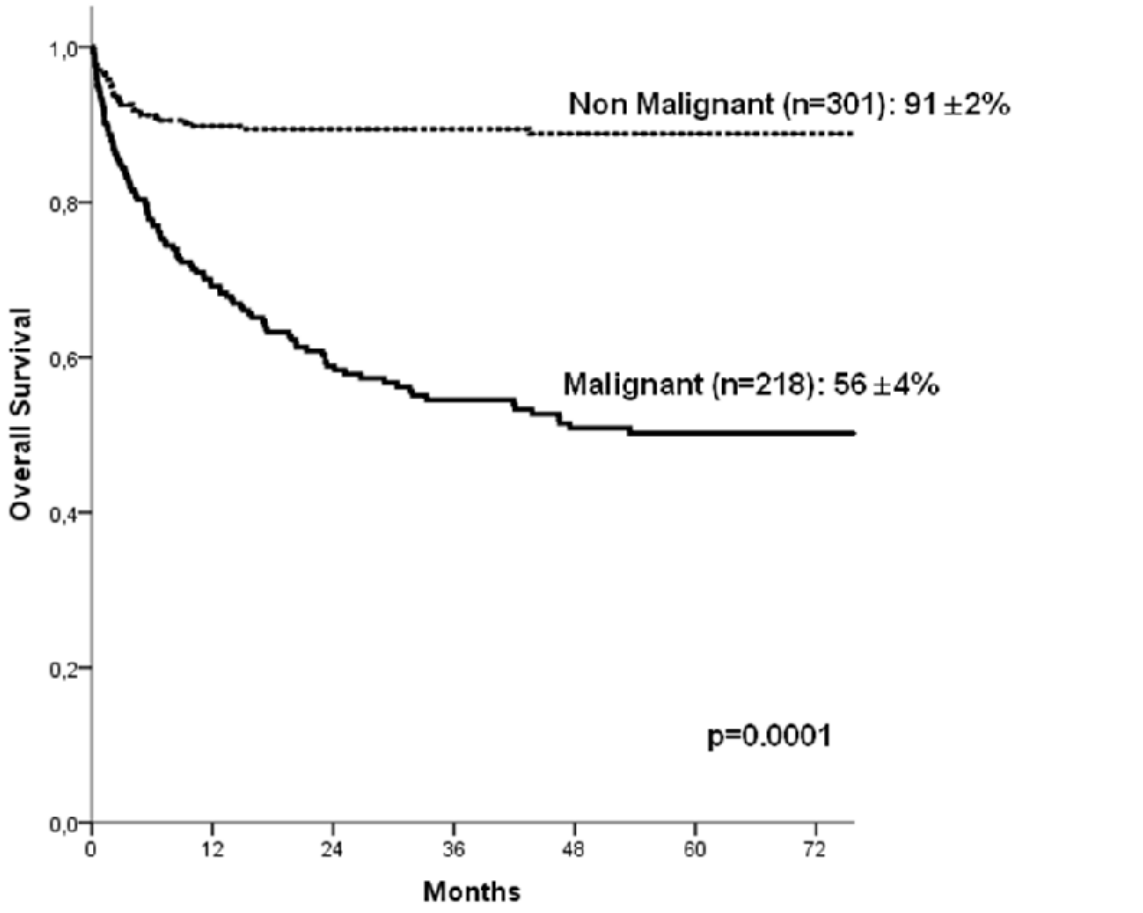
Figure 2. Overall survival at 4- year after related CB transplants (n=519) according to disease category (Eurocord unpublished data)



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Est. de Campinas / Bulgaria - Sofia : Children`s Onco-hematology Hospital / Croatia - Zagreb: University Hospital Center Rebro / Czech Republic - Prague: University Hospital Motol / Denmark - Copenhagen: Rigshospitalet / Finland - Helsinki: University of Helsinki, Hospital for Children & Adolescents / France – Angers : Centre Hospitalier Régional d'Angers / Besançon : Hôpital Saint Jacques / Bordeaux : Hôpital Haut-Lévêque, , CHU Bordeaux Groupe Hospitalier Pellegrin-Enfants / Clermont-Ferrand : Hôtel Dieu CHU/Jean Perrin / Créteil : Hôpital Henri Mondor / Grenoble : Tronche CHU-Albert Michallon / Lille : Claude Huriez / Lyon – Hôpital Debrousse (pédiatrie) / Marseille : Hôpital d'Enfants de La Timone / Nancy : Hôpital de Brabois / Nantes : Hôtel Dieu / Nice : Hôpital de l'Archet / Paris : Hôpital Necker (adulte), Hôpital Necker Enfants Malades, Hôpital Saint-Louis, Hôpital Robert Debré / Poitiers : Hôpital Jean Bernard / Rennes : Hôpital de Pontchaillou / Rouen : Hôpital Charles Nicolle (pédiatrie) / Saint-Etienne : Hôpital Nord Institut de Cancérologie de la Loire / Strasbourg : Hôpital de Hautepierre (pédiatrie) / Germany - Berlin : Charité-CVK, University Medicine Berlin / Dresden: Universitaetsklinikum Dresden / Düsseldorf : Universitaetsklinikum / Essen: University Hospital, Dept. of Pediatric Hematol./Oncol / Hannover: Hannover Medical School / Heidelberg: University of Heidelberg / Jena : University of Jena / Munich: Klinikum Grosshadern / Tübingen: Universität Tübingen, Medizinische Klinik / Ulm : Universitaet Ulm / Greece - Athens: St. Sophia` Children`s Hospital / Patras: Patras University Medical School / Hungary - Budapest: St. László Hospital, St. István / Miskolc: Postgraduate Medical School / India - Chennai: Apollo Speciality Hospital / Iran - Teheran: Shariati Hospital / Ireland - Dublin: Our Lady`s Hospital for Sick Children / Israel - Haifa: Rambam Medical Center / Jerusalem: Hadassah University Hospital / Petach-Tikva: Schneider Children`s Medical Center of Israel / Tel-Hashomer: Edmond & Lily Safra Children`s Hospital, Chaim Sheba Medical Center / Italy - Bologna: Azienda Ospedaliero-Universitaria di Bologna / Brescia: Universitá degli Studi di Brescia / Genova : Ospedale San Martino, Department of Haematology II, Institute G. 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Relevant website: www.worldmarrow.org, www.marrow.org, www.bmdw.org, www.eurocord-ed.org, www.netcord.org, www.factwebsite.org, www.cibmtr.org.