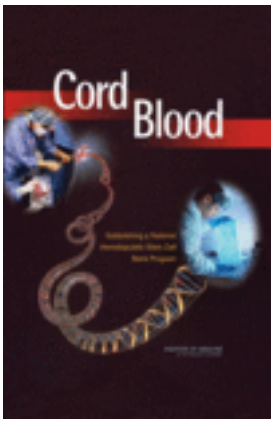

Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program

Committee on Establishing a National Cord Blood Stem Cell Bank Program, Emily Ann Meyer, Kathi Hanna, and Kristine Gebbie, Editors

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Cord Blood

Establishing a National Hematopoietic Stem Cell Bank Program

Committee on Establishing a National
Cord Blood Stem Cell Bank Program

Board on Health Sciences Policy

Emily Ann Meyer, Kathi Hanna, and Kristine Gebbie, *Editors*

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Nancy Ascher, Professor and Chair of the Department of Surgery, University of California, San Francisco, and Enriqueta Bond, President, Burroughs Wellcome Fund, Research Triangle Park, North Carolina. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

PREFACE

An effective National Cord Blood Stem Cell Bank Program should take into account current and future science; the needs of patients, physicians and donors; quality assurance; and outcomes assessment. Balancing of all these perspectives presents a substantial challenge, and tensions among current organizations active in the field led, in part, to the request for this report from the Institute of Medicine and formed a background for all of the committee's information gathering and deliberations.

The small number of extremely knowledgeable specialists in this field—many of whom have very close ties to at least one of the major participants in the organizational debate—meant that in order to ensure inclusion of all important perspectives on equity, access, and outcomes, membership on the committee changed several times. Although the changes ensured an extremely rich range of viewpoints, it may have confused some observers.

The following truths regarding cord blood collection and transplantation became apparent at the first meeting and informed the committee's discussions and recommendations throughout the study:

- The goal of ensuring the best care for patients requires that transplant physicians be provided with timely, complete, and accurate information on available hematopoietic stem cells from both adult donors and umbilical cord blood at the time of decision making about a transplant. Information about bone marrow donor programs and experiences had to be considered.

- Quality assurance for the collection, storage, and use of cord blood is essential, as is a coordinated approach to the collection of complete information on the outcomes of all hematopoietic stem cell transplants.

The committee appreciates the generosity of the many bankers, transplant physicians, transplant recipients, and scientists who shared their experiences and data during open meetings and site visits and in correspondence with the committee. Invaluable knowledge was gained, none of which could have been fully assimilated without the assistance of the very able staff supporting this report.

Finally, a fully coordinated quality national system to support hematopoietic stem cell transplantation cannot be accomplished by any one action or organization. This report includes both a discussion of what such a system should look like when it is complete and focuses on the key steps that respond to immediate concerns and move toward the long-term goal. The interested community is urged to keep the goal of comprehensive support for hematopoietic stem cell transplantation in mind while struggling with the inevitably messy process of arriving at that point. The committee's overall goal of a seamless program of access to hematopoietic stem cells points directly to a single national program encompassing the existing marrow donor programs and this cord blood program. Providing meaningful recommendations on how to accomplish such a program, however, would have required study of the existing National Marrow Donor Program and other adult hematopoietic progenitor cell programs and the ways to merge them with the specifics of a cord blood program well in excess of the time and resources available to the committee. For that reason, the report highlights the need for coordination at many points, expects analysis of outcomes from all sources of cells, leaves the door open to contractual arrangements with core components of the existing program when consistent with policy direction, and anticipates that the question of full integration will be dealt with in the future.

Kristine M. Gebbie
Chair

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The committee wishes to acknowledge the valuable contributions that were made to this study by many individuals who shared their expertise with the committee. Special thanks go to James Burdick, Shelly Carter, Jeffrey Chell, Phil Coelho, Dennis Confer, Jeff Couglin, Michael Fitzpatrick, Captain Robert Hartzman, Liana Harvath, Valerie Hurt, Brent Jaquet, Naynes Kamani, Joanne Kurtzberg, Ellen Lazarus, David Leitch, Pam Murph, Sudip Parikh, Pablo Rubinstein, Karen Shoos-Lipton, Edward Snyder, Cladd Stevens, Susan Stewart, Phyllis Warkentin, Jill Warner, Elizabeth Wagner, and Thomas Weignand.

We would also like to thank the following banks, which graciously allowed the committee to tour their facilities: CyroBanks International, New York Blood Center, Children's Hospital Oakland, Cord Blood Registries, St. Louis Cord Blood Bank, J.P. McCarthy Cord Stem Cell Bank, and Michigan Community Blood Centers Cord Blood Bank.

The committee would also like to thank the commissioned paper authors, whose contributions assisted greatly in the understanding and thorough evaluation of the subject: Karen Ballen, Robert Gibbons, Margaret Goodell, David H. Howard, and Carolyn Katovich Hurley.

Thanks also go to Siddarth Puram, who worked as an intern the summer of 2004 and provided extensive help in compiling and summarizing literature and in the development and distribution of the cord blood bank survey.

Finally, the committee would like to thank Philip Pizzo and the Board on Health Sciences Policy for their oversight and the IOM staff: Judy Estep,

Shira Fischer, Benjamin Hamlin, Emily Ann Meyer, Andrew Pope, and Andrea Schultz for their support in the coordination of this project.

The contributions of Kathi Hanna, who served as a consultant to the committee, are greatly appreciated.

CONTENTS

List of Tables, Figures, and Boxes

TABLES

FIGURES

BOXES

Cord Blood

Executive Summary

Umbilical cord blood, like bone marrow and mobilized peripheral blood, is rich in potentially life-saving stem cells called hematopoietic progenitor cells (HPCs). When they are transplanted, HPCs are effective for the treatment of blood disorders (e.g., leukemia, selected metabolic disorders and immunodeficiencies, and sickle cell anemia) and in recent years have been transplanted to more than 25,000 people in the United States alone. Increasingly, these transplants are performed with HPCs derived from cord blood.

Recognizing the need for a national system for the collection, distribution, and use of cord blood, the U.S. Congress asked the Institute of Medicine to review the options for such a system and to make recommendations on the ideal structure of a national program.

In its considerations, the committee was guided by two overarching goals: (1) easing access to timely, complete, and accurate information on the HPCs available from cord blood donors at the time that the physician is making the decision about the transplant, and (2) ensuring the best possible quality of the cord blood units that were to be used by patients.

The committee reviewed the available data and conducted original analyses of the data collected by the National Marrow Donor Program (NMDP), The National Cord Blood Program of the New York Blood Center (NYBC), and the Cord Blood Banking and Transplantation (COBLT) study of the National Heart, Lung,

and Blood Institute. The analysis confirmed the hypothesis transplants matched with the recipient for four of six human leukocyte antigens (HLAs) is not as effective those matched at six of six antigens. The study also demonstrated that, with increased cell dose, a five of six match has survival rates almost identical to that of a six of six match.

The committee proposes the creation of a National Cord Blood Stem Cell Bank Program. The committee makes specific recommendations for the organization and administration, data management, and quality control in the national program that would best serve the needs of both the donors and the patients requiring stem cell transplants.

Stem cells, a primitive type of cell found in all animals, are capable of both self-renewal and differentiation into more specialized cells. These capacities offer great potential for regenerative medicine. This report recommends the development of an integrated system for the therapeutic use of one specific type of stem cell found in humans, the hematopoietic progenitor cell (HPC), which is a multipotent stem cell responsible for the continual production of the diverse array of normal blood cells. Because of the potential of HPCs to reconstitute bone marrow and peripheral blood, they have been used for the treatment of patients with bone marrow damage from either chemotherapy or underlying hematological failure for several decades.

HPCs can be obtained from a variety of sources including bone marrow, mobilized peripheral blood, and umbilical cord blood collected from the placentas of recently delivered infants. HPCs obtained from cord blood appear to have some advantages over HPCs obtained from bone marrow or peripheral blood. Among them, immune cells from umbilical cord blood are less mature[1] than those from other sources, so their transplantation results in a lower risk of graft-versus-host disease, a common immune response to transplantation that can be fatal. In addition, cord blood is readily available, carries a low potential for infectious disease transmission, and involves minimal risk to the mother or the infant at the time of collection.

Because of these advantages over bone marrow, cord blood has the potential to be an excellent resource, opening up the possibility of transplantation to patients who either can not find a human leukocyte antigen (HLA) match within the bone marrow donor pool, or who are too ill to be able to wait for the sometimes lengthy process of searching and then har-

[1]Due to differences in T cells and other differentiated cells of the immune system.

vesting bone marrow from living adult donors. By increasing both the size and quality of the cord blood inventory, nearly 90 percent of all patients who need a transplant should be able to find a suitable HLA match in either the marrow or the cord blood inventories.

Over the past few decades, HPCs obtained from cord blood have been shown to be a suitable alternative to adult bone marrow or peripheral blood in transplants for the treatment of leukemia, lymphoma, aplastic anemia, and inherited disorders of immunity and metabolism. Additional research is required to clarify whether cord blood is as good as or superior to other HPC sources in all of these situations. Factors already shown to influence the outcome of cord blood transplantation include the number of HPCs in the unit of blood, the body size of the transplant recipient, and the degree of HLA mismatch between the donor and the recipient, which increases the likelihood of a poor transplant outcome.

IN SEARCH OF A MATCH

An appropriate HLA match is important for all types of HPC transplantation, regardless of the graft source. The number of patient candidates for an HPC transplant is estimated to be 11,700 annually; of those, only a small percentage have an HLA-identical living sibling donor, generally considered the best HPC source. In an attempt to make HPCs more widely available to the large number of patients who do not have an HLA-identical sibling, large international volunteer adult (bone marrow and peripheral blood) donor registries were created in the 1980s. Today, more than 9 million registered adult donors are listed in more than 40 registries worldwide. However, despite the large numbers of adult donors recruited over the past two decades, registries and transplant physicians still face several challenges, including:

- an inability to identify fully or closely matched HLA donors for a significant proportion of transplant candidates, particularly non-Caucasian individuals;
- permanent or transient unavailability of some potential donors, even if that individual was identified in a registry on the basis of HLA match;
- the prolonged interval between the time of a search request and the time of HPC acquisition (the currently reported median time is greater than 4 months); and
- risks associated with bone marrow and peripheral blood donation.

Several groups have recognized that larger and more accessible cord blood collections could resolve several of these issues, in part, because of the relative ease and safety of acquisition of cord blood and the potential to

obtain cells from a broad cross-section of the population and the ability to have successful transplant outcomes with a somewhat greater degree of HLA mismatch than with adult HPCs. As a result, at least 40 cord blood banks exist at present in the United States. Of these, approximately half store donations for use for transplantation between unrelated donors. These cord blood units are typed and stored anonymously for use by any patient who might have a medical need for them. The remaining banks are private banks, meaning that they store cord blood at the expense of the donor's family for potential future use only by the donor or a member of the donor's family. Such use could be allogeneic (i.e., for someone else), to treat a sibling of the donor, for example, or it could be autologous, meaning that the cord blood cells would later be used to treat a condition in the child from whom the cord blood originally was obtained.

THE CHALLENGES OF A FRAGMENTED SYSTEM

The proliferation of cord blood banks has raised questions related to accessibility; the adequacies of the cord blood inventories; the standardization of cord blood collection, processing, and storage methods and documentation; and quality control. Although independence can lead to innovation, it can also lead to inconsistency in cord blood quality from bank to bank, and the need for transplant centers to use different methods of accessing, thawing, and processing units received from different banks. In addition, most banks have developed practices and procedures independent of any consistent quality assurance or regulatory oversight, although many banks are accredited by independent organizations.

The lack of a single outcomes database has thwarted the scientific community's ability to determine best practice guidelines. Currently, outcomes are tracked by individual cord blood banks with varying degrees of success, dependent on resources and transplant center compliance. Furthermore, absence of a standard search format, differences in levels of HLA typing from bank to bank and between cord blood and adult donor registries, and the requirement for multiple searches to independent cord blood banks or consortia of cord blood banks at least in part reflects the fragmentation of the system. Reflecting the desires of the end user transplant centers, some aspects of the search process have become more uniform over time. However, other hindrances still exist—most notably, the lack of access to all transplant data.

Recognizing the potential contributions of umbilical cord blood transplantation and the need for a system that better serves patients, in the 2004 appropriations bill for the U.S. Department of Health and Human Services (DHHS), the U.S. Congress provided $10 million for the establishment of a National Cord Blood Stem Cell Bank Program under the leadership of the

Health Resources and Services Administration (HRSA). Although there is agreement on the need for a national program, there are major differences in perspectives as to how this goal might be accomplished with regard to governance, database management, unit selection processes, sources of material, financing and competition, standards, and other issues.

BACKGROUND OF THIS STUDY

The Congress's 2004 $10 million appropriation for the establishment of a National Cord Blood Stem Cell Bank Program recognized the different views on how such a program might be established. A portion of that appropriation was allocated to the Institute of Medicine (IOM) to provide HRSA with an assessment of existing cord blood programs and inventories and to make recommendations on the ideal structure, function, and utility of a National Cord Blood Stem Cell Bank Program. The charge to the IOM committee is as follows:

In response to Conference Report on H.R. 2673, Consolidated Appropriation Act 2004 (H. Rept. 108-401), IOM will assemble a committee of experts to conduct a study that will consider relevant issues related to the establishment of a National Cord Blood Stem Cell Bank Program within HRSA. The IOM study will make recommendations for the optimal structure for the cord blood program and address pertinent issues related to maximizing the potential of this technology (e.g., collection, storage, standard setting, information sharing, distribution, reimbursement, and research and outcome measures).

The following are among the more specific issues that the committee was asked to consider:

- What is the role of cord blood in HPC transplantation in the context of other sources of HPCs?
- What is the current status of the cord blood banks already in existence?
- What is the optimal structure for the cord blood program?
- What is the current use and utility of cord blood for stem cell transplants?
- What is the best way to advance the use of cord blood units for HPC transplantation (i.e., setting storage standards, collection procedures, information sharing, distribution, and outcome measures)?
- What is the best way to make cord blood units available for research?
- What consent procedures should be followed to obtain informed consent for both research and transplantation use?
- Should the cord blood program set practice guidelines for all banks

or just the public banks (e.g., what kind of HLA-typing would need to be done before blood goes into the cord blood bank, and how are the databases advertised)?

The IOM formed the Committee on Establishing a National Cord Blood Stem Cell Bank Program, which consists of experts in the fields of economics, HPC transplantation, outcomes analysis, biostatistics, stem cell biology, cord blood quality and standards, public health, health technology assessment, patient advocacy, ethics, and obstetrics and gynecology.

RECOMMMENDATIONS

A national program should have as its primary mission the goal to maximize access to high-quality HPC sources for patient care and research in the most efficient, cost-effective, and ethical manner possible. All committee findings and recommendations were weighed against this core mission and were developed after careful consideration of current experience with cord blood banking, the lessons learned from other organ and tissue transplant programs, and the current and potential uses of HPCs derived from cord blood. In the course of its work, the committee made extensive efforts to consider all points of view on the establishment of a national program. In the committee's view, the major parties interested in a successful cord blood program agreed on several key goals for a national program, including:

- **Simplicity.** A national program needs to avoid duplication of effort in terms of both the services provided and the steps necessary for a transplant center to access appropriate graft sources.
- **Quality.** The ultimate goal of a program should be to promote the best possible chance of patient recovery by establishing an inventory of high-quality, HLA-diverse, cord blood units.
- **Patient, physician, and donor support.** Support and education for all individuals involved in the program is an integral and necessary part of the program.

With these goals in mind, the committee developed recommendations to improve the operations of cord blood banks and banking procedures, ensure adherence to ethical standards, move toward an optimal inventory of cord blood units for a national program, create the structure and organization for a national program, and facilitate research in this area. In addition, oversight will be an important component of the functioning of a national program. In its recommendations on the structure and organization of a national program, the committee recommends that the Secretary

of DHHS establish a National Cord Blood Policy Board to set policy and advise the Secretary of DHHS and HRSA on policy regarding the donation, collection, and uses of cord blood, as well as on the research needed to improve and augment the uses of HPCs. Thus, several of the recommendations rely on the establishment of the structure proposed in Recommendations 7.1 to 7.6 (see below).[2]

Banks and Banking

Centers that collect, process, and store cord blood differ in their organization and governance as well as in their processing methods. When physicians attempt to access units for patients, they confront different search algorithms and informatics systems, depending on which bank or network of banks they search. Likewise, HLA typing requests might come to banks in different formats on the basis of different transplant center preferences.

Some federal and state laws and regulations govern the operation of cord blood banks, and many are accredited through one organization or another. Yet these rules and regulations are not standardized, and a more consistently applied set of standards would benefit both the cord blood banks and the end users. In addition, Food and Drug Administration (FDA) licensure of cord blood units will go a long way toward providing another layer of safety and quality assurance in the system and has the added benefit of creating requirements that are enforceable by law.

In addition, a single, uniform accreditation system for the evaluation and inspection of cord blood banking facilities is needed to ensure the safe and effective collection and storage of cord blood units for transplantation. Centers performing cord blood transplants should also be accredited to ensure the proper selection and thawing of cord blood units. FDA licensure of cord blood units is another means by which uniformity and high standards can be met. The committee believes that the interests of all parties would best be served if all banks, whether they are public or private, were to be licensed and were to adhere by these standards.

Finally, a particularly important barrier to the fundamental goal of unimpeded access to treatment is the fact that units in existing cord blood collections lack sufficient ethnic and racial diversity. This limits the availability of HLA types for some groups of potential recipients and indicates a need for even greater outreach to underrepresented populations to donate cord blood and for the development of innovative approaches to donor recruitment, recognizing that a deficiency in the representation of certain

[2]The numbering of the recommendations corresponds to the chapter in which they are located.

ethnic populations within cord blood inventories is due to many factors and not just recruitment.

Recommendation 4.1: ***Identify a Cord Blood Accrediting Organization.*** **The Health Resources and Services Administration should identify a Cord Blood Accrediting Organization by means of an open, competitive request for proposal process. This organization should be charged with the delineation of standards for any cord blood bank, collection center, or transplant center desiring to participate in the National Cord Blood Stem Cell Bank Program.**

Recommendation 4.2: ***Establish Uniform Standards for Cord Blood Collection.*** **Uniform standards for the collection of cord blood units without alteration of safe obstetrical practice should be established by the Cord Blood Accrediting Organization suggested in Recommendation 4.1 and should be required of all banks participating in the National Cord Blood Stem Cell Bank Program.**

Recommendation 4.3: ***Establish Uniform Quality Assurance Systems.*** **Uniform quality assurance standards and criteria should be established by the proposed Cord Blood Accrediting Organization for the collection, processing, and storage of cord blood, and adherence to these standards should be required of all banks participating in the National Cord Blood Stem Cell Bank Program. In addition, a system for the frequent performance of compliance reviews should be established**

Recommendation 4.4: ***Establish FDA Licensure of Cord Blood Units.*** **The Food and Drug Administration should move promptly to establish a system of licensure of cord blood units intended for clinical transplantation. As an interim measure until a licensure process is established, all banks participating in the National Cord Blood Stem Cell Bank Program should operate under an investigational new drug application.**

Recommendation 4.5: ***Apply Quality Standards to All Banks.*** **The committee strongly recommends that all cord blood banks, regardless of public or private status or participation in the national program, adhere to the established quality standards.**

Ethical and Legal Issues

The issues associated with the collection, storage, and use of tissue for transplantation are technical and medical, as well as ethical and legal. Donors of cord blood are not just depositing leftover byproducts of the birth process with interested researchers and physicians; rather, they are making a choice to do something that may potentially benefit another person. Some major questions the donor must fully comprehend before she

consents to donate cord blood include who has access to the cord blood unit once donated, where it will be stored, how it will be stored, how her privacy will be protected, and whether the donor stands to gain from the donation (e.g., by a future transplantation for herself or members of her family), or be harmed by the donation (e.g., subsequent discovery of information relevant to the health of the woman or her child).

Pregnant women receive a great deal of information—sometimes conflicting—about the donation process and the consequences of different types of banking. It is crucial to disclose several kinds of information to the potential donor, including who has access to the cord blood once it is donated, where it is stored, how it is stored, and how the donor's privacy is protected.

Recommendation 5.1: ***Cord Blood Centers Need Policies Regarding Who Must Provide Consent.*** **Cord blood collection centers should have clear policies about who must provide consent for donation and a plan to address paternal objections to the donation of cord blood.**

Recommendation 5.2: ***Informed Consent Should be Obtained Prior to Labor and Delivery.*** **Informed consent for the collection, storage, and use of cord blood should be obtained before labor and delivery, and after the adequate disclosure of information.**

Recommendation 5.3: ***Donors Must Be Provided with Clear Information about their Options.*** **The information provided to a donor must include a balanced perspective on the different options for banking. The information disclosed for allogeneic donation should not include language that gives the donor an impression that the unit will be available to the family after donation.**

Recommendation 5.4: ***Promote the Security of Medical Information.*** **Secure links between the medical records of the donor and the banked cord blood unit must be established to ensure the safety of transplantable products and the patients receiving the transplants. These records must be kept confidential and afforded the full protection of the law. If an abnormality is discovered during testing, the results must be delivered to the donor in a manner that is appropriate in relation to the severity of the abnormality.**

Recommendation 5.5: ***Cord Blood Donors Must Understand the Limitation of their Rights.*** **Those who collect cord blood for public banks should disclose to potential donors all possible clinical and research uses of the cord blood, and furthermore, that donation will terminate a prospective donor's ability to direct the use of the cells.**

Establishing a National Inventory

One of the largest unresolved issues in the establishment of a national cord blood program is determining how many units are needed at the national level and establishing a mechanism for projecting or estimating the need for cord blood on a continuing basis. On the basis of preliminary analyses of all existing outcome data and an economic analysis of the costs and benefits of various inventory sizes, the committee made preliminary estimates of an efficient inventory size. The committee estimates that at least an additional 100,000 new, high-quality cord blood units are needed in the national inventory. As more data are collected and as HLA match probabilities and relationships between HLA mismatch and cell dose and outcomes are reevaluated, the final inventory size will need to be determined by the proposed national oversight board (see Recommendation 7.1 below.) It is important that the determination of the final inventory size take into account clinical, policy, and economic interests.

To more clearly assess the relationship between HLA matching and the inventory size, the committee conducted its own outcomes analysis using data available from NMDP, the New York Blood Center, and the Cord Blood Banking and Transplantation study conducted by the National Heart, Lung, and Blood Institute. The committee found that a strong relationship between outcomes and both the degree of matching and the cell dose[3] in a cord blood unit, and that with a cell dose greater than 2.5×10^7 nucleated cells per kilogram of body weight needed to ameliorate the negative effects of transplanting units with one or two HLA mismatches.

Recommendation 6.1: *Establish a National Inventory Policy.* Forecasts of the required size of a national inventory of cord blood should be based on the principles of efficiency and equity for identifiable groups of patients. The program should regularly examine data on:

- **ways in which increases in cord blood inventory would benefit the length and the quality of life among potential transplant recipients;**
- **the benefits and costs per unit for identifiable groups of patients; and**
- **the effects of inventory policy on the financial viabilities of hematopoietic progenitor cell collection, storage, and distribution systems for HPCs.**

These assessments should be used by the National Board to respond to changes in need, indications, and technology for hematopoietic progenitor cell transplantation and future applications for cord blood cellular therapy.

[3]Prefreeze cell counts were used, as banks have found a large degree of variability between transplant centers in calculating postfreeze cell counts.

Recommendation 6.2: ***Continue to Conduct Outcomes Research.*** **The Health Resources and Services Administration and the National Institutes of Health should support further research directed toward understanding the relationships among inventory size, human leukocyte antigen match quality, cell dose, multiple-unit transplants, and the benefits of hematopoietic progenitor cell transplantation to the length and quality of life.**

Recommendation 6.3: ***Expand the Current Inventory.*** **Because an increased inventory size would increase the potential benefits of transplantation, the Health Resources and Services Administration should support inventory growth while it assesses the current inventory and establishes the optimal size of a cord blood unit inventory.**

The characteristics of existing units must be re-evaluated for their acceptability for transplantation by simultaneously considering both the cell dose and the degree of HLA match. The quality of the existing inventory should thus be reviewed in the context of the newly developed standards. As a result, it is likely that many existing units will be found unsuitable for clinical use based on low cell count or inadequate evaluation and storage. Resulting inventory policy should be flexible enough to support changes in the understanding of the HLA and cell-dose factors as well as evolving clinical practices (such as dual cord transplants), and should be re-evaluated on a regular basis. Finally, the current inventory should be assessed in the context of the global inventory; the harmonization of international standards will facilitate such an assessment.

Recommended Structure of a National Program

The committee's central charge was to advise HRSA on how a National Cord Blood Stem Cell Bank Program should be structured. The committee believes that the primary goal of any structure that is created should be to provide transplant physicians the assurance that when they determine that an HPC transplant from an unrelated donor is appropriate, the process for locating the best available cells is accurate and timely; that the procured cells are of high quality; and that information on the clinical experience of the transplant recipient is subsequently collected for ongoing research, quality assurance, and clinical improvement purposes. It is clear to the committee that at present, cord blood banks operate under various standards, that the outcomes of a significant proportion of cord blood transplants are not reported either to the bank from which the unit was obtained or to the transplant community generally, and that the economic status of cord blood banking is fragile. The structure that is ultimately identified should address all three of these critical issues.

The committee was aware that current participants in cord blood collection, banking, and transplantation hold strong views about the ideal structure of a national program. In addition, the committee recognized that some activities or components of a comprehensive structure already exist (e.g., a good patient education and advocacy system). However, what is in place is not sufficient for either present or future needs, and the NMDP as currently structured would not be able to fulfill that role. While many aspects to be performed by the proposed National Cord Blood Stem Cell Bank Network have analogs in the NMDP not all U.S. and few non-U.S. cord blood banks participate in the NMDP network, and the procurement and banking of donated cord blood are processes very different from those used to recruit and track potential adult donors.

Finally, any structure identified now needs to be responsive to emerging knowledge about HPC transplantation and should have the capacity to adjust its procedures and structure as necessary and appropriate to incorporate that emerging knowledge.

From many perspectives, a single national system for all sources of HPC (whether they be adult bone marrow, adult peripheral blood, or cord blood) would simplify many aspects of the transplantation process, including search efforts, outcomes data collection and analysis, research, and policy making. There are, however, substantial differences in adult and cord blood registries, and unifying them in a single database requires much better understanding of the science behind the two graft sources.

The lack of a complete, coordinated network for accessing banked cord blood units, assessing the characteristics of those units, and evaluating the outcomes of transplants with units from various banks made it difficult for the committee to accurately assess the status and quality of the cord blood units available at present and their current use for transplantation. Given these considerations, the following are goals that the committee has sought to incorporate into the final structure of the network:

- ensured clinical access to cord blood through substantial increases in the current inventory,
- maximal efficiency of processes,
- minimal redundancy of systems and investment,
- guaranteed cord blood unit quality,
- protected patient and donor confidentiality,
- timely data collection and outcomes reporting,
- transparent policies and procedures,
- long-term financial viability of banks,
- enhanced communication among all parties, and
- adherence to ethical standards.

In moving toward the structure recommended by the committee (see below) and in meeting the associated goals of quality assurance, information exchange, and transparency, DHHS is urged to make transparent to the transplant community, banks, patients, and the public the process for establishing, implementing, and evaluating a national program. Table ES-1 illustrates the main functions of the cord blood program and the way in which the committee envisions that they will be fulfilled. More specific recommendations follow.

TABLE ES-1 Key Functions of a National Cord Blood Program

Governance	A National Cord Blood Policy Board (the National Board) should establish policies and regularly monitor all issues related to cord blood uses. Day-to-day management should be done by a National Cord Blood Center, identified by HRSA through a competitive process.
Database	Data on both cord blood units available for transplantation and patient outcomes after the transplant are needed. As these two types of data serve different purposes, it is not necessary for them to be available in a single integrated database.
Unit Selection	The National Cord Blood Center should facilitate coordinated searches while allowing transplant centers to customize reports according to local selection practices and to work directly with cord blood banks. Search support should provide guidance or information on the selection of adult donor versus cord blood graft sources.
Source of Transplanted Material	The choice of the source for HPCs must be driven by the patients' needs and the best available evidence about the different sources of material for transplantation. This evidence about uses of all sources of material for transplantation must be regularly updated and made available.
Finances	Federal funds for support of cord blood banking should be allocated to the expansion of the inventory of banked units with some funds reserved for the national infrastructure that will be needed.
Cord Blood Bank Selection	Banks wishing to participate in the National Cord Blood Program should meet the standards to be established by the National Board and must meet all data requirements of the national program.
Standards	Quality standards for banks, donor centers, and transplant centers will be set by an accrediting agency that is independent of the National Cord Blood Center. The accrediting agency will be chosen by a competitive mechanism.
Outcomes Data	The National Board should have ready access to comprehensive data that allow for analysis of all transplants in which HPCs are used and that can be used to establish the desired inventory size and readily update the policies of the National Cord Blood Program.

Recommendation 7.1: ***Establish a National Cord Blood Policy Board.*** **The Secretary of U.S. Department of Health and Human Services (DHHS) should establish a National Cord Blood Policy Board (National Board) to set policy and advise the secretary of DHHS and the Health Resources and Services Administration on policy regarding the donation, collection, and uses of umbilical cord blood, as well as on research needed to improve and augment the uses of the cells in cord blood. The National Board should routinely review outcomes data for all clinical uses of umbilical cord blood and develop policy on changes in inventory size, procedures, and standards, as experience and emerging science indicate. The National Board should ensure active interactions among the various organizations involved in adult donor peripheral blood and bone marrow transplantation and umbilical cord blood transplantation.**

This new National Board should be established at the level of the secretary of DHHS to provide appropriate distance from the day-to-day concerns of HRSA, which is the agency directly responsible for managing the relationships between DHHS and adult donor and cord blood programs as well as allocating funding. The proposed board should be established as a chartered body subject to the requirements of the Federal Advisory Committee Act, such that the charter and all appointments would be publicly announced in the *Federal Register* and the meetings of the board would be open to the public. The National Board should include experts in cord blood transplantation; HPC collection, storage, and distribution; clinical transplantation; ethics; epidemiology; histocompatibility; statistics; informatics; health care services; and other relevant areas. In addition, the National Board should have representation from the public. Members of the board should, at a minimum, be free of financial conflicts of interest. The committee urges the board to play an active role in ensuring that the lessons learned during the development and growth of NMDP, the COBLT study, and the solid-organ transplant program are appropriately applied to all funding and policy decisions about the National Cord Blood Stem Cell Bank Program.

Recommendation 7.2: ***Establish a National Cord Blood Coordinating Center.*** **The Health Resources and Services Administration should use an open, competitive process to establish and fund a National Cord Blood Coordinating Center (the Cord Blood Center). The Cord Blood Center would have day-to-day responsibility for carrying out the policies promulgated by the National Board, including:**

- **managing a national network linking participating transplant centers with participating cord blood banks;**

- **collecting data on the outcomes of subsequent cord blood transplants; and**
- **ensuring that data regarding banked cord blood units and the outcomes of cord blood transplants are available to policy makers (including the National Board) for decision making, the participating banks and transplant centers for quality assurance purposes, and researchers seeking to better understand and expand the uses of cord blood.**

In soliciting proposals for the Cord Blood Center, there should be no requirement that all of the program components be centrally managed, provided that satisfactory mechanisms for coordination are proposed, nor should the central management of all program components be prohibited. Some members of the committee are concerned that a requirement to force all aspects of cord blood transplantation into a single, central organization might slow the matching process and might stifle the creativity of the participating banks and transplant centers and their ability to search for improved practices. Proposals, whether for a central organization or not, should provide mechanisms for fostering meaningful links between and among transplant centers and banks, some degree of standardization, and providing access to the information needed for clinical decision making.

Figure ES-1 illustrates the relationships that the committee envisions under the governance structure described in these recommendations. The shaded portions of the diagram illustrate components that will have to be newly created, whereas the other portions represent existing components of the structure.

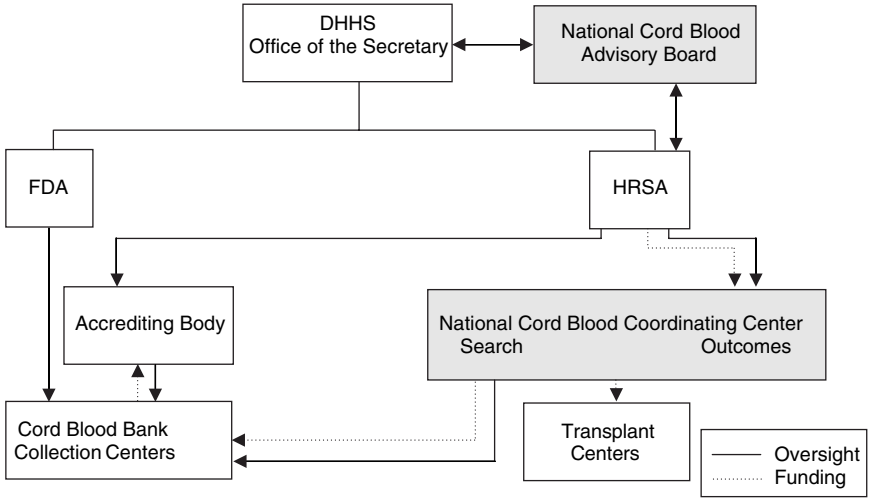

FIGURE ES-1 Proposed structure of a national program.

The National Board should set policy and the Cord Blood Center should perform its functions with the full recognition that cord blood, peripheral blood, and bone marrow are complementary alternative sources for HPCs. The source chosen must be driven by patients' needs and anticipated outcomes on the basis of the best available evidence rather than on *a priori* selection of the source. Thus, every effort should be made to collaborate, as appropriate, with NMDP. The National Board must be vigilant to ensure that the Cord Blood Center operations are transparent to all involved and that cord blood is allowed to mature as a therapy complementary to adult sources of HPC.

Inventory Database and Unit Selection

The Cord Blood Center should work to facilitate the best possible methods for database searches, confirmatory HLA typing, and the reservation and selection of units on the basis of the best available evidence. These methods should include a format for the reporting of search results that provides a coherent summary of all units available through the national program and that incorporates flexibility to allow transplant centers to customize reports to meet the needs of local selection practices. For clinical purposes, a central database of all available units is not essential (but also is not precluded), as long as information on the total inventory available in all participating banks is accessible at the time of a search. The data system and policies should allow for individual participating transplant centers to work directly with participating banks, if they so desire. In addition, the Cord Blood Center should work to facilitate efficient access to units collected internationally so long as they fulfill the quality requirements set by the national system.

Outcomes Data

Recommendation 7.3: *Develop an Outcomes Database for all Sources of HPCs.* The National Board should support the development of an outcomes database that can guide decisions on inventory size and track cord blood bank quality and other policies as well as assist with the assessment of outcomes from *all* sources of hematopoietic progenitor cells.

Collection of outcomes data by the Cord Blood Center should follow a standardized format and capture the appropriate clinical information that is required by cord blood banks to meet their quality assurance, accreditation, and regulatory requirements. This might be achieved internally by the new Cord Blood Center or, perhaps more economically, by contracting with an existing organization having appropriate capacity. Any transplant center desiring to participate in the national program should agree to supply timely data on the immediate and long-term outcomes for patients

receiving cord blood units supplied by the national program. The format for this data-reporting process should be consistent with that used for adult donor transplantation and, to foster the development of an algorithm to allow for single source searching, a single outcomes database for adult and cord blood HPC transplants should be considered, building on existing efforts if possible. This information would not only ensure that complete data on the clinical outcomes following transplantation are collected, but it would also provide data to qualified researchers as well as policy makers and clinicians interested in overall analysis of both national adult donor and cord blood resources. Because these data requirements will impose a burden on the participating organizations, and because the collection and submission of high-quality data are time-consuming activities, some financial support will be needed to assist transplant centers with their data collection and data transfer activities.

Finances

Recommendation 7.4: *Fund Banks to Promote Inventory Growth*. The national program should provide the participating banks with the financial support that they need to achieve an inventory sufficient to provide as many potential recipients as possible with a high probability of a therapeutically effective cord blood unit when one is clinically indicated.

Expansion of the current inventory with units that meet established standards should receive the highest priority in the near future. The National Board should offer support to participating banks that are designing expansion plans for their inventories to include cord blood units from racially and ethnically diverse populations, thus enhancing access to cord blood for individuals who are members of racial and ethnic minority groups. Participating banks should be reimbursed for the units supplied for transplant through health care payment systems in a manner that allows them to be self-sufficient.

Recommendation 7.5: *Provide Financial Support for Infrastructure Development*. Some portion of the funds dedicated to the establishment of the national program should be reserved to support the infrastructure described in this chapter.

The national program will require an infrastructure that includes quality assurance and accreditation systems, as well as the Cord Blood Center and the National Board. The ongoing program of accreditation of participating centers should be supported through participant fees. To ensure that the available cord blood units are used to the greatest advantage for patient care, federal funds should be provided for start-up and ongoing costs for the development of mechanisms for the sharing and publication of out-

comes data; verification that the participating banks and transplant centers meet quality assurance standards; and the encouragement of innovation and improvement in banking, matching, and related processes.

Cord Blood Bank Selection

Recommendation 7.6: *Establish Criteria for Data Sharing*. The National Board should establish minimum criteria for quality standards and data sharing for banks participating in the national program. The Cord Blood Center should monitor and manage the implementation of those standards and coordinate a competitive process for the distribution of funds to qualifying banks for inventory growth.

Banks should be selected on the basis of published criteria and demonstration of the quality of their operations (e.g., accreditation and licensure). Although international banks should not be eligible to receive federal funds for inventory expansion, they should be encouraged to participate in other aspects of the program including data sharing and the provision of clinician and patient support.

Standards

Quality standards for participating banks, collection sites and centers, and transplant centers should be established and overseen by an accreditation body, which should be independent of the Cord Blood Coordinating Center and should be identified through a competitive process open to the several existing groups as well as any other group(s) that may emerge and that may be chosen by an expert panel. Only accredited banks and transplant centers should be able to participate in the National Cord Blood Stem Cell Bank Program. As recommended above (Recommendation 4.4), Food and Drug Administration licensure of units should be required of any bank participating in the national program.

Research

Recommendation 3.1: *Develop a Mechanism to Make Nonclinical Units Available for Research Use*. Federally funded umbilical cord blood banks should have a mechanism by which they can make available for research use units not appropriate for clinical use according to the priority standards developed by the National Cord Blood Policy Board proposed by the committee.

Further research is needed to better understand the therapeutic potential of cord blood.

BOX ES-1
Summary of Recommendations for Establishing a National Cord Blood Stem Cell Bank Program

Research

Develop a mechanism to make nonclinical units available for research use (Recommendation 3.1).

Umbilical Cord Blood Banks and Banking

Establish a cord blood accrediting organization (Recommendation 4.1).
Establish uniform standards for cord blood collection (Recommendation 4.2).
Establish uniform quality assurance systems (Recommendation 4.3).
Establish FDA Licensure of Cord Blood Units (Recommendation 4.4).
Quality standards should apply to both public and private banks (Recommendation 4.5).

Ethical and Legal Issues

Cord blood centers need policies regarding who must provide consent (Recommendation 5.1).
Informed consent should be obtained prior to labor and delivery (Recommendation 5.2).
Donors Must Be Provided with Clear Information about their Options (Recommendation 5.3).
Promote the security of medical information (Recommendation 5.4).
Cord blood donors must understand the limitation of their rights (Recommendation 5.5).

Inventory of a National Cord Blood Stem Cell Bank Program

Establish a national inventory policy (Recommendation 6.1).
Continue to conduct outcomes research (Recommendation 6.2).
Expand the current inventory (Recommendation 6.3).

Recommended Structure of a National Program

Establish a National Cord Blood Policy Board (Recommendation 7.1).
Establish a National Cord Blood Coordinating Center (Recommendation 7.2).
Develop an outcomes database for *all* sources of hematopoietic progenitor cells (Recommendation 7.3).
Fund banks to promote inventory growth (Recommendation 7.4).
Financially support infrastructure development (Recommendation 7.5).
Establish criteria for data sharing (Recommendation 7.6).

1

INTRODUCTION

THE THERAPEUTIC PROMISE OF HEMATOPOIETIC PROGENITOR CELL TRANSPLANTATION

Stem cells are a primitive cell type found in all animals and are capable of both self-renewal and differentiation. Some stem cell types are more committed to a particular developmental fate than others. For example, they divide and mature into cells of a specific type or limited spectrum of types (e.g., heart, muscle, blood, or brain cells). In contrast, pluripotent stem cells are less committed and retain the potential to differentiate into most other types of cells.[1] One example of a pluripotent stem cell is the embryonic stem cell, found in the blastocyst stage of the developing embryo. It is believed that stem cells form reservoirs of repair cells to replace cells and tissues that degenerate over the life span of the organism. It is this capacity for self-renewal and for differentiation into repair cells that offers great potential for regenerative medicine.

This report focuses on the development of an integrated system for the use of one specific type of stem cell, the hematopoietic progenitor cell (HPC), which is a multipotent stem cell responsible for the continual production of the diverse array of normal blood cells.[2] HPCs can be obtained

[1]Pluripotent cells can differentiate into all cell types except those that make up the extraembryonic membranes (placenta, umbilical cord, and amnion), which are derived from the trophoblast.

[2]Throughout this report the committee uses the term hematopoietic progenitor cell and the abbreviation HPC to avoid confusion with other forms or sources of stem cells.

from a variety of sources including bone marrow, peripheral blood, and umbilical cord blood collected from the placentas of recently delivered infants. Because of the potential of HPCs to reconstitute bone marrow and peripheral blood, their use for the treatment of patients with bone marrow damage from either chemotherapy or underlying hematological failure has been under investigation for several decades. Transplantation of HPCs from healthy individuals could also reconstitute bone marrow or blood in individuals with a variety of blood-related disorders (human-to-human transfer is called "allogeneic transplantation").

Early research specifically into cord blood transplantation was based on the hypothesis that the immune cells in cord blood may be less mature than those in adult bone marrow or peripheral blood. Consequently, the risk of graft-versus-host disease (GVHD)[3] after a cord blood transplant might be less than that after a bone marrow transplant or peripheral blood transplant. Other advantages of cord blood over bone marrow include its ready availability, its low potential for infectious disease transmission, and the minimal risk at the time of collection. This opens up the possibility of HPC transplantation to patients who either could not find a match within the bone marrow donor pool or were too ill to be able to wait for the process of searching and harvesting of bone marrow from adult donors.

Since the first transplants in the late 1980s and early 1990s, cord blood has been shown to be a suitable alternative to adult bone marrow or peripheral blood as a source of HPCs for the treatment of leukemia, lymphoma, aplastic anemia, and inherited disorders of immunity and metabolism. Whether cord blood is as good as or superior to adult graft sources in all of these situations is as yet unknown. Factors already shown to influence the outcome of cord blood transplantation include the numbers of cells in the cord blood, the size of the recipient, and the degree of human leukocyte antigen (HLA) match[4] between the donor and the recipient. The committee holds the view that cord blood and marrow are complementary sources of HPC, each having specific advantages and disadvantages, and that the choice between the two should be made on a case-by-case basis, depending on the status of the patient.

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[3]GVHD occurs when donor cells attack the recipient's normal tissues after transplant and can lead to organ damage.

[4]HLA stands for *h*uman *l*eukocyte *a*ntigen, the major histocompatibility complex in humans. The closer the donor's and recipient's HLA antigens match, the less likely it is that the T cells (immune system cells) of the donated marrow will react against the patient's body. Within a family, siblings have one-in-four chance of being HLA-identical. Outside the family, the situation is very different. HLA antigens are highly polymorphic, with hundreds of different HLA antigens found in the human population (there are roughly 750,000 possible combinations of three HLA antigens alone). To find an unrelated HLA-matched donor requires searching very large numbers of people (Beatty et al., 1988).

The rate of use of cord blood for transplantation has increased rapidly, and in the United States, Europe, and Japan exceeds the use of bone marrow for childhood transplants. Clinical investigations indicate promising results in a variety of settings, although utilization and success are limited by several obstacles common to any form of transplantation, including the need for an HLA match (Kernan et al., 1993; Confer, 1997; Rubinstein et al., 1998; Goldberg et al., 2000; Rocha et al., 2000; de Lima and Champlin, 2001; Barker et al., 2001, 2003, 2005; Laughlin et al., 2001; Wagner et al., 2002; Barker and Wagner, 2003; Grewal et al., 2003).

Without a close match for HLA, HPC transplantation from any source is associated with high risk of rejection, in which the recipient's immune cells react against the donor cells, and of GVHD. Even with HLA compatibility, immunosuppressive therapy is required to prevent rejection and to reduce the incidence and severity of GVHD. Immunosuppressive therapy, plus the delay in reestablishing normal immune functions as donor cells restore recipient lymphohematopoiesis,[5] places patients at a high risk for bacterial, viral, and fungal infections. In the case of donor-patient HLA disparity, infection is an even greater problem.

IN SEARCH OF A MATCH

HLA matching is critical for all types of transplant, regardless of the source. The number of patient candidates for an HPC transplant is estimated to be 11,700 annually, of whom only 3,500 have an HLA-identical sibling donor.

In an attempt to make HPCs more widely available to the large number of patients who do not have an HLA-identical sibling, large international volunteer bone marrow and peripheral blood donor registries were created in the 1980s (Beatty et al., 1988). Unrelated adult donors are generally identified through these donor registries. As of December 2003, more than 9 million registered volunteer donors were listed in more than 40 registries worldwide (BMDW, 2004). Registries maintain lists of the HLA types (and other clinically relevant information) of individuals willing to allow the harvesting of HPCs from their bone marrow or peripheral blood for transplantation should a need arise.

Despite the large numbers of donors recruited over the past two decades, volunteer donor registries still face several challenges. These include:

- an inability to identify fully or closely HLA-matched donors for a significant proportion of transplant candidates, particularly non-Caucasian groups;

[5]Development of new lymphocytes.

- a permanent or transient unavailability of the potential donor, even if the individual was identified in a registry on the basis of HLA match criteria (Wagner et al., 2002); and
- the prolonged interval (median of 4 months) between the time of the request for a search and the time of HPC acquisition (Linch and Brent, 1989; Nash et al., 1992; Kurtzberg et al., 2000; Thomson et al., 2000; Barker et al., 2002).

Moreover, the donation of HPCs is not without risk for adults. In the case of bone marrow donation (Gluckman et al., 1997; Barker et al., 2002), the bone marrow must be surgically removed, generally by large-bore needle aspiration while the donor is under general or spinal anesthesia (Locatelli et al., 1999). Although fewer than 1 percent of donors experience serious complications, the procedure can result in significant postoperative discomfort to the donor at the aspiration site and may be a factor in recruiting donors to a registry (Buckner et al., 1984). Alternatively, HPCs can be collected from peripheral blood through a process called leukapheresis after the administration of drugs to mobilize HPCs so that they move out of the bone marrow and into the bloodstream. Leukapheresis can be associated with bone pain from the mobilization drugs, hypocalcemia,[6] decreased platelet counts, spleen enlargement or (rarely) rupture, and complications from venous catheter placement.

These registries of unrelated donors provide suitable donors for only about a third of the patients without a sibling donor; thus a shortage of suitable donors persists. In addition, the distribution of HLA alleles and haplotypes[7] found in individuals varies among different ethnic and racial groups. Some alleles and haplotypes are common to several populations; others are predominantly confined to one population group. Thus, some populations are more likely to be underserved by these registries.

DEVELOPMENT OF UMBLICAL CORD BLOOD BANKS

Several groups recognized the need to obtain HPCs more easily, more safely, and from a broader cross-section of the population and for this reason established cord blood banks with the central mission of maintaining a supply of HPCs for therapeutic use in transplantation. (More information about banks and banking can be found in Chapter 4.)

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[6]Abnormally low calcium concentration that can result in muscle cramps, abdominal cramps, spasms, and hyperactive deep tendon reflexes. See http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=hypocalcemia&action=Search+OMD [accessed March 23, 2005].

[7]Haplotyping is the determination of the HLA type of a patient or cord blood unit.

In 1992, the New York Blood Center (NYBC) recognized the need for a dedicated inventory of cord blood units for patients lacking an HLA-matched sibling and established a program for public cord blood banking (Rubinstein et al., 1998). In 1998, NYBC published a report summarizing the results of the first 562 transplants performed with units from its inventory. The results, primarily pediatric cases, indicated consistent engraftment, low rates of GVHD, and survival rates that appeared to be similar to those obtained with bone marrow transplantation (Rubinstein et al., 1998). Other banks were soon established, and today there are at least 40 cord blood banks in the United States. Of those known banks, 20 store donations for unrelated transplants. (More information about all banks can be found in Appendix C.) The remaining banks are private; that is, they store cord blood at the expense of the donor for potential future use by the donor or a member of the donor's family.

In 1998, the National Marrow Donor Program (NMDP), which also recognized the potential of cord blood as an alternative graft source, extended its network to include cord blood banks (GAO, 2002). NMDP grew out of the congressionally established National Bone Marrow Donor Registry (NBMDR), which began operation in July 1986. The Organ Transplants Amendment Act of 1988 reauthorized NBMDR by directing the establishment of a national registry. In June 1988, the NBMDR board changed the name to the National Marrow Donor Program. In 1990, NMDP became a separate nonprofit organization and took over the administration of the federal contract from the American Red Cross. The Transplant Amendments Act of 1990 further defined and expanded the functions of NMDP. The act wrote into law the network of centers, addressed the need for diversity, consolidated all of the registries, and established a system for patient advocacy.[8] At present, 14 cord blood banks in the United States and internationally are affiliated with NMDP.[9]

[8]See http://www.marrow.org/NMDP/history_of_transplants.html.

[9]Those banks are the American Red Cross North Central Blood Services in St. Paul, Minnesota; American Red Cross Western Area Community Cord Blood Bank in Portland, Oregon; Ashley Ross Cord Blood Program of the San Diego Blood Bank in San Diego, California; Bonfils Cord Blood Services, Belle Bonfils Memorial Blood Center in Denver, Colorado; Carolinas Cord Blood Bank in Durham, North Carolina; Children's Hospital of Orange County Cord Blood Bank in Orange, California; ITxM Cord Blood Services in Glenview, Illinois; J.P. McCarthy Cord Stem Cell Bank in Detroit, Michigan; LifeCord in Gainesville, Florida; New Jersey Cord Blood Bank at the Coriell Institute for Medical Research in Camden, New Jersey; Puget Sound Blood Center in Seattle, Washington; St. Louis Cord Blood Bank in St. Louis, Missouri; StemCyte International Cord Blood Center in Arcardia, California; and StemCyte Taiwan National Cord Blood Center in Taipei County, Taiwan.

THE CHALLENGES OF A FRAGMENTED SYSTEM

Although independence often leads to innovation, it can also lead to inconsistency in quality from bank to bank and a need for transplant centers to access multiple banks. Thawing and processing the units received from different banks can also vary depending on the bank accessed. The proliferation of cord blood banks has raised the challenges of accessibility, the adequacy of the inventories, the standardization of techniques and documentation, and quality control. In addition, most cord blood banks have developed practices and procedures independent of any consistent quality assurance or regulatory oversight, although many banks are accredited by independent organizations such as the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Cellular Therapy (FACT).

The complexity of the search and matching process for cord blood units remains an issue for many transplant physicians. No standardized search algorithm is available, and the level of HLA typing differs from registry to registry and between cord blood units and bone marrow donors. At present, transplant coordinators must often search multiple registries and banks to find potential adult donors or cord blood units for a given patient before deciding on the best graft source. Within the United States, searches of the vast majority of adult donors in national and international registries (and the 14 participating cord blood banks) can be accomplished with a single search process through NMDP, although this process may sometimes take weeks, time that ill patients may not have. However, no single point exists for access to the entire cord blood inventory. In 2001, NetCord, an international organization, was established to facilitate searches of multiple cord blood banks to seek a match. This organization is an affiliation of 15 international banks with a combined inventory of 86,914 units[10] (NetCord, 2005). Because not all banks belong to this network, one-request searches are still not possible.

Recent reports suggest that cord blood searches are becoming more uniform, but no uniform search algorithm exists. However, lack of a single portal and the absence of an evidence-based HPC search algorithm have hampered the increased use of cord blood. Therefore, until this uniform outcomes reporting is established, such an algorithm cannot be developed, and there will be no mechanism by which to establish a single search system.

[10]They are: AusCord (Australia), Barcelona (Spain), Düsseldorf (Germany), France Cord (France); Helsinki (Finland), Jerusalem (Israel), Leiden (The Netherlands), Leuven (Belgium), Liege (Belgium), London (Great Britain), Milan (Italy), New York (United States), Prague (Czech Republic), Tel Hashomer (Israel), and Tokyo (Japan).

In the 2004 appropriations bill for the U.S. Department of Health and Human Services, the U.S. Congress, recognizing the potential contributions of cord blood transplantation and the need for a system that better serves patients, provided $10 million for the establishment of a new national cord blood stem cell bank program under the leadership of the Health Resources and Services Administration (HRSA).

Although consensus on the need for a national banking program exists, major differences in perspectives on how that might be accomplished remain. These differences are over governance, database management, unit selection processes, sources of material, financing and competition, and standards, among other issues. Many of these differences in perspective can be understood by examining the evolution and focus of the two major U.S. programs currently involved in HPC transplantation.

TWO VIEWS OF A NATIONAL CORD BLOOD PROGRAM

The federally funded NMDP is the hub of a worldwide network of more than 500 medical facilities engaged in both bone marrow and blood cell transplantation. Through this network, NMDP has facilitated approximately 350 cord blood transplants since 1999, in addition to the 20,000 bone marrow transplants that it has facilitated since 1987. It neither collects nor banks cord blood. NMDP, however, has a long-standing history of linking patients in need to the best possible stem cell match, initially from adult bone marrow or peripheral cells, but now its efforts have been extended to cord blood via member cord blood banks. It also has strong patient advocacy and education functions. Supported by $73,753,000 annually in search and procurement fees, $40,707,000 in federal contracts and cooperative agreements, $3,854,000 in contributions, and $1,864,000 in other income, NMDP represents a comprehensive program that has devoted a great deal of its effort to developing an informatics infrastructure to support the search and procurement process, as well as the collection and use of outcomes data for research (NMDP, 2004).

The National Cord Blood Program of NYBC[11] is the single largest U.S. cord blood bank and since 1993 has shipped more than 1,765 units for transplantation into 1,660 patients.[12] It is not a part of NMDP's cord blood network. This program started as one of NYBC's research activities and later became a separate center. The program works directly with transplant

[11]This is the name of the New York Blood Center's cord blood bank and is not to be confused with the topic of this report. Unless otherwise specified, references to NYBC in this report should be taken as references to that cord blood program.

[12]Some patients received multiple units or follow-up transplants.

physicians seeking a unit from those in their inventory to ensure the best match for patients and has devoted substantial energy toward promoting cord blood transplantation and research. In the 12 years since its inception the program has been supported by $23 million from the recovery of the costs for units shipped for transplantation, $9 million in individual contributions, and $10.6 million from NYBC. Between 1992 and 1995, it also received $4.2 million from an NIH grant (Stevens, 2004). The program collects extensive outcome data, which it uses to publish research to promote a better understanding of cord blood transplantation and science.

In the committee's view, the NMDP, NYBC, and other interested parties agree on several key goals for a national program:

- **Simplicity.** A national program needs to avoid duplication of effort in terms of both services provided and the steps necessary for a transplant center to access appropriate graft sources.
- **Quality.** The ultimate goal of a program should be to promote the best possible chance of patient recovery by establishing an inventory of high-quality, HLA-diverse cord blood units
- **Patient, physician, and donor support.** Support and education for all individuals involved in the program are integral and necessary parts of the program.

However, each organization describes the preferred shape of the program differently in ways that are not readily integrated. Table 1-1, describes the ideal shape of a national program according to NYBC and NMDP.

BACKGROUND OF THIS STUDY

In its 2004 appropriation of $10 million for the establishment of a National Cord Blood Banking Program, the U.S. Congress recognized the different views on how such a program might be established. A portion of the appropriation was allocated to the Institute of Medicine (IOM) to provide HRSA with an assessment of existing cord blood programs and inventories and to make recommendations on the ideal structure, function, and utility of a national cord blood stem cell bank program. The charge to the IOM committee is as follows:

> In response to Conference Report on H.R. 2673, Consolidated Appropriation Act 2004 (H. Rept. 108-401), the Institute of Medicine (IOM) will assemble a committee of experts to conduct a study that will consider relevant issues related to the establishment of a National Cord Blood Stem Cell Bank Program within the Health Resources and Services Administration, DHHS. The IOM study will make recommendations for the optimal

TABLE 1-1 Views from NYBC and NMDP on an Ideal National Stem Cell Cord Blood Bank Program

Component	New York Blood Center	National Marrow Donor Program
Governance	The network should be independent, with its own board of directors to set policy and monitor participants' compliance with network rules and regulatory agencies.	The network should operate under already existing NMDP infrastructure. Time and money can be saved by not re-creating that which already exists. The NMDP board should be representative of parties who should provide oversight. Committees of the board should be in place to oversee issues unique to cord blood.
Database	The best chance of finding a match is obtained when each bank searches its up-to-date local database. A centralized database would duplicate banks' databases and would be expensive to maintain or almost always out of date.	A centralized database would allow transplant coordinators a location for 'one-stop shopping' for both adult HPC donors and cord blood units and would avoid the potential for the same unit to be reserved through more than one channel.
Unit Selection	Banks must be able to interact directly with the transplant centers to help select the best units for transplantation. If a central search mechanism is adopted, it must be transparent to everyone. Banks must have input in the development of the search algorithm used to define, sort and display matches and must be able to monitor whether their units are listed appropriately.	The program must establish and maintain a standard mechanism to search for units, confirm the HLA type, and to reserve and select the units. A mechanism should be available to update the HLA search algorithm as new alleles are developed or new match criteria are identified.
Source of Transplant Material	Cord blood and adult donors compete as sources of stem cells for hematopoietic reconstitution.	Cord blood, peripheral blood, and bone marrow are complementary alternative sources for HPCs.
Finances	Banks distribute manufactured products, are reimbursed, and should become self-sufficient, like regular blood and tissue banks. To jump-start that process, federal appropriations funding should be in the form of direct grants to the network banks.	Funds should be distributed through the program to all banks meeting the criteria under the oversight of HRSA in a manner that ensures the equitable distribution of responsibility. Goals including the collection of an appropriately diverse registry of units should be established.

TABLE 1-1 Continued

Component	New York Blood Center	National Marrow Donor Program
Cord Blood Bank Selection	Cord blood banks should compete for participation in the national program according to criteria that should be published in advance of the competition.	Role of competition is misplaced, as goal should be ensuring a large, diverse registry of units that meet current standards regardless of where collected and stored. The registry and its network should be examined every five years to assure they are functioning well as a unit.
Standards	Regulatory rules and standards should be the responsibility of the Food and Drug Administration.	Standards should be established by the program and should include Food and Drug Administration regulations, as they become available.
Patient Support	The network's board of directors should establish patient, donor, and physician education programs.	The program should address issues of access to transplant therapy for all patients including financial ability, literacy, language, patient advocacy, etc.
Outcomes Data	Collection of the outcomes of transplants is a responsibility of each bank. Banks should obtain these data as part of quality control whether or not there is a central mechanism for outcomes data collection.	The program should establish and maintain a means to define and collect outcomes data for transplants performed as part of the program. Data submission should be monitored, and a formal error correction mechanism should be used. Data should be available to the wider research community to support the submission of peer-reviewed journal article submission to professional scientific journals to expand knowledge of cord blood transplantation.

structure for the cord blood program and address pertinent issues related to maximizing the potential of this technology (e.g., collection, storage, standard setting, information sharing, distribution, reimbursement, research and outcome measures).

The following are among the more specific issues to be considered:

- What is the role of cord blood in HPC transplantation in the context of other sources of HPCs?

- What is the current status of the cord blood banks already in existence?
- What is the optimal structure for the cord blood program?
- What is the current use and utility of cord blood for stem cell transplants?
- What is the best way to advance the use of cord blood units for HPC transplantation (i.e., setting storage standards, collection procedures, information sharing, distribution, and outcome measures)?
- What is the best way to make cord blood units available for research?
- What consent procedures should be followed to obtain informed consent for both research and transplantation use?
- Should the cord blood program set practice guidelines for all banks or just the public banks (e.g., what kind of HLA-typing would need to be done before blood goes into the cord blood bank, and how are the databases advertised)?

IOM formed the Committee on Establishing a National Cord Blood Stem Cell Bank Program, which consists of experts in the fields of economics, HPC transplantation, outcomes analysis, biostatistics, stem cell biology, cord blood quality and standards, public health, health technology assessment, patient advocacy, ethics, and obstetrics and gynecology. Throughout the course of its work, the committee's perspective was that the program that is eventually established should have as its primary mission the goal to maximize access to high-quality HPC sources for patient care and research in the most efficient, cost-effective, and ethical manner possible. All committee findings and recommendations were weighed against this core perspective and were developed after careful consideration of current experience with cord blood banking, the lessons learned from other organ and tissue transplant programs, and the current and potential uses of HPCs derived from cord blood. (Information on the methods and information gathering strategy that the committee used can be found in Appendix A.)

In the course of its work, the committee made every effort to consider all points of view on the establishment of a national program, hearing from patient advocates, transplant physicians, individuals from existing banking facilities, and the research community, all of whom have expressed concerns about the need for openness and fairness in policy making about cord blood banking.

ORGANIZATION OF THIS REPORT

This report is structured as follows: Chapter 2 describes the history of HPC transplantation and the current use and utility of cord blood for this

purpose. Chapter 3 explains the current research applications of cord blood and potential future uses. Chapter 4 discusses banking processes and the current status of cord blood banking in the United States. Chapter 5 describes some of the ethical and legal implications of cord blood banking and of a national program. Chapter 6 discusses the inventory needs for a national program. Finally, Chapter 7 presents the committee's view of the ideal structure of a national program. Though the structure chapter comes last, there will be references to structural elements throughout the report. The committee believed it was necessary to discuss the background of banking, HPC transplantation, and other relevant matters prior to discussing the structure.

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2

Hematopoietic Stem Cell Transplantation

BIOLOGICAL CHARACTERISTICS OF UMBILICAL CORD BLOOD

Blood cell differentiation begins with multipotent hematopoietic progenitor cells (HPCs), which are located in the marrow spaces of the bone. These primitive cells undergo division and differentiation to form the various peripheral blood cells. As the cells reproduce, they commit to a particular task or cell line and become known as *committed progenitor cells*. These committed progenitor cells are difficult to discern from the original multipotent cells but can be cultured to form colonies of specific types of blood cells (Guyton and Hall, 2000). These cultured cells, or colony-forming units (CFUs), are coded according to the type of cells that they will ultimately produce (e.g., CFU-M cells will produce megakaryocyte cells) (Figure 2-1). Umbilical cord blood is a rich source of these committed progenitor cells and, presumably, multipotent HPCs (Knudtzon, 1974). In fact, cord blood has a significantly higher concentration per volume of primitive HPCs than does bone marrow (Nakahata and Ogawa, 1982; Smith and Broxmeyer, 1986), thereby making it a potential source of cells for transplantation (Bodger, 1987). In laboratory analyses, these cells were found to have higher proliferative responses (indicating a higher engraftment potential) than similar doses of marrow (per 10^5 nucleated cells per kilogram [kg] of graft) (Mayani and Lansdorp, 1998; Barker and Wagner, 2003b). In the last decade, the number of transplantations of HPCs derived from cord blood has increased, particularly for children.

Numerous literature reports document the feasibility and efficacy of the transplantation of cord blood from a related donor for the treatment of

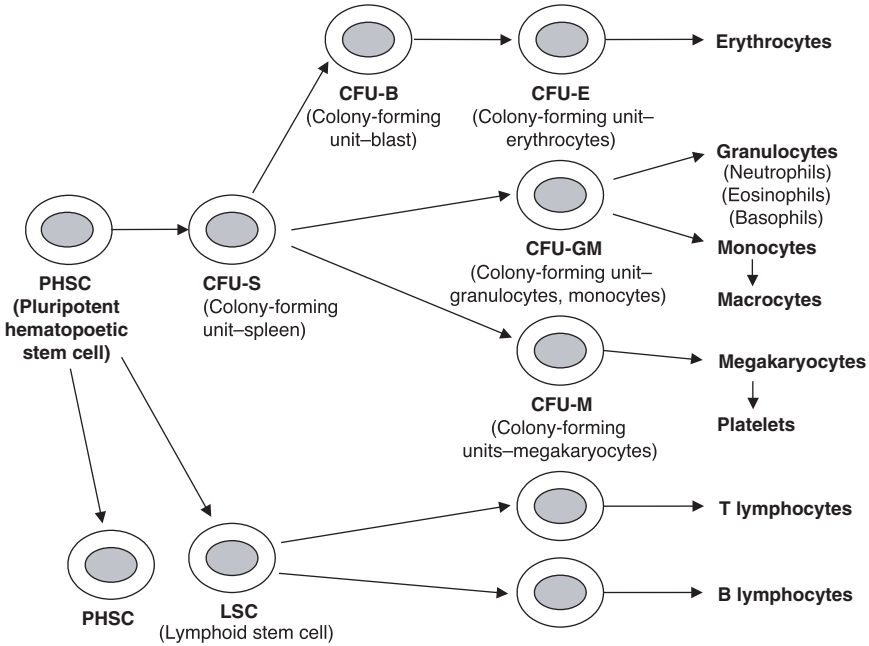

FIGURE 2-1 Formation of the multiple peripheral blood cells from multipotent hematopoietic stem cells.
SOURCE: Guyton and Hall, 2000.

a broad range of disorders for which transplantion of HPCs from an adult donor is also successful, including hematological malignancies, solid tumors, constitutional and acquired bone marrow failure syndromes, hemoglobinopathies, congenital immune deficiencies, and inherited disorders of metabolism (Gluckman et al., 1997; Locatelli et al., 1999; Rocha et al., 2000; Locatelli et al., 2003). After the early success of transplantation of cord blood from related donors, cord blood banks were established to provide rapidly accessible, human leukocyte antigen (HLA)-typed units predominantly for transplantation of HPCs from unrelated donors. Since then cord blood banking programs throughout the world have expanded rapidly (Broxmeyer, 1998), with the estimated number of units stored to date exceeding 155,000 (BMDW, 2004).

The establishment of at least three independent, international registries of outcome data—the International Cord Blood Transplant Registry (ICBTR) in 1992 (which was transferred to the International Bone Marrow Transplant Registry [IBMTR] in 1996, and to the Center for International

Blood and Marrow Transplant Research [CIBMTR] in 2004), the European Research Project on Cord Blood Transplantation (Eurocord) in 1993, and the Japanese Cord Blood Banking Network in 1996—expedited the clinical evaluation of the efficacy and safety of transplantation of cord blood from unrelated donors. With more than 6,000 transplants of cord blood from related and unrelated donors performed thus far, cord blood has emerged as an acceptable, alternative source of HPCs that has some advantages over adult sources of HPCs and the availability of which represents an important development in the field.

One advantage of cord blood over adult sources of HPCs is the fact that cord blood banking does not have the same donor attrition issues because the units are collected and stored before they are needed. In addition, the time from unit identification to transplantation can be a matter of days to weeks rather than the weeks to months required for adult HPC donation. Another major benefit of cord blood is the reduced capacity of cord blood cells to produce an alloreactive response (i.e., an immune response against the recipient). This results in less frequent and less severe graft versus host disease (GVHD) and the ability to perform transplants with greater degrees of donor-patient HLA disparity compared with the disparity associated with adult HPC transplants, which must be minimized as much as possible (see Box 2-1). This is thought to be due to both quantitative and qualitative differences in the lymphoid cell content of cord blood (Risdon et al., 1995; Roncarolo et al., 1996; Leung et al., 1999; Gluckman and Locatelli, 2000).

Compared with adult HPCs, cord blood cells have immune naiveté because of their minimal previous exposure to antigens (Sirchia and Rebulla, 1999). However, immune suppression is still required, as is the case for adult HPC transplantation, to prevent both rejection and GVHD. In addition, although the recipient can tolerate some degree of HLA mismatch, the clinical results are generally better with closer HLA matches. Furthermore, cord blood-derived HPCs possess higher expansion and proliferation potentials than HPCs derived from bone marrow. Similar differences may also account for the replicative capacities of cells (Allsopp et al., 1992; Vaziri et al., 1994; Lansdorp, 1995a, 1995b).

However, cord blood has some important limitations. Even though cord blood units have higher concentrations of HPCs, they have relatively small volumes (~100 milliliters) and, therefore, fewer total cells than bone marrow grafts. This can result in very low cell doses (the number of cells in the graft per kilogram patient weight) for larger children and adults (HRSA, 2000). In addition, the use of very low overall cell doses ($<1.5 \times 10^7$ nucleated cells in the graft per kilogram of patient weight) results in a higher risk of nonengraftment. Immune reconstitution with cord blood can also be slower, and, on account of this delayed immune reconstitution, the

BOX 2-1
HLA and HLA Matching

Proteins that control tissue compatibility were first detected on the surface of white blood cells and were named human leukocyte antigens (HLAs). Located in a cluster on chromosome 6, the genes encoding these cell surface molecules are named the major histocompatibility complex (MHC) (Dausset, 1981; Benacerraf, 1992; Snell, 1992; Janeway et al., 2005).

These molecules are then further divided into class I, which is made up of HLA-A-, HLA-B, and HLA-C, and class II, which is made up of HLA-DR, HLA-DQ, and HLA-DP. Although, these two classes are composed of different polypeptide chains, they assume a very similar structure on the cell surface (Bjorkman and Parham, 1990). Figure 2-2 provides a diagram of the HLA protein, its location on chromosome 6, and its function.

An individual's HLA genotype reflects two haplotypes (the genes inherited on a single chromosome), one inherited from mother and one inherited from the father. Within a family, siblings have a one-in-four chance of inheriting the same two haplotypes and, thus, of being HLA identical. Outside the family, the situation is very different. HLA antigens are highly polymorphic, with hundreds of different HLA antigens found in the human population (the HLA-A, HLA-B, and HLA-DR antigens alone have roughly 750,000 possible combinations). However, many of these potential combinations have not yet been encountered because HLA alleles are in linkage disequilibrium. Only a subset of all possible HLA haplotypes have been encountered in the entire population.

At present, the donated HPC cells (including cord blood) are routinely typed for HLA-A, HLA-B, and HLA-DR loci. Each individual has two antigens at each of these sites. Thus, when a transplant physician speaks of a 4/6, 5/6, or 6/6 match, he is talking about the number of antigens a particular donor has in common with the patient. Many transplant centers also type the units for HLA-C and HLA-DQB1 because some data suggest that disparities at these loci can also affect the outcome of a transplant (Hurley et al., 2003). There is ongoing research about which, if any, loci are better able to tolerate a mismatch.

rate of infection can sometimes be higher. Some data indicate that this can be overcome by combining cells from multiple units or by combining cord blood with highly purified HPCs from mismatched related donors. Several investigators have also explored the ex vivo expansion of cord blood cells, but no data supporting faster engraftment by this approach are available and few comparative studies of the clinical outcomes obtained by transplantation of HPCs from adult donors and cord blood have been conducted.

The fact that cord blood transplants can be successful, even though they involve degrees of HLA disparity typically associated with an increased risk of GVHD in the adult donor setting, allows transplant physicians some leeway in determining which units can be selected for transplantation.

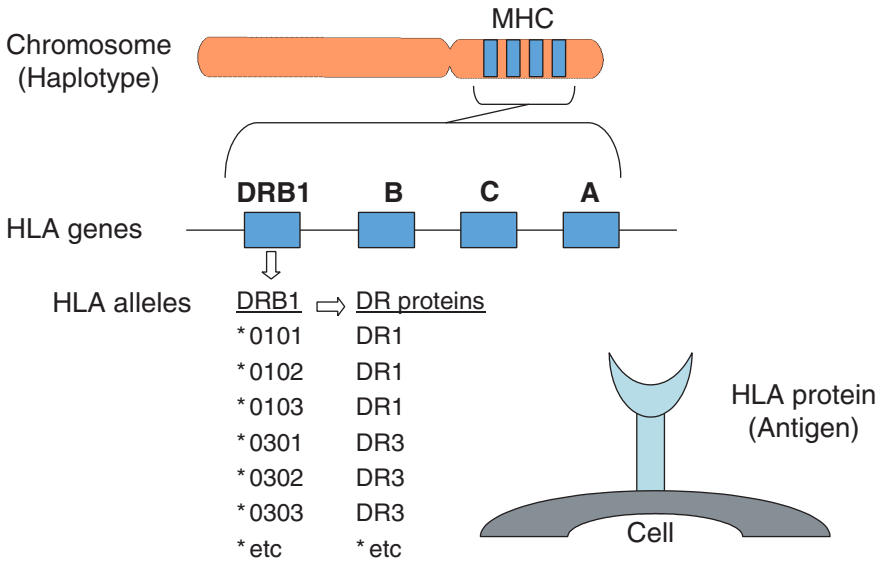

FIGURE 2-2 The human histocompatibility genes.
SOURCE: Hurley (2005). See also Appendix F.

Transplant physicians can select units with higher cell counts instead of a closer HLA match to increase the chances of a successful engraftment. However, some degree of HLA compatibility is necessary, although the minimum acceptable level is somewhat controversial (see also Appendix G). Most cord blood transplants are done with units mismatched for a maximum of two HLA antigens (HLA-A and HLA-B) using low-resolution typing techniques and for DRB1 antigens by using high-resolution typing techniques.

The detection of a suitable cord blood unit for a given patient is difficult. First, significant differences in HLA types exist among various ethnic populations. For example, HLA-Bw53 is found in 5.4 percent of the haplotypes in African Americans but only 0.05 percent of the haplotypes in Caucasians (Margolis and Casper, 2000). Because of the number of possible HLA combinations, which are enhanced by the differences inherent in the various ethnic populations, the likelihood of finding an exact match is extremely small.

HLA-types have traditionally been identified with serologic typing (also called "low/intermediate resolution" typing) methods. Sequencing (one of the many methods referred to as "high resolution typing") of HLA genes revealed that each of the serologically defined HLA antigens represent many different protein structures. Thus, a unit typed at the low resolution level

may appear to be a match but may be mismatched when typed at high resolution. More information about HLA and matching can be found in Appendix F.

CORD BLOOD TRANSPLANTATION

Allogeneic Transplantation

Most cord blood banking involves the collection, storage, and distribution of cells for transplantation to unrelated individuals. These units are typed and stored anonymously so that any patient who might have a medical need may use them. This transplantation involving the transfer of cells from one individual to another genetically different individual is referred to as allogeneic transplantion, and the individual receiving the transplant may or may not be related to the donor.

HPC transplantation can also be done using autologous cells, in which an individual's own cells are collected and stored and then reinfused, generally after high-dose anticancer therapy. Allogeneic and autologous transplantation each have benefits and disadvantages. The benefits of allogeneic transplantation include the ability to treat a wide range of conditions, both inherited and acquired, with HPCs from a healthy, unaffected donor. Allogeneic cells may also have immune effects that may aid in eradicating the recipient's malignancy. Autologous transplantation carries the risk of the reinfusion of abnormal cells if the cells are collected after the onset of the disease and it lacks any immune-mediated anticancer effects. The major disadvantage of allogeneic transplantation is the use of non-native tissue for the graft, which necessitates the use of immunosuppressive therapy to avoid rejection and GVHD. Table 2-1 describes the details of conditions that may be treated by allogeneic or autologous HPC transplantation.

Outcomes of Transplantation of HPCs from an Unrelated Donor

Engraftment of an HPC transplant is generally considered successful when neutrophil recovery is found. Neutrophils are the white blood cells that form the first line of defense against infection. Neutrophil recovery is an indication that the patient has begun to generate new blood cells and hematopoiesis[1] is being restored. Neutrophil recovery, however, is not synonymous with the restoration of full immune function, which requires the production and maturation of various other types of white blood cells and

[1]The development of blood cells.

TABLE 2-1 Indications for Allogeneic and Autologous Stem Cell Support

Disease	Allogeneic Transplantation	Autologous Transplantation
Leukemia (acute lymphoblastic, acute myelogenous, chronic myelogenous)	• Effective	• Controversial for acute lymphoblastic leukemia and chronic myelogenous leukemia • Acceptable for acute myelogenous leukemia
Lymphomas (Hodgkin's disease, non-Hodgkin's lymphoma)	• Effective, but generally indicated only when autotransplantation is not possible or not effective because of higher toxicity	• Effective
Myelodysplastic Syndromes	• Given the high doses of chemo- or radiotherapy required, generally used on patients under 50. • Nonmyeloablative transplants are showing promise in older and/or weaker patients.	• Effective, but only following chemotherapy. Generally used in patients under 50 years of age
Neuroblastoma (stage IV)	• Controversial studies are ongoing to define role related to conventional therapy and autologous transplantation	• Controversial; studies are ongoing to define the role related to conventional therapy and allogeneic transplantation
Bone and soft tissue sarcomas, Wilms' tumor, brain tumors	• Very rarely indicated	• Rarely indicated and effectiveness unproven
Aplastic anemia and other cytopenias (not environmentally caused)	• Effective	• Not indicated
Immune deficiency (e.g., severe combined immunodeficiency disease)	• Effective	• Not indicated
Hemoglobinopathies, thalassemia, sickle cell anemia	• Effective; controversial in unrelated subjects	• Not indicated
Metabolic storage disorders, Hurler's syndrome, metachromatic leukodystrophy	• Controversial; may be effective in selected patients	• Not indicated

continues

TABLE 2-1 Continued

Disease	Allogeneic Transplantation	Autologous Transplantation
Renal Cell Cancer/Melanoma	• Under investigation	
Autoimmune disease	• Under investigation	• Under investigation

SOURCE: AAP (1999).

which can take many months. It is, however, an important milestone, indicating a high likelihood of normal hematopoiesis.

The incidence of neutrophil recovery[2] after cord blood transplantation, as reported in a larger series of studies, ranges from 65 to 92 percent (Laughlin et al., 2001) and is generally lower than that after adult bone marrow or peripheral blood transplantation. More rapid neutrophil and platelet recovery occurs in patients receiving higher cord blood cell doses (Wagner et al., 1996; Barker et al., 2001; Rubinstein et al., 2001; Grewal et al., 2003). The nucleated cell dose in a graft required for consistent engraftment, as reported by Gluckman et al. (1997), is greater than 3.7×10^7 cells in the graft per kilogram of patient weight; this was associated with a shorter time to neutrophil recovery (25 days with lower doses versus 35 days with higher doses). Rubinstein et al. (1998) suggested the use of a threshold cryopreserved nucleated cell dose greater than or equal to 2.5×10^7/kg of graft, whereas Wagner et al. (2002) reported success with a threshold dose of infused $CD34^+$ cells of greater than or equal to 1.7×10^5/kg of graft.

It has also been demonstrated that a stepwise increase in the nucleated cell dose in the graft is associated with a progressively shortened time to neutrophil recovery (Rubinstein et al., 1998; Rubinstein and Stevens, 2000) and that the $CD34^+$-cell dose predicts the speed of recovery (Wagner et al., 2002).

Several but not all studies show a relationship between HLA match and neutrophil recovery (Rubinstein et al., 1998; Gluckman et al., 2004). Using data provided by the National Marrow Donor Program, the New York Blood Center, and the National Heart, Lung, and Blood Institute (NHLBI) Cord Blood Transtplantation Study (COBLT), the committee conducted its

[2]Neutrophil recovery is defined as the achievement of an absolute neutrophil count $\geq 0.5 \times 10^9$/liter, on the first of 3 consecutive days.

own analysis of the significance of the degree of HLA match and cell dose on outcome. This report can be found in its entirety in Appendix G.

The probability of survival after cord blood transplantation, as reported in a large series of studies, has ranged from 18 to 78 percent (Gluckman et al., 1997; Rubinstein et al., 1998). The variation is explained, in large part, by marked differences in patient characteristics (Wagner et al., 2002). In terms of graft parameters, however, nearly all studies demonstrate a significant relationship between cell dose and survival after cord blood transplantation.

The association between the level of HLA match and survival is controversial, in part because of the limited numbers of patients who have been studied and a lack of data for all age groups. For example, Locatelli et al. (1999) reported on the outcomes for pediatric patients with acute leukemia reported in Eurocord[3] registry and found that the number of HLA mismatches did not influence survival. Similarly, in a study of 68 adult recipients ofcord blood with zero to three HLA mismatches, Laughlin et al. (2001) also found no association between the degree of HLA mismatch and the overall rate of survival. In contrast, Rubinstein et al. (1998), Rubinstein and Stevens (2000), and Wagner et al. (2002) observed a significant negative association between HLA mismatch and survival. Other studies have attempted to link the association between HLA mismatch and the occurrence of GVHD but have so far been unsuccessful in formulating reliable estimates of the risk of GVHD from transplants with HLA mismatches (Laughlin et al., 1998), although a positive association between the two has been reported (Amos and Gordon, 1995; Gluckman et al., 2004).

Outcomes of HPC Transplantation from Unrelated Adult Donors

Transplantation of HPCs from unrelated donors for the treatment of acute leukemia in adults is associated with a high risk of GVHD and treatment failure (Ash et al., 1991; Laughlin et al., 2004). Cord blood transplantation may have an advantage in adult patients because of a potentially decreased risk of GVHD. However, as the cell dose is an important determinant of the outcome and adults require higher absolute numbers of cells to achieve adequate doses, the pool of cord blood units suitable for adult patients is considerably smaller than that suitable for children.

Laughlin et al. (2001) reported on the first major series of cord blood transplants done in adults by pooling data from five U.S. centers. The patients (68 subjects) weighed a median of 69.2 kg (weight range, 40.9 to

[3]Eurocord is an international cord blood registry that operates as part of the European Group for Blood and Marrow Transplantation.

115.5 kg); 54 patients had a hematological cancer, and 50 of these patients were considered at intermediate or high risk of rejection. In 97 percent of the grafts, HLAs between the donor and the patient were mismatched at one of three antigens, and the median nucleated cell dose infused was 2.1×10^7/kg of graft (range, 1×10^7 to 6.3×10^7/kg of graft). The rate of engraftment was similar to that in studies with pediatric populations, with an estimated probability of myeloid recovery of 90 percent by day 42 (median time to engraftment was 28 days).[4] The probabilities of grade II-IV and grade III-IV GVHD (see below) were 60 and 20 percent respectively. Nineteen of 68 recipients survived 22 months after the engraftment. Faster rates of myeloid recovery as well as longer lengths of disease-free survival were reported for the patients who received higher nucleated cell and $CD34^+$-cell doses. No significant association between the extent of HLA mismatching and the kinetics of myeloid recovery, graft failure, and acute GVHD was reported and the risk of severe acute and chronic GVHD was lower than that typically reported after the transplantation of bone marrow from unrelated donors. (Hansen et al., 1990, 1998; Kernan et al., 1993; McGlave et al., 1993; Schiller et al., 1994; Szydlo et al., 1997; Cornetta et al., 2005).

Sanz et al. (2001) reported on the results of a study in which 20 of 22 adult patients (weight range, 41 to 85 kg) who received an unrelated cord blood transplant (total nucleated cell dose ranging from 1.01×10^7 to 4.96×10^7/kg of graft) survived more than 30 days and showed myeloid engraftment at a median of 22 days. In a separate Eurocord report of 42 adults receiving cord blood from unrelated donors, the median time to neutrophil recovery was 35 days, and no patient who received less than 1.0×10^7 nucleated cells per kilogram of graft survived (Locatelli et al., 1999). Both of these studies underscore the importance of the graft cell dose to achieving the optimal results after cord blood transplantation, suggesting that the minimum effective nucleated cell dose is at least 1.5×10^7 nucleated cells/kg of graft.

Two recent comparative studies of bone marrow and cord blood transplantation in adults retrospectively examined the results of transplants performed over several years (Laughlin et al., 2004; Rocha et al., 2004). Both studies concluded that cord blood grafts in adults were acceptable alternatives to bone marrow grafts if no suitably matched bone marrow donors were available, even though the cord blood units transplanted contained lower numbers of nucleated cells. The two studies differed in that Rocha

[4]The time to a neutrophil count $>0.5 \times 10^9$/liter was associated with the graft nucleated cell dose ($<1.87 \times 10^7$ versus $>1.87 \times 10^7$; $p = 0.003$).

and colleagues reported that the results obtained with HLA-matched bone marrow were similar to those obtained with HLA-matched and mismatched cord blood, whereas Laughlin et al. found somewhat better results with HLA-matched bone marrow than with HLA-mismatched cord blood. Both found lower rates of acute GVHD among individuals who received cord blood, although Laughlin and colleagues (2004) found that this was true only when they compared the outcomes for HLA-mismatched bone marrow transplants receipients with those for HLA-mismatched cord blood transplant recipients. The rates of recurrence of leukemia and the incidence of chronic GVHD did not differ significantly by graft type. The outcomes of transplants of cord blood HLA mismatched at one and two antigens did not differ significantly (Laughlin et al., 2004).

Cornetta et al. (2005) recently published a report describing the results of cord blood transplantation in high-risk adults in connection with the COBLT study. Of the 30 subjects infused with cord blood as a part of that study, 19 achieved engraftment in an estimated median time of 31 days. The survival probability of these 30 subjects was 47 percent to day 180, although only 17 percent were alive at 1 year. Analysis on the basis of HLA match showed no significant difference in survival. Significant causes of death included relapse and acute GVHD.

With the paucity of cord blood units available in general and the even smaller number of units with an acceptable cell dose, adults are more frequently offered a unit that is mismatched at two HLAs and that also contains a suboptimal cell dose, a scenario that is especially true for non-white adult patients.

Autologous Transplantation

Autologous transplantation is the process by which blood or bone marrow samples from a patient are saved from a patient before the patient receives extensive chemo- or radiation therapy as treatment for a disease. The reintroduction of one's own progenitor cells generally results in the rapid reconstitution of the immune and blood systems and avoids the need for immunosuppressive therapy.

Private cord blood banks perform this service for people who wish to be prepared in the event their child becomes ill. This type of treatment is useful only for a limited number of diseases or disorders, however, as pre-existing genetic conditions are not treatable because the saved cord blood contains the same dysfunctional genetic code that results in the expression of the condition in the first place. For this reason, saving cord blood for autologous use on a large scale may be impractical because of the limitations to its use and the infrequency of the conditions that can be treated with the unit (Catlin et al., 2000).

Eurocord has taken the public position that that there is little scientific justification for preservation unless: (1) the disorder may be corrected by reinfusion of the preserved cord blood cells after correction of the genetic defect, and (2) it would not be considered advantageous to attempt such a correction with cells from any other source (Fernandez, 1998). However, the committee is aware of at least 14 autologous cord blood transplant procedures. With only one autologous transplant reported in the literature thus far (in a child with aplastic anemia), the technique's usefulness remains speculative (Fruchtman et al., 2004).

Outcomes of Transplantation of HPCs from Related Donors

Information reported in IBMTR, ICBTR, and the Eurocord registry has demonstrated that the transplantation of cord blood from a related donor will reliably reconstitute hematopoiesis after myeloablative therapy. In these studies the probability of neutrophil recovery by day 60 after engraftment was 84 percent in one such study, with a median time to neutrophil recovery of 17 days. Platelet recovery[5] was observed at a median of 56 days with a probability of platelet engraftment of 85 percent by day 180 after engraftment (Locatelli et al., 1999). In their report of the results a comparative study, Rocha et al. (2000) reported that cord blood transplantation results in a delayed and lower cumulative incidence of hematopoietic recovery compared with that achieved with bone marrow transplantation. The factors significantly associated with superior engraftment included younger age (Gluckman et al., 1997; Rocha et al., 2000), lower weight (Gluckman et al., 1997), the use of GVHD prophylaxis regimens that did not contain methotrexate (Atkinson, 1990; Rocha et al., 2000; Locatelli et al., 2003), the use of a higher cell dose (Gluckman et al., 1997; Locatelli et al., 1999) and the transplantation of units with closer HLA matches (Gluckman et al., 1997).

In patients with bone marrow failure syndromes, inborn errors of metabolism, and hemoglobinopathies, there appears to be a trend toward a higher risk of primary graft failure, regardless of graft source (Gluckman et al., 1997).

The assessment of the risk of a relapse after the transplantation of cord blood from a related donor is limited by the short duration of monitoring in published studies (median 24 to 34 months) and the inclusion of patients with a range of malignancies at various stages of disease (Gluckman et al., 1997; Locatelli et al., 1999; Rocha et al., 2000). The risk of a relapse of the malignancy in the studies in the Eurocord registry was 26 percent with a

[5]Platelet recovery is defined as an unsupported platelet count $\geq 20 \times 10^9$/liter.

median follow-up time of 29 to 34 months (Nash et al., 1992; Gluckman et al., 1997; Locatelli et al., 1999) and was significantly higher in those who received the transplant during an advanced stage of disease and those with low body weights (<20 kg) (Locatelli et al., 1999). The probability of event-free survival in the studies reported in IBMTR was 41 percent at 2 years. Notably, no increase in the rate of disease-related mortality in cord blood recipients compared with that in those receiving bone marrow was observed (48 and 49 percent, respectively, after a median follow-up time of 27 months) in IBMTR and the Eurocord registry.

IBMTR and the Eurocord registry have reported overall survival rates after the transplantation of cord blood from a related donor of 0.61 (95 percent confidence intervals [CI] 0.49 to 0.83) at 2 years (Barker and Wagner, 2003b) and 0.63 (95 percent CI, 0.57 to 0.69) at 1 year, respectively (Gluckman et al., 1997). In the HLA-identical sibling donor setting, there was no significant difference in the 3-year survival rates between cord blood transplants (survival rate, 0.64; 95 percent CI, 0.53 to 0.74) and bone marrow transplants (survival rate, 0.66; 95 percent CI, 0.64 to 0.68).

These studies demonstrate that the transplantation of cord blood from a related donor results in reliable engraftment, a reduction in the incidence of acute and chronic GVHD, and an overall survival rate equivalent to that achieved with bone marrow transplants.

Graft Versus Host Disease

GVHD is one of the primary complications of transplantation of HPCs from any source. Donor T cells in the transplanted graft attack the tissues of the recipient, a process that occurs even after the transplantation of HPCs from an HLA-identical sibling. The T cells can be depleted from the graft to reduce the possibility of GVHD; however, T cells also have some beneficial effect. Donor T cells can destroy residual recipient lymphocytes, thereby reducing the likelihood that the recipient cells will reject the graft. Evidence also indicates that T cells from the donor actually attack residual cancer cells, thereby increasing the likelihood of a cure.

GVHD is classified into two forms: acute, which generally occurs within the first 100 days post-transplantatation, and chronic, which generally occurs later. Different immune cells and cytokines appeared to be involved in each form of the disease, and different subsets of organs are most affected in each form. Acute GVHD is generally graded from I (mild) to IV (severe); chronic GVHD is generally graded as limited or extensive. There is, however, extensive variability on the part of transplant centers in the diagnosis of acute GVHD. For this reason, any discussion of the relative instances of GVHD should be viewed with careful scrutiny.

The transplantation of cord blood from a related donor is associated

with incidences of grade II to IV (3 to 18 percent) and grade III and IV (0 to 5 percent) acute GVHD and chronic GVHD (4 to 14 percent) lower than incidents that would be expected with bone marrow or peripheral blood transplants (Gluckman et al., 1997; Rocha et al., 2000; Locatelli et al., 2003).

The incidence of grade II to IV acute GVHD (33 to 44 percent), grades III and IV acute GVHD (11 to 22 percent), and chronic GVHD (0 to 25 percent), as reported in studies with large numbers of tranplantations of cord blood from an unrelated donor, varies widely (Gluckman et al., 1997; Rubinstein et al., 1998; Wagner et al., 2002; Grewal et al., 2003). However, all of these incidences are lower than those that would be expected with bone marrow transplants, because most donor-patient pairs were HLA mismatched at one or two antigens. However, most recipients of cord blood have been young (children generally have lower rates of GVHD) and far fewer data are available for adult patients. Rubinstein et al. (1998) reported a low rate of acute GVHD in recipients of HLA-matched cord blood grafts and no increase with increasing HLA disparity (one, two, or three antigen mismatches).

Current data indicate that an HLA mismatch may be better tolerated with cord blood grafts. An IBMTR and Eurocord study that compared the outcomes from children who received a cord blood transplant from an HLA-identical sibling with those from children who received bone marrow from an HLA-identical sibling observed significantly lower incidences of acute and chronic GVHD in the cord blood transplant group (Rocha et al., 2000). That study perhaps provides the clearest indication of a difference in biological properties between the two progenitor cell sources, as the interpretation of GVHD after transplantation of unrelated cord blood and after transplantation of bone marrow is often complicated by different levels of HLA histocompatibility and other patient heterogeneities.

Two other studies have compared the frequencies of GVHD in the receipients of bone marrow and cord blood from unrelated donors (Barker et al., 2001; Rocha et al., 2001). The findings of a matched-pair analysis from a single institution found that the risk of acute GVHD and that of chronic GVHD were similar when the outcomes for recipients of unmanipulated bone marrow matched for HLA-A, HLA-B, and HLA-DRB1 were compared with those for the recipients of cord blood from an unrelated donor mostly mismatched by one or two antigens (Barker et al., 2003). In another study, transplants involving cord blood at zero to three antigen mismatches were associated with a significantly lower risk of acute and chronic GVHD compared with the risk of GVHD from transplants involving unmanipulated, mostly HLA-matched bone marrow transplants (Barker et al., 2001). Study data indicate that despite the greater degrees of HLA disparity that are accepted in cord blood transplantation, the risk of devel-

oping acute and chronic GVHD after the transplantation of cord blood from an unrelated donor with one to two HLA mismatches is similar to or even less than that reported after the transplantation of HLA-matched bone marrow (Barker et al., 2001; Rocha et al., 2001).

The reason for this lower risk of GVHD after cord blood transplantation is not clear. Researchers speculate however that the functional and phenotypic immaturity of cord blood lymphocytes or the reduced T-cell dose infused with cord blood grafts may contribute to the reduced alloreactivity of cord blood (Barker and Wagner, 2003a).

Relapse and Graft-Versus-Leukemia Effect

Current experience comparing the risk of relapse after cord blood transplantation with that after bone marrow transplantation is limited. In an analysis of transplants between HLA-matched siblings, the 3-year survival rates among patients with a diagnosis of a malignancy were comparable after cord blood and bone marrow transplantation ($p = 0.69$) (Laughlin et al., 2004). In another study of HPC transplantation as treatment for acute leukemia in children, Rocha et al. (2001) compared the outcomes among children receiving cord blood and those receiving unmanipulated bone marrow or bone marrow depleted of T cells. The proportion of individuals with advanced-stage leukemia was larger among the individuals receiving unmanipulated bone marrow and cord blood than among the individuals receiving T-cell-depleted bone marrow (9 percent). Interestingly, although the recipients of both T-cell-depleted bone marrow and cord blood had lower incidences of acute and chronic GVHD than the recipients of unmanipulated bone marrow, only the group that received T-cell-depleted bone marrow and not the group receiving cord blood had an increased risk of relapse ($p = 0.02$).

Overall, no evidence available thus far suggests that the risk of a leukemia relapse is higher after cord blood transplantation.

A study in mice and humans showed that the infusion of donor-derived alloreactive natural killer (NK)[6] cells not only provides a graft-versus-leukemia (GVL)[7] effect, but may also protect against GVHD by targeting patient antigen presenting cells (Harris, 1995). Cord blood contains levels of NK cells and inducible NK-like cytotoxic activity similar to those in adult peripheral blood (Harris et al., 1994), which might explain the preserved GVL effect.

[6]Immune cells that do not need to recognize a specific toxin.

[7]The GVL effect is the ability of the immune cells in transplanted HPCs to recognize cancer cells as foreign and attack them.

NHLBI Cord Blood Transplantation Study

NHLBI began the Cord Blood Banking and Transplantation Study (COBLT), a prospective, multicenter study, in 1996 to examine the nascent field of cord blood transplantation. The intent of the study was to collect data from studies on the banking and transplantation of cord blood to create a coherent set of guidelines and standards for the collection, preservation, and transplantation of cord blood (COBLT, 2000b). The primary end point of the COBLT study was the 180-day survival rate among patients who had received a cord blood transplant for the treatment of hematopoietic or immune system disorders. Patients were considered eligible to receive a cord blood unit if they were either unable to find an appropriate bone marrow match or unable to wait for the transplant because of the severity of their illness. An appropriately HLA-matched cord blood unit (a high-resolution match at HLA-DRB1 and a low-resolution match at HLA-A and HLA-B) for the patients also had to be identified, and the patients were required to provide informed consent for the transplantation of cord blood (COBLT, 2000a).

Although the original goal of the study was to bank more than 15,000 cord blood units from a racially and ethnically diverse population, University of California, Los Angeles (UCLA) and the Carolinas Cord Blood Bank of Duke University banked only 8,000 units from 1998 to 2000. Between 1999 and 2003, 326 patients were enrolled to receive a cord blood transplant at 1 of the 28 transplant centers around the country (Carter, 2004). After the patients were enrolled in the study, their HLA types were determined by high-resolution DNA typing methods and were categorized into the 10 strata shown in Box 2-2.

In addition to the 180-day survival end point, the study also collected data on long-term patient survival; incidences of neutrophil engraftment, primary and secondary graft failure, platelet engraftment, red blood cell engraftment, complications, relapses, and appearance of other malignancies; and immune reconstitution. A medical coordination center managed the coordination and statistical analysis of the data from the banks and transplant centers. The center created and maintained a World Wide Web-based data management system to track the multiple variables and provided periodic statistical analysis of the results.

Eligibility

Mothers who gave birth at hospitals affiliated with the UCLA or Duke University banks between 1998 and 2000 were considered possible cord blood donors for the study. Donors were recruited through brochures placed in obstetrical office waiting rooms and presentations to community groups

BOX 2-2
Stratification Variables for the COBLT Study

1. Malignant disease (infant leukemias), total body irradiation/cytokine (TBI/Cy) conditioning regimen, high-resolution HLA match (five or six of six HLAs, ≤18 years of age
2. Malignant disease (infant leukemias), TBI/Cy conditioning regimen, high-resolution HLA match (four of six HLAs), ≤18 years of age
3. Malignant disease (infant leukemias), TBI/Cy conditioning regimen, high-resolution HLA match (three of six HLAs), ≤18 years of age
4. Malignant disease (infant leukemias), TBI/Cy conditioning regimen, high-resolution HLA match (one or two of six HLAs), ≤18 years of age
5. Severe aplastic anemia, Fanconi anemia, and other marrow failure syndromes

6a. Inborn errors of metabolism or storage diseases
6b. Combined immune deficiencies
6c. Other nonmalignant diseases

7. Malignant disease (infant leukemias) with alternative conditioning regimen (bisulfan and melphalan)
8. Adult patients (>18 years of age)

SOURCE: COBLT (2003).

in the areas of the collecting hospitals. Informed consent was obtained before admission to the hospital for labor. However, in the event that it was not possible for the mother to provide informed consent, verbal consent or preliminary informed consent was obtained immediately before or during labor and was reaffirmed after delivery. Of the 35,799 available donors, 20,710 consented to the collection of their cord blood. After the exclusion of units with low cell counts, microbial contamination, and positive serological test results for an infectious disease, and of the units that could not be collected after consent was obtained because of a lack of collection staff, the study was able to cryopreserve 8,731 cord blood units (Cairo et al., 2004).

In 2000, NHLBI convened an ad hoc committe when it realized that the study was not going to meet its goals for collection and transplantation on schedule. The study staff was having difficulty encouraging potential transplant recipients to use what was essentially an experimental product (i.e., cord blood transplantation), and it was competing with other banks outside the study that often had more suitably matched units for the transplant patients. Participation in the COBLT study was increased to include an additional 21 U.S. transplant centers, as well as access to cord blood units banked at the New York Blood Center, NMDP-approved banks, or U.S.

banks meeting FACT/Netcord standards. All transplant centers followed COBLT protocols and reported transplant outcomes according to COBLT protocols. The increase in the number of transplant centers and access to additional units facilitated the completion of the COBLT study. In addition, cord blood units were made available to patients who did not meet specific transplant criteria for the COBLT study strata through a separate protocol called the Expanded Access Protocol. Transplant centers using COBLT units in the Expanded Access Protocol were required to report the transplant outcome data to the COBLT medical coordinating center. The study allowed the use of these external transplant data, as long a COBLT laboratory performed the HLA typing and the transplant center complete the forms required for participation in the COBLT protocol. These requirements were developed to ensure that all outcomes data for the patients with cord blood transplants analyzed in the COBLT study were consistent with those from the centers already participating in the study.

The study made a concerted effort to increase the ethnic and racial diversity of their cord blood inventory, which by extension would increase the diversity of the HLA types with different ethnic and racial populations. The collection centers were specifically tasked to retrieve specified proportions of cord blood specimens from targeted minority populations to ensure that potential minority recipients had a similar chance of locating a unit to any other group. The target distribution of the sources of the cord blood specimens in the bank was 43 percent Caucasian, 30 percent African American, 17 percent Hispanic, and 10 percent Asian American (COBLT, 2000b). As of 2003, the distribution of the blood specimens in the COBLT cord blood banks by ethnicity and race were 42 percent Caucasian, 15 percent African American, 22 percent Hispanic, 9 percent Asian, 11 percent mixed, and 1 percent other (Baxter-Lowe et al., 2003). The study team came to the conclusion that it was possible to provide at least one unit matched at four of six HLAs (minimum cell dose, 1×10^7 total nucleated cells) to 94 percent of patients who were searching for a cord blood unit for transplantation (Baxter-Lowe et al., 2003).

Although the study results are still being evaluated, a definite relationship between the volume of cord blood collected and the nucleated cell counts and $CD34^+$ levels was observed. The study has reported that cord blood samples from African-American women generally have lower nucleated cell and $CD34^+$-cell counts per milliliter of cord blood (Kurtzberg et al., 2004) than samples from Caucasian women. The study also reported that birth weight, gender, gestational age, and type of delivery (vaginal versus cesarean) affect the size and the quality of the cord blood units. It has found that these factors are significant in the selection of units and are important in the development of plans to recruit donors (Cairo et al., 2004).

SUMMARY

This chapter summarizes what is known to date about the relative effectiveness of cord blood transplantation, either allogeneic or autologous in terms of engraftment and GVHD compared to HPC transplantation from other sources (bone marrow or peripheral blood). It also describes the federally funded COBLT, which aims to collect data from the banking and transplantation of cord blood to create a coherent set of guidelines and standards for the collection, preservation, and transplantation of cord blood.

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3
RESEARCH

As the full potential for of cord blood is as yet unknown, there is a great deal of research currently being undertaken to discover its capabilities. This chapter summarizes the current state of that research and discusses the potential future applications of cord blood both for research and for the treatment of different diseases and conditions. In addition, because researchers have cord blood unit selection needs that differ from those of transplant physicians, the committee proposes an approach to prioritizing use.

IMPROVING CURRENT TRANSPLANT TECHNOLOGY

As discussed in Chapter 2, cord blood transplantation as a treatment for children with hematological, immunological, metabolic, and neoplastic diseases has been highly successful. The advantage of cord blood transplants is the relatively low rate of graft-versus-host disease (GVHD) compared with the rates of GVHD that occur as a result of bone marrow or peripheral blood transplants. This low rate of GVHD related to cord blood transplantation allows for the use of partially human leukocyte antigen (HLA)-mismatched cord blood units. However, because of the comparatively low number of hematopoietic progenitor cells (HPCs) in a single cord blood unit, transplantation of cord blood into larger and heavier adult patients presents a unique set of complications. The primary problem for larger patients has been prolonged time to hematopoeitic recovery and immune reconstitution related to the low progenitor cell dose per kilogram

of patient weight. This delayed recovery is associated with a high rate of treatment-related morbidity and mortality.

Research related to the improved clinical use of cord blood is being conducted in four general areas: (1) enhancement of cord blood engraftment, (2) improvements in immune reconstitution, (3) reduction in the rates of treatment-related mortality, and (4) augmentation of immune recognition of infectious agents and tumors. Further research is needed to better understand how cord blood may be used as a source of effector cells (i.e., performing a specific function in the immune system in response to a stimulus) outside the transplant setting. This includes the development of immune regulatory cells that might be useful in solid-organ transplant or for the treatment of autoimmune diseases. Cord blood could also be a source of pluripotent stem cells. Research suggests that these pluripotent stem cells, which are capable of differentiation into, for example, hepatocytes and neural progenitor cells, might be present in cord blood.

Research that may improve the effectiveness of cord blood transplantation for the treatment of a variety of conditions is ongoing, including: nonmyeloblative regimens; the use of ex vivo expansion to increase the numbers of HPCs and the development of new approaches to the acceleration of immune recovery; the use of multiple units in transplantation; the coinfusion of mesenchymal stem cells (MSC); and facilitation of the upregulation of homing receptors.

Cord Blood Transplantation After Nonmyeloablative Therapy

While cord blood as an alternative HPC source has several advantages, including rapid availability and lower risk of GVHD despite HLA-disparity, many older patients, or those with extensive prior therapy or serious co-morbidities, are unable to tolerate conventional myeloablative conditioning. In myeloblative conditioning, the patient's healthy cells are destroyed along with the cancer cells during chemotherapy and total body irradiation. Therefore, reduced intensity or nonmyeloablative regimens are being investigated using either related or unrelated volunteer donors. However, given that many patients will not have a suitable adult donor, use of unrelated donor cord blood in combination with nonmyeloablative conditioning is being investigated in adults to further extend access to allogeneic transplant.

Several studies have been reported thus far. McSweeney et al. (2001) observed engraftment in 2 of 3 evaluable patients receiving fludarabine and total body irradiation 200 cGy. Chao et al. (2002) observed engraftment in 3 of 5 in patients receiving fludarabine cyclophosphamide and antithymocyte globulin. Barker et al. (2003) observed an incidence of sustained donor

engraftment in 90 percent (of 51 patients) at a median of 8 days (range 5–32) with complete chimerism[1] in all. Importantly, in a patient population whose median age was 50 years (range 19–60), the incidences of grade II-IV and III-IV acute GVHD were 61 percent and 27 percent, respectively. Despite this risk of acute GVHD, the 6-month treatment related mortality was low at 18 percent. Factors influencing treatment-related mortality at 6 months were age and poor fitness. Notably, patients older than 45 years of age had a treatment-related mortality of 11 percent. Together, the results indicate that cord blood transplantation after a nonmyeloablative therapy can be associated with a high probability of chimerism, indicating that the alloreactive response of cord blood lymphocytes is sufficient for engraftment and a low incidence of treatment-related mortality despite older age.

Ex Vivo Expansion of Cord Blood Derived Hematopoietic Progenitor Cells

Due to the relatively low volumes of cord blood typically collected, researchers have been interested in developing approaches to increase the volume ex vivo prior to transplant. Ex vivo expansion involves the use of a growth factor to culture a portion of the cord blood unit to increase the numbers of progenitor cells available for transplantation. Cairo and Wagner (1997) have found that 14-day expansion cultures stimulated with interleukin-2 (IL-2) and granulocyte colony-stimulating factor achieved an 80-fold increase in the number of $CD34^+$ cells as compared with the increase in the number of $CD34^+$ cells achieved with similar bone marrow cultures. The cord blood units are generally divided. One part is cultured, and the remainder is frozen so that the expanded portion of the cell culture can be enriched before transplantation (Cairo and Wagner, 1997; Timeus et al., 2003). The cells for culture are purified and then plated in liquid culture for several days.

There are, however, several challenges with regard to ex vivo expansion of cord blood. Notably:

- there is a time delay in increasing the cell dose based on the number of immature progenitor cells available within the sample (Kogler et al., 1998),
- cord blood is generally frozen as a single product; however, clinical trials involve ex vivo expanding a fraction of the unit and then recombining it with the remainder to increase cell dose (McNiece, 2004), and
- some of the companies that produce clinical grade reagents for laboratory trials have begun limiting availability to academic centers.

[1]The presence of more than one genetically distinct set of cells in an individual.

One primary concern is that expansion may induce commitment of and differentiation in HPCs and exhaust their capacity to self renew (Jaroscak et al., 2003). At this point, there has been no late graft failure from ex vivo expanded units in humans, but the follow-up period post-transplant ranges only from 8–51 months (Kogler et al., 1999; Pecora et al., 2000; Fernandez et al., 2001; Shpall et al., 2002; Jaroscak et al., 2003). Clearly, more research is needed to determine if long-term engraftment is successful and whether expanded units maintain functional hematopoietic repopulating cells. In addition, some argue that the cost and resources required to perform expansion far outweigh the minimal clinical benefit demonstrated to date (McNiece, 2004).

Approaches to Accelerate Immune Recovery

The success of allogeneic HPC transplantation regardless of graft source (including cord blood) is limited in part by slow immune reconstitution and consequent increased risk of opportunistic infection. After the infusion of marrow, peripheral blood, or cord blood, immune recovery first results from the immune cells already present in the graft and subsequently from immune cells derived from the HPC. The pace of immune recovery is dependent upon a number of host and donor factors including: HLA match, age of the recipient, development of GVHD, and duration of and types of immune suppressive therapy employed.

Considerable research to effect more rapid immune recovery includes: pharmacological approaches to induce tolerance, infusion of immune cells that specifically target the more common lethal infectious agents (e.g., cytomegalovirus [CMV], aspergillus), and infusion of T-regulatory cells. These potential solutions are being explored and are not specific to any one graft source (Godfrey et al., 2005).

Multiple Cord Blood Unit Transplantation

Based on outcomes data and risk factor analysis, it is clear that limited cell dose is an important obstacle for recipients of cord blood. One strategy to overcome the limitation of cell dose is infusion of multiple units of partially HLA-matched cord blood from different donors.

Literature review reveals the prior use of multiple cord blood units in the treatment of malignancy as early as the 1970s (Ende and Ende, 1972; Shen et al., 1994; Weinreb et al., 1998; Barker et al., 2001; De Lima et al., 2002). However, only more recently have chimerism assays by molecular techniques been used to determine the contribution of each unit to hematopoiesis after cord blood transplantation. Barker et al. (2001) and De Lima et al. (2002) were the first to report "double chimerism" after the infusion

of cord blood from two partially HLA matched units. In contrast, Fanning et al. (2003) observed a high rate of graft failure in a study investigating the safety of multi unit cord blood transplantation to achieve a goal of $\geq 5 \times 10^7$ nucleated cells/kg. Seven adults (median age 56 years) with malignancy received cord blood units containing a median of 5.4×10^7 nucleated cells/kg and 2.2×10^5 CD34/kg. While neutrophil recovery occurred at a median of 11 days in six patients (with one patient dying on day 55 with mixed chimerism but without neutrophil recovery), four failed to have sustained chimerism.

Barker et al. (2001; 2005) reported short-term outcomes in 23 adults (median weight, 73 kg) with high-risk hematological malignancies, using two unrelated cord blood grafts that were 1–2 HLA-mismatched with the patient and each other in 91 percent of the patients. Forty-three percent of the patients received grafts with both units (4/6 matches). Of the 21 evaluable patients, all engrafted at a median of 23 days (ranging from 15 to 41 days), with 24 percent of patients engrafting from both donor units. The remaining patients engrafted from only one donor. In all patients, one unit predominated by day 100. These data demonstrate the safety of double cord blood transplantation in terms of engraftment, thus eliminating the theoretical concern of complete bidirectional immunological rejection. Further, the incidence of grade II-IV was 65 percent and the incidence of III-IV acute GVHD was 17 percent, with 6-month transplant related mortality being 22 percent. With a median follow-up of 10 months (range: 3.5 months–2.5 years), the probability of disease-free survival at 1 year was 57 percent. For those in remission, the disease-free survival rate was 72 percent. The results of these trials indicate that the coinfusion of two partially HLA matched cord blood units is safe as manifested by high incidence of engraftment.

Alternative strategies using two stem cell sources are also being explored. For example, Fernandez et al. (2001) have demonstrated engraftment of cord blood that has been coinfused with T-cell depleted haploidentical peripheral blood HPC. This approach may represent another important clinical strategy for obtaining an earlier transient wave of long-term neutrophil recovery with hematopoiesis derived from a single cord blood unit.

Coinfusion of Mesenchymal Stem Cells

MSC are multipotent stem cells capable of self-renewal and differentiation into multiple cell lines (Pittenger et al., 1999; Deans and Moseley, 2000). These cells produce hematopoietic growth factors within the bone marrow environment and as such play an important role in normal hematopoiesis (Dorshkind, 1990; Deans and Moseley, 2000).

In various laboratory studies, MSCs have demonstrated the ability to: promote engraftment by inducing HPC homing receptors (see below); replace stromal cells damaged by the conditioning regimens; produce hematopoietic growth factor; and suppress T-cell responses to allogeneic stimuli (Blair and Thomas, 1997; Deans and Moseley, 2000; Bartholomew et al., 2002; Noort et al., 2002). This has led to a great deal of interest in MSCs among researchers.

In the mouse, cotransplantation of fetal MSC and low doses of $CD34^+$ cord blood cells increased engraftment in Severe Combined Immunodeficient (SCID) animals by three- to fourfold (Pecora et al., 2000). Similarly, Kim et al. (2004) have recently successfully infused third-party MSC into mice that were receiving a dual-unit cord blood transplant and achieved a higher level of engraftment.

Thus far, one human study of the use of MSCs with cord blood transplantation has been conducted. In that study, eight pediatric patients with high-risk acute leukemia were coinfused with cord blood from unrelated donors and parental MSCs. There were no serious adverse events, and all patients achieved neutrophil engraftment by day 19 (MacMillan et al., 2002). Although this study demonstrates that MSC can be successfully coinfused with HPC, it is still largely untested and will require more research before any conclusions can be drawn about effectiveness.

Upregulation of Homing Receptors

Research has shown that one of the reasons for delayed hematopoietic reconstitution after HPC transplantation may be the disadvantageous transmigratory behavior of HPCs from cord blood. Short-term treatment with recombinant human stem cell factor (rHuSCF) increased levels of homing-related molecules, thereby increasing their ex vivo transmigratory potential as well as their in vivo homing potential. Recent studies have revealed that homing receptors and chemoattractants have an important association with the engraftment mechanism after stem cell transplantation. If the numbers of progenitor cells as well as homing potential could be increased by the ex vivo expansion of cryopreserved and unselected cord blood, it would be beneficial for transplantation into adult patients, and it could also improve the engraftment speed (Lee et al., 2004).

Zheng et al. (2003) suggest that optimal engraftment might be expected from ex vivo manipulation of cord blood progenitor cells to "reverse their disadvantageous transmigratory behavior in the clinical setting."

Another study showed that although expansion of the cord blood $CD34^+$ cells may affect other cell properties, it can preserve most of the homing-related characteristics and activities of cord blood (Zhai et al., 2004).

OTHER CLINICAL USES OF CORD BLOOD

In addition to treatment of blood and blood-related diseases, cord blood has the potential to be an effective therapy in certain inherited diseases. The current literature on these uses is summarized in Box 3-1. A comprehensive listing appears in Table 3-1.

BOX 3-1
Examples of Effective Clinical Use of Cord Blood in Treating Inherited Diseases

Fanconi Anemia. First use of cord blood was a sibling with Fanconi anemia. Several subsequent studies have verified that cord blood is an effective alternative to marrow for the treatment of this disease (Gluckman et al., 1990; Auerbach et al., 1990; Kohli-Kumar et al., 1993; Aker et al., 1999; Guardiola et al., 2003, 2004.

Sickle Cell Anemia. Sibling cord blood transplantation has been an effective treatment. Recent research is focused on the use of nonmyeloablative preparatory regimens (Brichard et al., 1996; Vermylen and Cornu, 1997; Vermylen et al., 1998; Miniero et al., 1998; Gore et al., 2000; Locatelli et al., 2003; Barker et al., 2005).

Beta Thalessemia. Sibling cord blood or mixed marrow and cord blood transplantation have been successful. Research on unrelated cord blood transplantation is in the beginning stages (Issaragrisil et al., 1999, 1995; Gedikoglu, 2001; Goussetis et al., 2000; Orofino et al., 2003; Locatelli et al., 2003; Miniero et al., 1998).

Hurler Syndrome. Unrelated transplant trials involving 20 patients at Duke University have been successful. The stage of the disease at time of transplant has been shown to affect outcome. Larger clinical trials are needed to better understand the full range of cord blood's potential as a treatment (Staba et al., 2004; Muenzer and Fisher, 2004).

Severe Combined Immunodeficiency. Long-term engraftment has been demonstrated in mice. A 2-month-old female was successfully treated with no pretreatment with a transplant from a fully matched donor (Hogan et al., 1997).

Osteopetrosis. Bone marrow transplantation is the only fully proven treatment. However, bone reabsorption has been achieved with cord blood transplantation. Due to the strain of conditioning regimines, this treatment is generally only reserved for the most severe cases (Locatelli et al., 1997; NIH, 2000).

Wiskott-Aldrich Syndrome. In a data set involving 33 patients transplanted with units provided by the New York Blood Center, 90 percent engrafted, and 63 percent achieved 5-year survival (New York Blood Center, unpublished).[a]

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[a]Personal communication between John Wagner and Cladd Stevens of NYBC (3/13/05).

TABLE 3-1 Genetic Diseases Treatable by Transplantation of Cord Blood

Disease
Immune Deficiency
• X-linked SCID
• X-linked a-γ-globulinemia
• Wiskott-Aldrich syndrome
• Chédiak-Higashi syndrome
• Chronic granulomatous disease
• Adenosine deaminase (ADA) deficiency
• Purine nucleotide phosphorylase deficiency
• Gaucher disease, type 1
Bone Marrow Failures
• Osteopetrosis
• Thalassemia
• Sickle cell disease
• Fanconi anemia
• Dyskeratosis
Metabolic Storage Disorders
• Adrenoleukodystrophy
• Metachromatic leukodystrophy
• Adrenoleukodystrophy
• Metachromatic leukodystrophy
• Mucopolysaccaridoses
– Hurler syndrome
– Hunter (X-linked)
– Sanfillippo
– Morquio
• Maroteaux-Lamy
• Lesch-Nyhan syndrome (X-linked)

Umbilical Cord Blood as Effector Cells

More recently, there has been increasing interest in the immune cell populations present in cord blood as a potential source of cells for adaptive immune therapy. For example, cord blood derived natural killer (NK) progenitor and T-cell subpopulations have been isolated and expanded in culture as anti-tumor therapeutic reagents (Miller and McCullar, 2001). Furthermore, $CD4^+$ $CD25^+$ T cells with profound immunoregulatory properties have been expanded in culture to be used as agents to induce tolerance (Miller and McCullar, 2001) Therefore, it is possible that partially matched or mismatched cord blood units may be important as a source of immune cells and not just as an HPC source for transplant medicine.

UMBILICAL CORD BLOOD IN REGENERATIVE MEDICINE

Although the primary use of cord blood has been to restore hematopoietic function, a number of other potential applications are possible, but these require further research. While there have been limited successes in controlled laboratory settings, it is unlikely that any of these studies will translate into clinical applications in the near future. Rather, they should be considered a guide for future studies using carefully thought-out animal models. Table 3-2 summarizes the present areas of nonclinical research underway with cord blood.

One of the earliest reports that HPC might be capable of generating other tissues was in 1998 (Goodell, 2004). In that study, researchers lethally irradiated rats and damaged their skeletal muscles. After the rats received a bone marrow transplant, donor nuclei were found in the skeletal muscles at very low frequencies. Similar studies found that donor-derived cells could also be found in heart, liver, gastrointestinal, and neural tissues. The prevalence of these transdifferentiation events has varied widely, and some researchers feel the event is actually cell fusion rather than transdifferentiation. However, research has continued.

TABLE 3-2 Summary of Current Research

Type of Research	Reference	Status
Cardiac repair	Perry and Roth (2003)	Capillary-like tubes are grown in culture
	Vanelli et al. (2004)	Transplants in animals have led to improved cardiac function
Central nervous system disease	Newman et al. (2004)	Mice with amytropic lateral sclerosis improved after transplantation
Spinal cord injury	Saporta et al. (2003)	HPCs engrafted in the area of injury in rats
Stroke	Taguchi et al. (2004)	Vascular activity in damaged area in mice increased post-transplantation
	Willing et al. (2003)	Motor improvement was noted in mice post-transplantation
Brain damage	Jensen et al. (2003)	Hypoxic mice showed improvement posttransplantation
Liver injury	Di Campli et al. (2004)	Potential for transdifferentiation was first noted in humans posttransplantation
Gastrointestinal	Ishikawa et al. (2004)	Minimal transdifferentiation for intestinal tissue was noted

Because early research focused on whole bone marrow, the next step was to refine the marrow to ensure that it was the HPCs and not other cells in the bone marrow that served as the source of the observed donor cells. This has been achieved in several cases and the donor cells have been observed at very low frequencies.

Researchers have observed donor cells in nonhematopoietic tissue among humans who have received sex-mismatched transplants. Most scientists believe, however, that this does not demonstrate transdifferentiation so much as it demonstrates the ability of the donor cells to circulate (Goodell, 2004).

A final open question with regard to cord blood in nonhematopoietic applications is the presence or absence of the more plastic MSCs. MSCs are a rare form of multipotent progenitor cells capable of supporting hematopoiesis and of differentiating into osteogenic, adipogenic, myoblastic, and chondrogenic cell lines. Several investigators (Wexler et al., 2003; Gang et al., 2004; Bieback et al., 2004) have been able to culture MSCs from human bone marrow, but they have been unable to do so with umbilical cord blood. For this reason, these researchers have concluded that given the current level of knowledge, cord blood is unsuitable for cell therapy applications. Similarly, research by Yu et al. (2004) demonstrated the ability to isolate MSCs from cord blood collected after preterm deliveries, but not from blood extracted after full-term pregnancies.

Bieback et al. (2004) have, however, been able to isolate MSC-*like* cells from cord blood. Their success, however, is relatively isolated (63 percent of 59 units), and they were successful only under optimized isolation and culture conditions. It is also worth noting that they were able to generate only osteogenic and chondrogenic progenitor cell lines but were not able to develop adipogenic-like cells. Gang et al. (2004) were able to grow myogenic precursor cells; however, their ability to do so was limited and growth seemed to peak at day 3 after the initiation of culture, indicating the need for further research.

Some of the more specific research being conducted is summarized in the following sections.

Cardiac Repair

Perry and Roth (2003) have described the present potential for reconstructing human cardiac cells from bone marrow, peripheral blood, and cord blood. They described a study in which cord blood stem cells were treated with vascular endothelial growth factor and basic fibroblast growth factor and noted the formation of capillary-like tubes. Other research discussed by Perry and Roth isolated HPCs from cord blood, cultured them in a pulse duplicator bioreactor on a conduit artery scaffold, and found that

the constructs were very similar to those of native tissues (Perry and Roth, 2003).

Vanelli et al. (2004) indicated that the study of cardiac stem cell precursors in human cord blood and bone marrow will lead to a better understanding of the biology of human cardiac cell differentiation, in addition to providing practical applications. They write that studies with animal models have shown that transplantation has led to improved cardiac function. They further note, however, that when transplanting large populations of unsorted marrow or unmanipulated cord blood, researchers should take into account the fact that only a small fraction of such cells will reach the desired organ.

Central Nervous System Disease

Newman et al. (2004) have described some of the current research being conducted using HPCs from cord blood to treat diseases of the central nervous system. A study involving the transplantation of HPCs into mice with amyotropic lateral sclerosis found that the mice showed improvements in motor function, lost weight, and lived longer than the mice that did not receive the HPCs. The mice in that study received the transplant before the onset of significant motor deficits. They were then analyzed for evidence of donor cells. Some of the donor cells located in the central nervous system were found to express neural cell phenotypes. These are the first data to suggest that donor HPCs are capable of both in vivo differentiation and migration to the brain and spinal cord in the absence of injury.

Again, however, much more research is needed before these successes can be considered indicative of what might happen in humans.

Spinal Cord Injury

Saporta et al. (2003) noted the ability of cord blood cells to target and migrate to areas of damage and engraft therein after intravenous infusion. Building on this knowledge, they examined the ability of cord to target a zone of compression injury in the spinal cord of adult male Sprague-Dawley[2] rats.

The researchers compressed the spinal cords of these rats and infused cord blood at either 1 or 5 days post injury. By prelabeling the cells, the researchers were able to demonstrate that the cord blood engrafted in the areas of the spinal cord injury. They postulate that the cord blood entered the areas of damage through damaged blood vessels at the site of the injury

[2]A widely accepted, dependable, and general-purpose strain of rat used as a research model.

or through a compromised blood-brain barrier at sites of secondary damage. The harvested cells did not, however, show evidence of differentiation.

In addition to the evidence of engraftment, the rats also showed significant behavioral improvement compared with the behaviors of the rats that had not received the cord blood. The number of cells transplanted, however, was not enough to restore significant motor function.

Recent reports (AFP, 2004) from Korea, however, indicate that cord blood transplantation may have promising applications in humans with spinal cord injury. A 37-year-old woman who had been paralyzed for almost 20 years reportedly regained the ability to walk after she received a cord blood injection directly in the damaged part of the spinal cord. Other researchers (Willenbring et al., 2004) caution against drawing conclusions from this isolated incident and believe that this research needs to be reliably replicated before it can be regarded as a potential therapy.

Brain Injury

Stroke

In individuals with stroke, blockage of the blood vessels leading to certain areas of the brain causes focal ischemia and subsequent degeneration of the tissue (Peterson, 2004). The severity of degeneration depends on the location and the extent of the injury. In most cases, however, recovery from stroke is not a result of the recovery of the tissue but, rather, is a result of the development of new neural pathways in undamaged regions.

Taguchi et al. (2004) modeled stroke in genetically modified SCID mice. Human $CD34^+$ cells from cord blood were administered to the mice via the tail vein within 48 hours after an induced stroke. Mice that received the cells displayed new vascular activity within 24 hours of the transplant and had significantly enhanced cerebral blood flow (Taguchi et al., 2004). These mice also displayed significant improvement on behavioral tests compared with behaviors of control mice and mice that received $CD34^-$ cells (Taguchi et al., 2004).

Willing et al. (2003) have found that mononuclear cells in cord blood function similarly to MSCs in bone marrow. These investigators also transplanted cord blood into rats with stroke, and although the number of rats was small, they also noted significant improvements in motor skills and behavior compared with those of the rats that did not receive cord blood.

Non-Stroke-Related Brain Damage

Jensen et al. (2003) researched the potential of cord blood transplantation as a treatment for children who were brain damaged because of hy-

poxic incidents during birth. They note that the central nervous system, unlike other tissues, has a limited regenerative potential. The transplantation of cord blood, they argue, could be a new therapy.

They reproduced the hypoxic injuries in rats and after transplantation noted markedly improved behavior in the rats that received cord blood transplants compared with the behavior of untreated control rats.

Toxic Liver Injury

Di Campli et al. (2004) compared several studies using both animal models and humans and have highlighted the potential of HPCs to transdifferentiate into nonhematopoietic cells. Marrow-derived hepatocytes were first noted in a rat model that showed male cells in female recipients. Those cells not only had the physical characteristics of liver cells, but also demonstrated the appropriate synthetic and metabolic functions.

Di Campli et al. (2004) noted, however, that the time course of the transdifferentiation process has never been fully explored. They also noted that the number of cells present is well below the therapeutic level needed for the effective treatment of some disorders.

Gastrointestinal Disorders

Inflammatory bowel disorders, such as Crohn's disease and ulcerative colitis, often require novel treatments. Ishikawa et al. (2004) analyzed the capacity of human bone marrow- and cord blood-derived progenitor cells to generate gastrointestinal epithelial cells. To do this, they analyzed gastrointestinal specimens from pediatric and juvenile recipients of allogeneic sex-mismatched progenitor cell transplants and looked for evidence of donor-derived cells (Ishikawa et al., 2004). None of the human patients exhibited any chimerism. However, upon closer inspection under an electron microscope, donor-derived cells could be found at frequencies between 0.4 and 1.9 percent.

The researchers then performed similar experiments with mice and T-cell-depleted human bone marrow and cord blood mononuclear cells. They injected these cells into newborn mice after the mice were subjected to total body irradiation. After determining that the mice exhibited hematological chimerism, the researchers harvested gastrointestinal tissues from the mice. The results of this experiment indicated that xenogenic transplantation can regenerate epithelial cells in intestinal tissue as well as reconstitute lymphocytes.

Gene Therapy

Newman et al. (2004) postulated that HPCs are promising targets for gene therapy. In theory, the progenitor cells within the mononuclear cell population of cord blood can be used as cell-based gene therapy.

DEVELOPING RESEARCH PRIORITIES

The general consensus is that HPCs can be incorporated into nonhematopoietic tissue, but with very low efficiency. Whether cord blood will be the optimal source for the regeneration of nonhematopoietic tissues is unknown (Goodell, 2004). However, strategies are being developed to improve the efficiency of transdifferentiation with the long-term aim of using HPCs in therapies for nonhematopoietic diseases. Further research, including adequate animal studies, is clearly needed to better understand the nonhematopoietic potential of cord blood. Furthermore, given the limited availability of cord blood for research purposes it is important that nonclinical units not be discarded or destroyed.

Recommendation 3.1: Federally funded umbilical cord blood banks should have a mechanism by which they can make available for research use units not appropriate for clinical use according to the priority standards developed by the National Cord Blood Policy Board proposed by the committee (see Chapter 7).

The committee suggests that the proposed National Cord Blood Policy Board consider that the following types of research be given priority for nonclinical use of cord blood:

- research funded by the National Institutes of Health,
- peer-reviewed research receiving other government funding,
- other peer-reviewed research, and
- other unfunded but innovative research proposals.

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4

Umbilical Cord Blood Banks and Banking

The centers that collect, process, and store umbilical cord blood differ in their organization and governance as well as in the cord blood processing methods that they use. The absence of a standard, generally accepted search algorithm and differences in cord blood bank quality make it difficult for transplant physicians to know when it is most appropriate to use cord blood instead of an alternative sources of hematopoietic progenitor cells (HPCs). Furthermore, difficulties with human leukocyte antigen (HLA) typing of HPCs to the level required for cells from adult and cord blood donors make it difficult to compare and contrast the results of a search for HPCs from these two types of HPC donor sources.

Federal and state laws and regulations govern the operation of cord blood banks, and many are accredited through a variety of mechanisms. Yet the rules are not standardized and a more consistently applied set of regulations would benefit both the cord blood banks and end users. Finally, existing cord blood collections lack sufficient ethnic and racial diversity to ensure adequate probability of finding HLA-matched units for some ethnic and racial groups, which is a particularly important barrier to the fundamental goal of unimpeded access to needed treatment. Thus, donor recruitment efforts should include greater attempts at outreach to populations whose HLA types are underrepresented in cord blood collections and the development of innovative approaches to donor recruitment.

This chapter discusses the results of a survey that the committee conducted to assess current cord blood banking practices; describes procedures for the collecting and processing of cord blood; discusses the procedures used to access units; and delineates the current status of laws, regulations,

and professional standards as they are applied to cord blood banking. The committee also makes recommendations on how to improve the system of cord blood collection, processing, and storage.

DEFINITION OF A CORD BLOOD BANK

A cord blood bank is a center whose central mission is to maintain a supply of cord blood for therapeutic use in transplantation. Figure 4-1 depicts the various aspects of the collection, storage, search and transplantation processes.

In most cases, a mother will register with a bank prior to giving birth. Upon adequate completion of the informed consent (more on the informed consent process can be found in Chapter 5), the mother's obstetrician is informed of her wish to be a donor, and arrangements are made to collect the cord blood. This is either by providing the mother with a kit or, if the delivery hospital is affiliated with a bank, by noting it in the mother's chart. In most cases, the collected blood is then transported to the bank in order to obtain volume and cell count. If both are high enough, the unit is processed, and samples are taken for infectious disease testing. If the review of the maternal history and infectious disease testing are both within the bounds established by the bank, another sample is sent for HLA testing. Because obtaining HLA type is the most expensive part of the process, this is generally not done until the unit meets the bank's requirements in all other ways and is the last step before listing in a database.

Cord blood banks have been established in response to the needs of different patient populations, and the motivation to store cord blood varies from person to person. For some, there might be an immediate need within the family to treat a disease amenable to transplantation, for example to a sibling or a closely matched family member. Alternatively, a woman or a couple might donate altruistically (as with blood donation) by offering the cord blood as a public resource to be available for others with the need for an immediate transplant. Finally, some donors choose to contribute to research. Table 4-1 summarizes the primary banking options available to new mothers.

For the purposes of this report, the committee has classified cord blood banks into three main categories. *Public banks* store unrelated cord blood units that are philanthropically donated for transplantation or research purposes. The relevant information (e.g. HLA types, cell counts, and in some cases, the donor's medical history) is then stored in a database made available to transplant centers searching for a cord blood unit for patients. Some public banks also store a limited number of units for autologous or family use when a disease that is treatable by cord blood transplantation is known to exist within the donor's family. In these circumstances, the blood

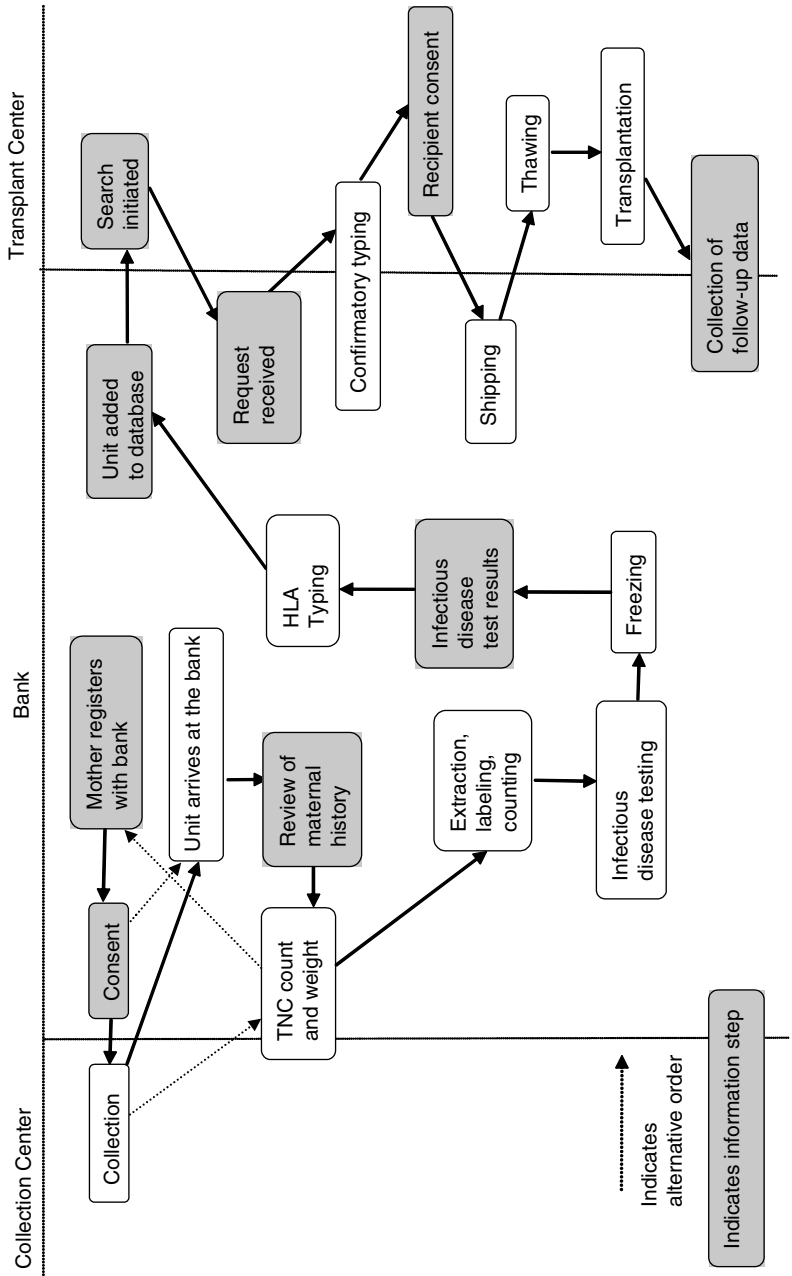


FIGURE 4-1 Major components in the process of cord blood collection, banking, and transplantation.

TABLE 4-1 Cord Blood Banking Options

	Type	Purpose Fee
Option 1: autologous banking (banking for future use by the infant from whom the cord blood was obtained or immediate family members)	Maintain a stored unit in the event that donor or a family member needs a hematopoietic stem cell transplant	Variable; involves an initial banking cost ($1,000 to $2,000) and then a yearly maintenance fee ($50 to $150)[a]
Option 2: philanthropic donation	Unit will be saved for potential use by the general public	No fee
Option 3: research donation	Procurement directed to an institution researching the properties of umbilical cord blood units	No fee to family but some research organizations are charged
Option 4: directed donation[b]	Collection to serve a patient in need, usually a sibling or other family member	Usually offered by the transplant centers no cost to the family; also offered by some public and private banks; transplant centers may be charged to procure the unit

[a]If there is a history of a genetic disease or condition or a malignancy within the family, it is possible that insurance will cover these costs. Select banks waive the fees for individuals with a family history of a disease or a condition or a malignancy.

[b]Cord blood banking options should be presented to the family if a family member has a current or a potential need to undergo a stem cell transplant.

is often stored for a short time and the bank provides the necessary processing and testing to aid the transplant physician Units that do not meet standards for clinical use may be used for quality improvement or research.

Private banks store cord blood units only for autologous or family use. These banks generally charge a fee for the collection, processing, and storage of the cord blood and leave any decisions regarding the use of the unit to the donor or the donor's family. These banks tend to describe their service as offering "biological life insurance" that provides peace of mind to families that might be concerned about future health conditions in the child or a close relative for which cord blood transplantation might be a possible treatment. If the family decides to discontinue banking the unit, with their consent it may be made available for research.

Mixed banks not only collect unrelated units donated for transplantation to unrelated recipients but also operate facilities for cord blood bank-

ing for autologous use and use by family members. The money received from private banking activities can help to offset the costs of public banking activities at these facilities. Both public and private units are processed and stored at the same facility; however, as with fully private banks, the private units are the property of the donor's family and are not available for general use. As with fully public banks, units that do not meet quality standards may be used for quality improvement or research. If a family decides that it no longer wishes to maintain ownership of a unit, it is conceivable that the unit would then become available to the public for unrelated transplantation to patients unrelated to the family or for research, if the family consents.

Some cord blood companies exist on a for-profit basis by obtaining unrelated units, expanding them, and making the same unit available to multiple recipients. However, this very small field was one that the committee chose not to focus on.

As an expectant mother's primary source of information about banking options is her obstetrician, it is very important that obstetricians fully understand the different options available, and be able to effectively convey that information to the mothers. Further, as the obstetricians are not reimbursed by the public banking system the way they are with many private banks, it is also important that they fully "buy in" to the advantages of the public system.

STATUS OF CURRENT BANKS: RESULTS OF A SURVEY

The committee identified 40 cord blood banks in the United States (see Appendix C). Based on the responses (both full and partial) of 21 of those 40 banks to a survey that the IOM committee distributed in the summer of 2004, the committee found that 9 banks store both public and private units, 8 store only public units, and 4 store only private units. However, among those banks that store both types of units, most banks predominantly stored public units, with small private programs on the site.

The committee's survey asked banks to indicate their accreditation status (e.g., American Association of Blood Banks [AABB] and Foundation for the Accreditation of Cellular Therapy [FACT]), although the committee could not always verify this information when it consulted with the agencies providing accreditation to confirm the information. Slightly more responding banks (n = 11) self-reported AABB accreditation than FACT accreditation (n = 6). Only LifeCord indicated that it is accredited by both AABB and FACT. One bank indicated pending FACT accreditation, and two other banks responded that they will be or are in the process of accreditation. Four of the banks also indicated accreditation by the National Marrow Donor Program, which is not considered an accrediting agency. Thus,

the accreditation status of the banks varies substantially, which also reflects the diverse practices and goals that exist among the banks.

One practical example of this diversity is the different standards for banking cord blood units. Most banks require at least 40 to 50 ml for banking, although the volumes range from 10 to 50 ml.[1] The total nucleated cell (TNC) count dose requirement was most often 8×10^8 or 9×10^8 cells, but that, too, varied among the banks.[2] Some private banks indicated that they may store units that are smaller than what is currently considered clinically useful after they inform the parents of the donor and receive confirmation of their wishes.

Without a single system of accreditation, the banks' standards can be expected to remain quite variably enforceable.

Recommendation 4.1: The Health Resources and Services Administration should identify a Cord Blood Accrediting Organization by means of an open, competitive request for proposal process. This organization should be charged with the delineation of standards for any cord blood bank, collection center, or transplant center desiring to participate in the National Cord Blood Stem Cell Bank Program.

Size of Identified Banks

The committee's survey found that the number of units collected by banks also varied considerably and were as follows: Viacord, >60,000 units; St. Louis Cord Blood Bank, >40,000 units; the National Cord Blood Program of the New York Blood Center, 29,525 units; the American Red Cross Cord Blood Program, 18,680 units; Lifebank USA, 17,228 units; the Carolinas Cord Blood Bank, 17,000 units; Cryobanks International, Inc., 15,429 units; and StemCyte International Cord Blood Bank and Cord Blood Family Trust, 13,566 units.

Collection Processes

All but three of the cord blood banks indicated that obstetricians are among those who perform the cord blood collection. Staff nurses and designated collectors from the cord blood bank were also among the collectors at most delivery centers. No banks selected the "researcher" or the "other" category for this question, which was phrased as "Who collects the blood?"

[1]National Marrow Donor Program's protocol requires 40 ml. Lifebank USA requires 35 ml. Sibling Cord Blood Program (CHORI) requires 20 ml. Viacord requires 10 ml, and StemCyte requires 10 ml.

[2]Engraftment speed and survival are related to the TNC count of the graft.

Variation in this arena, including training of the cord blood collection staff, may account for the differences in the volume collected and the rates of disqualification of units for contamination and other reasons.

Storage Methods

Most cord blood banks store units as a red blood cell-depleted product (also referred to as a mononuclear cell[3] product) with the exceptions of ITxM Cord Blood services, the Sibling Donor Cord Blood Program, and StemCyte International Cord Blood Banks and Cord Blood Family Trust. The most popular anticoagulant and cryoprotectant agents were citrate-phosphate-dextrose (CPD) and dimethyl sulfoxide (DMSO), respectively. The majority of banks also indicated that they store the units in the vapor phase of liquid nitrogen.

There are limited data available relating to the viability of cord blood units stored long-term. Though research suggests that units can be stored for extended time frames (as many as 12 years) with no reduction in viability, proof of this concept is needed, and research into this area is critical (Broxmeyer, 1995).

Although some researchers argue that the vapor phase of liquid nitrogen is inadequate because the temperatures are slightly higher than those of liquid nitrogen itself and also allow for temperature variations when the lid of the storage container is opened, use of the vapor phase is substantially more economical, given the reduced liquid nitrogen needs, and this method also assists in the prevention of the spread of potential contaminants.

PROCESSING PROCEDURES

Screening Maternal Donors and Cord Blood

Cord blood acquisition must be done carefully because of the potential presence of transmissible diseases or pre-existing genetic conditions and possible contamination with maternal cells and microbial agents. As mentioned above, the collection and processing practices and procedures vary substantially among the cord blood banks. Both banks and transplant centers should use current best practices to ensure that the transplanted unit is safe and that everything possible has been done to ensure the success of the graft as well as the health of the patients who have received the graft.

Once consent for the collection of cord blood has been obtained (see the discussion of consent issues in Chapter 5), an extensive behavioral

[3]Includes precursors to white blood cell macrophages.

history is undertaken to determine whether the mother is likely to belong to a group that engages in a behavior that might pose a health risk to the recipient of the banked cord blood unit (e.g., risky sexual behaviors or illicit drug use). In addition, maternal and family histories for inherited genetic disorders are taken. The unit is screened for bacterial, viral, and fungal infections through testing of specimens obtained from the unit before it is frozen. A portion of the cord blood specimen is generally frozen as separate segments that may or may not be attached to the main unit to allow further, more complete testing for infectious diseases or genetic disorders if the unit is identified to be useful for transplantation or is able to fulfill some other need.

Collection of Cord Blood Units

Cord blood can be collected from the placenta at two different times. It can be collected after delivery of the baby but before the placenta has been delivered, or it can be collected in a separate room after the placenta has been delivered. In either case, after sterilization of the umbilical cord to minimize the possibility of contamination, a large-bore needle is used to drain the cord blood, which is placed into a closed bag containing an isotonic anticoagulant at a neutral pH (Rubinstein et al., 1995).[4] The former method is generally performed by obstetrical staff (e.g. the physician, nurse, or midwife) as part of the delivery procedure, whereas the latter method is generally performed by trained technicians or nurses outside of the delivery room.

Collection methods that rely on individuals other than cord blood bank staff can offer the possibility of cord blood collection in remote locations, which could greatly expand the donor pool. However, means for the ongoing training of the collection personnel and the promotion of standard protocols would have to be developed to ensure the quality of the units.

Wall et al. (1997) found few differences in either the volumes collected or in the total cell counts of the units collected either before or after delivery of the placenta. Other studies reported higher volumes and $CD34^+$ cell counts if collection was performed before the delivery of the placenta (Surbek et al., 2000; Solves et al., 2003). These variations may be due to the additional time involved in the ex utero collections, which allow the formation of microscopic clots, thereby reducing the number of cells available in the unit (Wong et al., 2001). Alternatively, uterine contractions after delivery of the fetus may enhance drainage of placental blood. Collection after delivery of the placenta results in no difference in the volumes of cord blood

[4]At least one private bank also offers obstetricians the option of collecting the cord blood in a large syringe.

recovered. However, higher rates of microbial contamination in the units collected ex utero have been reported, possibly as a result of the additional handling of the placenta before cord blood collection (Solves et al., 2003).

Several factors have been shown to affect the $CD34^+$ counts and the numbers of colony forming units of granulocytes-macrophages (CFU-GM) in the cord blood units, including gestational age, length of labor, time of cord clamping after delivery, birth weight, placental weight, and birth order (Donaldson et al., 1999; Ballen et al., 2001). The first baby in the birth order, an extended duration of labor, and increased neonatal weight are all associated with a higher overall cell count, whereas more advanced gestational age has been noted to increase the number $CD34^+$ cells until 37 weeks of gestation, at which point they begin to decline. Smoking has been shown to have a negative effect on the $CD34^+$ cell count because smokers tend to have lower birth weight babies (Ballen et al., 2001). Grisaru et al. (1999) reported that placement of the infant on the mother's abdomen after delivery significantly increases the number of cells in the cord blood units collected. Attempts to increase the number of units successfully collected should not be undertaken, however, if the collection of cord blood will change normal obstetrical attention to the health of the mother and infant.

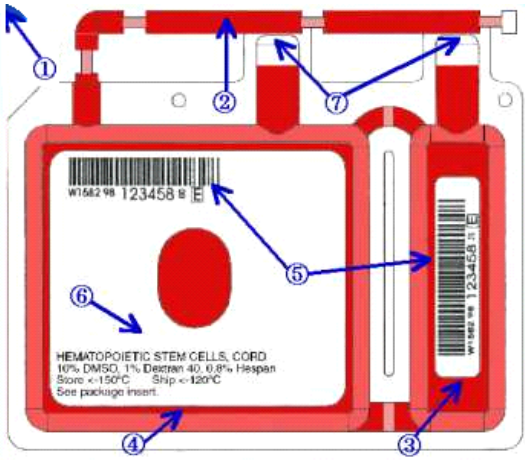
All of those factors will need to be taken into account when considering the standards for the collection of cord blood. In addition, it is very important that the accrediting organization contact those currently in the practice of both collecting and storing cord blood in order to ensure that the standards are both reasonable and effective.

Recommendation 4.2: Uniform standards for the collection of cord blood units without alteration of safe obstetrical practice should be established by the Cord Blood Accrediting Organization suggested in Recommendation 4.1 and should be required of all banks participating in the National Cord Blood Stem Cell Bank Program.

Transport of Cord Blood and Cell Viability

A decentralized system has certain cost benefits because the infrastructure needed to support the processing, screening, and storage of cord blood units is expensive and requires significant space and resources. However, the transport of cord blood from the remote collection site to the processing and storage site is a quality concern because of the lack of temperature control and the potential for a decline in cell viability.

Through regression analysis, a 1 percent drop in cell viability was demonstrated for every 4-hour increase in transit time (Wada et al., 2004). That study also detected a noticeable decline in the viabilities of the cells in lower-volume units, although this was hypothesized to be the result of a



1 A hermetically sealed over wrap bag serves as a quarantine bag
2 Detachable aliquots of the cell solution for confirmatory testing
3 A detachable compartment of the freezing bag for optional ex vivo expansion of 20% of the volume
4 Main compartment of the freezing bag containing 80% of the cells (sufficient for engraftment)
5 Bar codes linking both compartments, the canister and the donor of the cells
6 Label with product name, cryoprotectant solution, required storage and transit temperatures
7 Spike entry ports to allow transfer of the thawed cells

FIGURE 4-2 Example of storage container for cryopreservation of cord blood units.
SOURCE: Courtesy of Thermogenesis Corp.

greater effect of the anticoagulant on the pH of the lower-volume units; the higher volume units were not as affected (Wada et al., 2004). Hubel et al. (2004) found that the cells in units stored for up to 24 hours at room temperature before processing and cryopreservation exhibited very little loss of viability.

Storage

Cryopreservation[5] is the standard practice for long-term storage of cord blood units for transplantation. Engraftment of stem cells from cord blood has been shown to be successful from cryopreserved units that were subsequently thawed by careful, specific procedures (Galmes et al., 1995, 1999; Rubinstein et al., 1995; Rubinstein, 2001, 2004; Timeus et al., 2003). Additional studies have examined the proliferative potential of cells stored for up to 10 and 15 years and reported good results with in vitro expansion of these samples (Broxmeyer and Cooper, 1997; Kobylka et al., 1998). During the processing and freezing of the unit, alterations in the rates of cooling during the initial stages of cryopreservation have been shown to affect the recovery of cord blood after thawing. Rates of cooling in excess of –5°C per minute were found to significantly reduce the colony-forming cell (CFC) activity after thawing (Creer, 2004). An example of a storage bag is shown in Figure 4-2.

[5]Preservation of biological materials at extremely cold temperatures.

The entire, unprocessed unit is generally not frozen, as storage in a liquid nitrogen freezer is quite expensive and the maximization of storage space is important. Various processing methods that reduce the volume required for storage but that maintain the viability of the cells in the finished product have been identified. These processes have been designed to remove the cells not needed for successful engraftment, leaving the desired transplantable stem cell material available for storage.

A plasma volume expanding medium (e.g., Hespan or Pentaspan) is added to the unit to facilitate separation of the red cells from the white cells containing the progenitor cells needed for engraftment. The units are then centrifuged to remove excess red blood cells and to reduce the unit to a volume more suitable for efficient long-term storage (Alonso et al., 2001). After additional centrifugation, the plasma is extracted to reduce the volume to about 20 ml.

A 10 percent DMSO solution is added as a cryopreservative to protect the cells from damage as a result of the freezing process. The units are then frozen before they are stored in liquid nitrogen, where they remain until they are ready to be used for transplantation.

Studies have shown that cross-contamination among units in a freezer is possible even at the extremely low temperatures provided by liquid nitrogen (Tedder et al., 1995; Fountain et al., 1997). For this reason, it is also important to protect against the possibility of transmission of such pathogens as hepatitis B virus (HBV) and contamination with other microbes during storage of the cord blood unit. Banks should use protective measures to prevent any inadvertent transmission of an infectious agent from occurring during the storage of their units.

Before the units are used for transplantation, they are thawed in ambient air or a water bath, or both. The cryopreservative agent (DMSO) is often diffused out of the cells by use of an isotonic salt solution (5 percent Dextran 40 and 2.5 percent human albumin), centrifuged, and then resuspended in a albumin-dextran solution for infusion (Rubinstein et al., 1995). Rubinstein et al. (1995) have reported that failure to wash the cryopreservative off of the cells may result in a 65 percent reduction in the viabilities of the leukocytes (white blood cells) and a 40 percent reduction in the viability of the cord blood units compared to units that have been washed. There is also a concern of DMSO toxicity in some patients, especially very young recipients.

Matsumoto et al. (2002) have attempted to further simplify the process of short-term storage of cord blood units by using supercooling instead of freezing the units in liquid nitrogen. Although this technique results in significantly better cell survival rates than cryopreservation, it has been studied only for time intervals up to 72 hours; thus, at present, long-term storage of cells is probably best achieved with cryopreservation.

Before the use of a cord blood unit, additional confirmatory testing is often required to ensure the accuracy of the HLA type and the unit selection. This is usually performed by detaching a segment from the stored unit and then submitting it for either high- or low-resolution typing at the request of the transplant center. This operation requires the removal of the unit from storage and can subject the whole unit to unintentional warming. Transient warming events (TWE) can occur not only during this process but also during shipment to the transplant center; thus, the number of times that the unit is subjected to temperature fluctuation should be kept to a minimum. Multiple transient warming events of up to 1 minute have relatively little effect on CFC recovery, although relatively few data for longer duration events are available (Creer, 2004). Another study reported that units can be frozen and thawed up to three times without a significant reduction in cell viability (Timeus et al., 2003).

It is thus apparent that cord blood processing is a complex process necessary for such a product. For this reason, standards should be consistent, scientifically validated, and designed with the input of current cord blood bankers and cord blood experts.

Recommendation 4.3: Uniform quality assurance standards and criteria should be established by the proposed Cord Blood Accrediting Organization for the collection, processing, and storage of cord blood, and adherence to these standards should be required of all banks participating in the National Cord Blood Stem Cell Bank Program. In addition, a system for the frequent performance of compliance reviews should be established.

RACIAL AND ETHNIC COMPOSITIONS OF THE UNITS IN CORD BLOOD BANKS

One goal of cord blood banking is to increase the HLA diversity in the inventory, particularly the HLA types of ethnic and racial minorities. However, early efforts aimed at increasing the recruitment of minority populations as donors of cord blood encountered difficulties similar to those faced in the early days of the bone marrow registries, resulting in lower than desired representations of units from members of minority populations.

In one study, the racial and ethnic compositions of the units in five cord blood banks in the NMDP network were compared with those of the individuals who signed up for bone marrow donor registries from the same geographical areas (Ballen et al., 2002). That study examined 9,020 cord blood donors and the racial and ethnic characteristics of the hospitals where collections were performed and compared them with the characteristics of 417,676 bone marrow donors and the census data of the donors'

geographical area. The California, Florida, and Massachusetts cord blood banks recruited a lower percentage of minorities than the corresponding bone marrow donor centers. In four of the five areas studied, cord blood banks recruited a lower percentage of minorities (in comparison with the census data for the corresponding collection hospitals).

A more recent study from the American Red Cross showed that racial diversity can be achieved in a national network of cord blood banks (Ballen et al., 2004). The population of that network is 64 percent Caucasian, 16 percent African-American, 12 percent Hispanic, 4 percent Asian, 1 percent Native American, and 3 percent other. Diversity was achieved by focusing collections in specific geographic areas; Detroit, for example, had the highest percentage of African-American donors and San Diego had the highest percentage of Hispanic donors.

Individual sites reported wide ranges in the distributions of their units by race and ethnicity. For example, the Karmanos Cancer Institute/JP McCarthy Cord Blood Bank in Detroit is a smaller, minority-focused bank that stores about 442 cord blood units; 81 percent of these units are from African-American donors, and less than 10 percent are from Caucasian donors. Duke University provided information on 3,870 banked units; 59 percent of these are from Caucasian donors, 19 percent are from African-American donors, and 9 percent are from Hispanic donors. Fifty-six units from this bank have been transplanted, but a disproportionately high percentage (14 percent) of units from Hispanic donors were chosen for transplantation.

ACCESSING UNITS

Information Flow

One of the most challenging aspects of cord blood acquisition is the selection of an appropriate unit for transplantation. The lack of an agreed-upon search algorithm creates a challenge for transplant physicians searching for treatment options for their patients. At present, physicians must search several unrelated databases to identify all units that might be compatible. They must also compare these results of these searches with information on potential donors in adult bone marrow registries to see whether a suitable marrow match is available. Figures 4-3 and 4-4 show outlines of the typical decision-making procedures that a physician must perform when he or she is searching for HPCs for transplantation. Multiple factors, such as cell dose requirements, HLA match requirements, and the geography of the transplant center are important in the search process.

An ideal search algorithm would encompass a scalable system that is capable of searching every available cord blood unit banked by all accred-

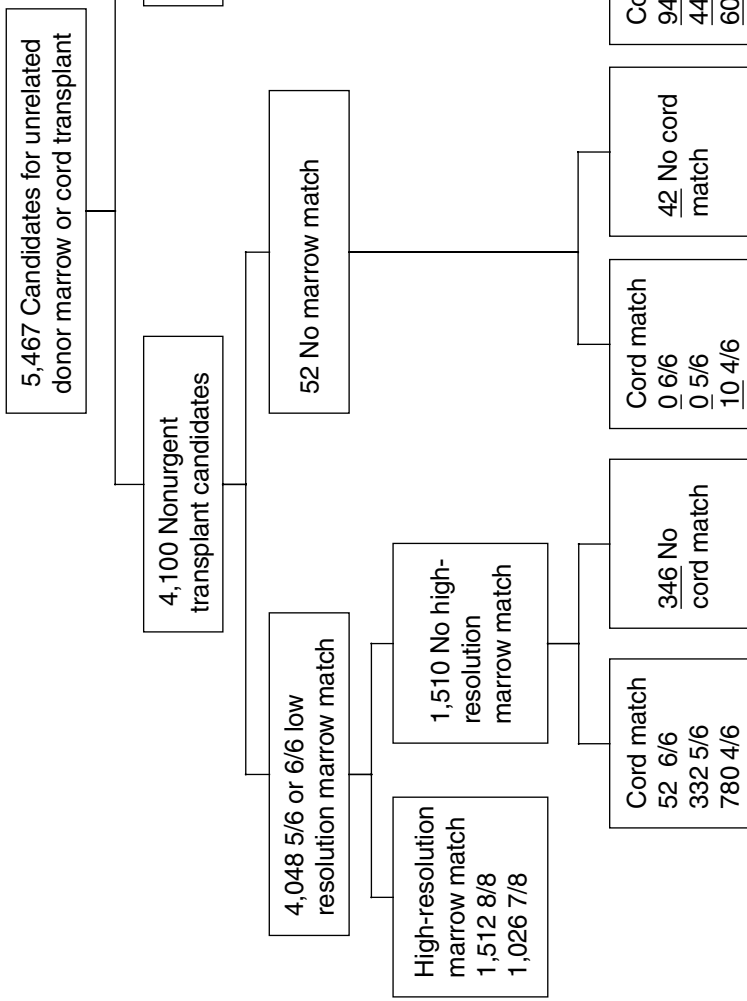


FIGURE 4-3 Algorithm for selection of bone marrow versus umbilical cord blood for patients more than 20 years of age. Underlined numbers = number of patients in the scenario with 50,000 cord blood units and a minimum cell dose of 3.0×10^7 cells. SOURCE: Howard et al. (2005). See Appendix E.

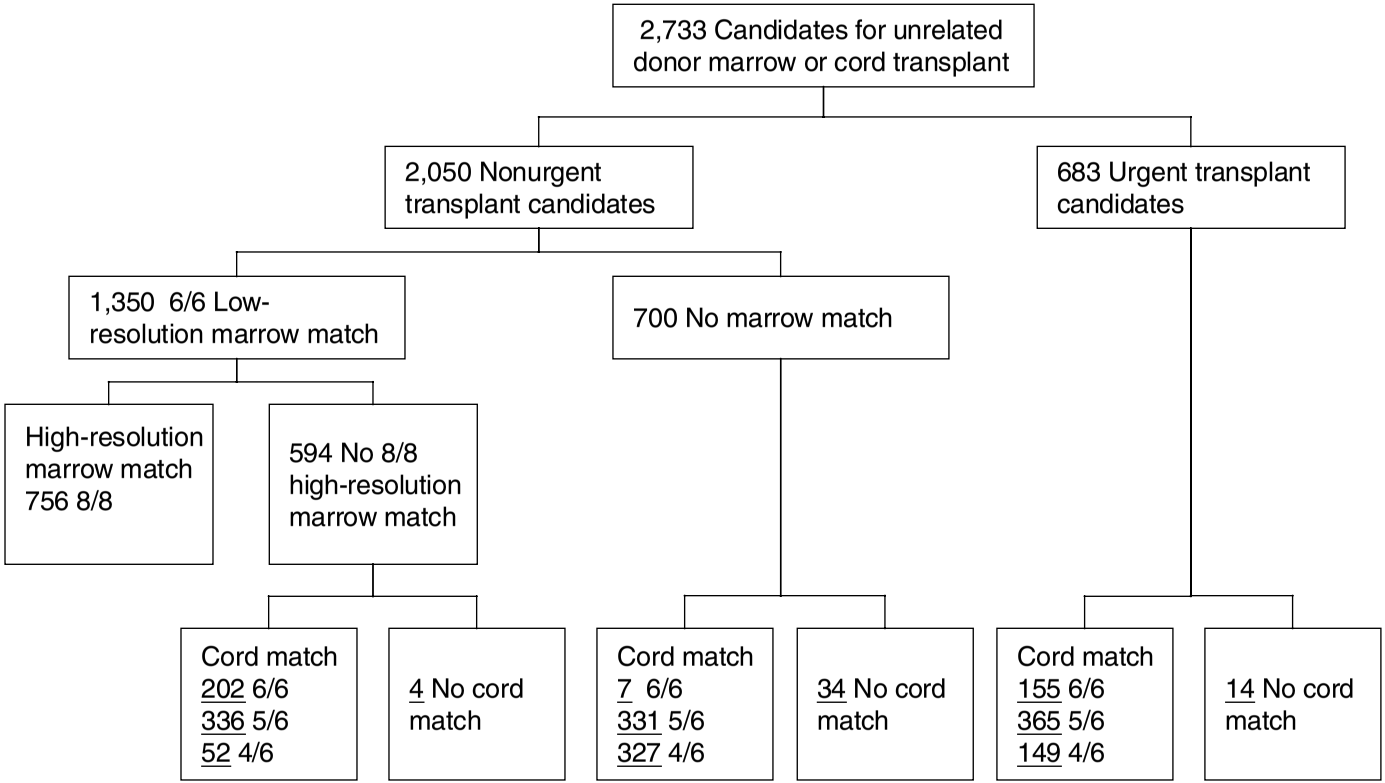


FIGURE 4-4 Algorithm for selection of bone marrow versus umbilical cord blood for patients less than 20 years of age. Underlined numbers = number of patients in the scenario with 50,000 cord blood units and a minimum cell dose of 3.0×10^7 cells.
SOURCE: Howard et al. (2005). See Appendix E.

ited facilities (see Recommendation 4.1). The searches would be based on HLA matching, and results would indicate whether the HLA-typing was high- or low-resolution and score each of these depending on the degree of match, cell dose, and availability. The algorithm should also be flexible enough so that transplant physicians could modify it depending on their own search criteria or ones the physician feels are important for a particular patient.

The availability of a unit depends on the overlapping demands of multiple clinicians with patients with similar needs. Although the requesting physician should be notified that a potentially matching unit has been identified, the bank and the cord blood center should assist with making the ultimate decision to use a particular unit for transplantation in a particular individual. Units "held" for a particular patient should not be reserved by or shipped to any other transplant centers. However, units should not be able to be reserved indefinitely, and thus it is important that the bank and cord blood center work with transplant centers to ensure that reserved units are shipped or cleared within a reasonable amount of time.

All parameters in the search should be traceable and should be maintained by the cord blood center. The units available from different banks should be comparable to one another, and thus standardization of the processes and the procedures used for the collection and storage of the units is essential. A set of protocols (e.g., infectious disease testing, steps in processing, storage guidance, and matching requirements) for all banks supplying information to the cord blood center is required to ease the processes used to search for and identify cord blood units. Lack of compliance with these protocols would result in punitive measures by the cord blood center (see Chapter 7).

Ideally, with any search algorithm, the available cord blood units and adult donors would appear in the same search results, although listed separately, ranked by availability and HLA match. This would enable transplant physicians to compare all possible options for their patients and select the best match for their patients' needs.

Probability of Finding a Donor

At the request of the Institute of Medicine committee, the New York Blood Center (NYBC) completed a voluntary simulated search of cord blood unit matches for 9,970 patients within its inventory of 20,444 cord blood units for which high resolution HLA typing had been completed. A 4/6 HLA match or better could not be found for 94 patients (1 percent). Fifty-seven of these patients were non-Caucasian.

Cord blood banks have been able to recruit a diverse donor population, but it is not fully consistent with the census data on the racial and ethnic

diversity of the American population. Data on HLA diversity in the American population requires further investigation. Of further interest and concern are the lower $CD34^+$ counts among cord blood units from African-Americans reported by several banks.

Physician Support in the Search and Transplant Process

At present, as described above, a transplant physician seeking a cord blood unit is required to search the cord blood unit databases of several organizations. The resolution and accuracy of HLA testing, the method of cord blood processing and even the quality of the unit itself can vary widely among these different banks. For this reason, some transplant physicians are unwilling to use units from banks with which they are not familiar or even to use cord blood in an HPC transplant. Organizations such as NYBC have attempted to make this process easier by implementing programs that facilitate the use of cord blood and increase the referrals for transplantation. Cord blood banks rely on the use of these units, as reimbursement comes with the clinical transplantation of a cord blood unit and not with the donation.

Banking organizations, patient advocacy groups, and adult donor registries like the National Marrow Donor Program have been hosting physician education programs and providing updates through publications and Web-based resources to increase the chances that a transplant physician will quickly be able to identify a suitable match for his or her patient. The registries also provide live support in the search process by providing access to qualified individuals with expertise in the relevant fields (e.g., HLA compatibility) to assist the physicians with selecting the best unit. The registries also often assist with the financial aspects of the search by offering suggestions for reimbursement and by educating the insurance companies as much as possible on the issues surrounding HPC transplantation.

Patient Support in the Search and Transplant Process

The responsibility of caring for a patient waiting for an HPC transplant falls on the transplant physician and the staff at the transplant center. Registries and banks often assist these health care providers by providing informational brochures, videos, and audio programs that educate the patient and the patient's family on the process, risks, and outcomes. These are designed to accommodate individuals who speak a variety of languages other than English and individuals with different comprehension levels to ensure that no matter what the health literacy level of the patient and his or her family, they will have a good understanding of the process. The registries also provide counseling services and act as a support mechanism in this very difficult process.

Registries also have an opportunity to provide outreach programs for patients in underserved areas who might not otherwise enter the transplant referral system because of their remote geographical location or the lack of availability of comprehensive medical care in their area. Advertising materials directed toward the local community and continuing medical education programs directed toward local physicians can help accomplish this goal.

GOVERNMENT REGULATION

Food and Drug Administration Regulation of Human Cell, Tissue, and Cellular and Tissue-Based Products

The Food and Drug Administration (FDA) first announced its proposed approach to the regulation of cell and tissue products in 1997 (FDA, 2004b). Since then, FDA has released a series of guidelines and regulations that provide a regulatory framework for the use of human cell, tissue, cellular, and tissue-based products (HCT/Ps). FDA published a set of proposed regulations in January 2001. This proposal introduced FDA's concept of current good tissue practices around three major goals: 1) preventing the unwitting use of contaminated tissues with the potential for transmitting infectious disease; 2) preventing improper handling or processing that might contaminate or damage tissue; and 3) ensuring that clinical safety and effectiveness is demonstrated for most tissues that are highly processed, used for nonhomologous purposes, or combined with no tissue components, or that have systemic effects on the human body (Gee and Biol, 1999; FDA, 2004a; 2004b).

A final rule put into place provisions requiring establishments that work with cells and tissues for transplantation to register with FDA and list their products was published January 19, 2001.[6] Additional regulations incorporating comments on the draft regulations received from the public were incorporated into the final rule, which was released in two parts in 2004. They are scheduled to become effective in May 2005. The main focus is to ensure that all processing of HCT/Ps is controllable and accountable during the collection and processing of the units. The FDA proposal contains several exceptions involving minimally manipulated cells, including cells that are harvested for autologous or reproductive use but that are not processed and stored for commercial use, such as for the directed donation of cord blood units or ova for infertility (FDA, 2004b). FDA has assumed a role in HCT/P regulation because the manufacturing and transplantation of these products often involves interstate commerce. For example, cord blood units can be collected in one state, processed and stored in another, and

[6] 66 FR 5447.

transplanted in a patient in yet another state. The FDA-regulated HCT/Ps are summarized in Table 4-2.

Despite these regulations, however, FDA has not yet licensed cord blood as a standard therapy. Its most recent discussion of the topic was at the FDA Biological Response Modifiers Advisory Committee (BRMAC) meeting on February 27, 2003, during which the committee was asked to discuss:

1. factors that FDA should consider in determining the safety and efficacy of the use of cord blood transplantation for hematopoietic reconstitution,
2. the role of the $CD34^+$ cell count in the selection of cord blood units, and
3. other measures of quality that should be considered (BRMAC, 2003).

On the basis of data provided to BRMAC by Pablo Rubinstein and Cladd Stevens of the NYBC, it found that older recipients, as opposed to

TABLE 4-2 FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

Product Regulated	Specific Product
HCT/P that are or will be regulated as biological products	• All allogeneic, unrelated HCT/Ps derived from cord and peripheral blood • HCT/Ps that are more than minimally manipulated (e.g. expanded, activated, or genetically modified) • HCT/Ps that are combined with a drug, device, or biological product • HCT/Ps that are intended for nonhomologous use (e.g. HCT/Ps intended for use for cardiac repair)
HCT/Ps that are currently subject to investigational new drugs (IND) and Biologics License Application (BLA) requirements	HCT/Ps that are • more than minimally manipulated; or • intended for nonhomologous use; or • combined with a drug, device, or biological product
HCT/Ps that are subject to the phase-in of FDA approval requirements	• Allogeneic, unrelated minimally manipulated HCT/Ps for hematopoietic reconstitution are subject to biological product requirements, including licensure • FDA is not enforcing IND and BLA requirements pending determination of whether a standards-based approach to licensure can be developed • FDA may implement a standards-based approach to licensure if data exist to show safety and effectiveness when a product is manufactured in accordance with defined product specifications and process controls

children, have poorer outcomes because of their higher body weights. They also noted that although the only true measure of the success of an HPC transplant is hematopoietic reconstitution in a myeloablated recipient, the $CD34^+$ cell content is an accurate predictor of engraftment success (BRMAC, 2003).

BRMAC did agree that cord blood transplantation is an accepted approach for the treatment of a variety of diseases and that the use of bone marrow or cord blood for the treatment of particular diseases should be made on the basis of medical judgment and availability. Finally, BRMAC agreed that the general outcome parameters recommended for clinical trials of other types of HPC transplantation are suitable for clinical trials of cord blood transplantation (BRMAC, 2003).

As of January 2004, all public and private cord blood banks were required to register with FDA. However, licensure of cord blood units is still pending. The committee believes that this licensure will go a long way toward providing another layer of safety and quality assurance in the system and has the added benefit of creating requirements that are enforceable by law. Furthermore, licensure will clarify the legal status of the cord blood units to be shipped across state lines and make it easier for cord blood banks to be reimbursed at a fair market price for the units used for transplantation.

Despite of the lack of licensure, many of the public cord blood banks have voluntarily submitted investigational new drug applications (INDs) to the FDA and have actively collected clinical data to be used to support the development of product standards and licensure. The IND process requires a full application explaining the study goals and methods of a new therapy. The investigator must also file periodic reports on the progress of the trial and immediate reports upon occurrence of unexpected adverse events. This allows FDA supervision in the absence of any other control and provides a feedback mechanism that is not present in the accreditation process.

Recommendation 4.4: The Food and Drug Administration should move promptly to establish a system of licensure of cord blood units intended for clinical transplantation. As an interim measure until a licensure process is established, all banks participating in the National Cord Blood Stem Cell Bank Program should operate under an investigational new drug application.

State-Legislated Programs

A number of state laws have been recently enacted to further the development of and access to public cord blood banks. In Florida, for example, a statewide consortium called the Public Cord Blood Tissue Bank is respon-

sible for the "collection, screening for infectious and genetic disease, tissue typing, cryopreservation, and storage of cord blood as a resource to the public" (Florida State Legislature, 2004b). The banks participating in the consortium are charged with "aligning their outreach programs and activities to all geographic areas of the state, covering the entire state" (Florida State Legislature, 2004b). Interestingly, the Florida Public Health Provision identifies the need for outreach programs targeted to Hispanics, African-Americans, Native Americans, and other ethnic minorities. The law also provides for a religious exemption where "blood transfer is contrary to the moral principle the denomination considers to be an essential part of its beliefs" (Florida State Legislature, 2004b). Although the consortium is allowed to charge transplant centers, the statute requires written disclosure of any financial remuneration for collection.

The state legislatures in Maryland and Illinois have also enacted laws regarding the collection of cord blood for public use. In those states, the responsibility for public cord blood collection is largely that of the hospitals. Under these laws, a hospital "shall allow a pregnant patient to arrange for the donation of the blood extracted from the umbilical cord of the patient's newborn child to a certified[7] public cord blood bank" (State of Illinois, 2004; State of Maryland, 2004a, 2004b). Under both statutes, a patient who agrees to donate cord blood to a public bank "may not be charged for the costs of collection, storing, or transporting the cord blood." As with the Florida statutes, exceptions to this general rule are provided in cases in which blood collection conflicts with the religious denomination of the hospital or a hospital employee or if cord blood collection would threaten the health of the mother or the newborn child.

In contrast to the statutes described above, Oklahoma has also passed legislation pertaining to cord blood, but it does not specify a precise structure for a program. Rather, the Danielle Martinez Act requires that an Advisory Council on Cord Blood Donation be established (Oklahoma State Legislature, 2004). That advisory council is charged with providing recommendations on a cord blood donor program to the legislature by an original deadline of November 1, 2004, which was recently extended to December 1, 2006 (Oklahoma State Legislature, 2005).

Although New Jersey does not have a public cord blood program like those in Florida, Maryland, or Illinois, or an advisory council like that in Oklahoma, the state is considering legislation that would offer the Coriell Institute for Medical Research a $5 million loan to provide additional funds to expand collection efforts of the New Jersey Cord Blood Bank, which the Coriell Institute maintains (Quinn, 2004; Anonymous, 2004). The legisla-

[7]The definition of "certified" is not provided in the text of either bill.

tion in Texas is similar to the New Jersey bill and provides a $1 million grant to the Texas Cord Blood Bank to start public cord blood collection efforts (Foy, 2003). In addition, the state is offering to match every dollar donated to the project up to a maximum of $3.5 million.

In New Mexico, the Umbilical Cord Blood Banking Act, introduced in February 2005 by State Senator Nancy Rodriguez, would provide $25,000 to the New Mexico Department of Health for the publishing and distribution of pamphlets on cord blood donation (Associated Press, 2005).

Sates have also passed statutes that pertain to the encouragement and promotion of cord blood research. For example, the Florida legislature recently established the Florida Center for Universal Research to Eradicate Disease (Florida State Legislature, 2004a). Under this legislation, the center is responsible for coordinating voluntary donations of cord blood as necessary to maintain an adequate supply for research.

ACCREDITATION

American Association of Blood Banks (AABB)

AABB first included standards relating to HPCs and bone marrow in 1991 as part of the 14th edition of *Standards for Blood Banks and Transfusion Services* (Section Q). In 1996, AABB published a separate volume of standards for HPC-related activities, *Standards for Hematopoietic Progenitor Cells*. AABB's standards in this arena have evolved in conjunction with cellular therapy. In 2001, AABB published a separate volume of standards for cord blood activities, *Standards for Cord Blood Services*. Shortly thereafter, the AABB board of directors approved the creation of the Somatic Cell Standards Program Unit to draft requirements for facilities involved in this kind of cellular therapy. Rather than publish a third set of standards for cellular therapy, the AABB board of directors ultimately approved the merger of the publications on adult HPC, cord blood, and somatic cell therapy into a single, unified publication, *Standards for Cellular Therapy Product Services,* which will become effective in May 2005. This document, prepared by the Cellular Therapies Standards Program Unit, encompasses all types of cellular therapy and is intended to minimize the need for duplicative AABB assessments of facilities that collect, store, or issue different types of cellular therapy products.

AABB's voluntary, peer-based accreditation program offers facilities a means to assess their compliance with AABB standards, including the HPC and cellular products standards and cord blood standards. Each year, AABB conducts more than 800 assessments of blood-related facilities, including more than 60 facilities involved in HPC, cord blood, and cellular product collection, processing, storage and distribution activities. Cellular therapy

facility assessments are based on AABB standards which are designed with both quality management system and technical requirements. Each assessment is customized to fit the activities of the facility. Reassessment documents are required for a "desk assessment" before the assessors visit. Areas of concern are identified in advance so that the assessors can carry on a dialogue with a facility to allow it to make necessary changes or additions. An AABB lead assessor and a cell therapy subject matter expert assessor perform the assessments. Any questions concerning the assessment are referred to the AABB Standards Committee before accreditation is given. Otherwise, accreditation is awarded without further board review. At present, AABB has approximately 60 trained assessors with expertise in HPCs and cord blood. AABB assessments are intended to ensure compliance with AABB requirements, provide education, improve the efficiency of operations and ensure consistency in the provision of safe and efficacious products.

Foundation for the Accrediatation of Cellular Therapy

FACT is a nonprofit organization founded in 1996 by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT). ISCT is a professional society established in 1992 to represent scientists and physicians working in the area of hematopoietic stem cell graft manipulation. ASBMT was formed in 1993 as a professional organization to represent physicians and investigators involved in the clinical aspect of HPC transplantation. The two societies established FACT to develop standards and a voluntary inspection and accreditation program.

The primary purpose of FACT is to develop standards for hematopoietic stem cell collection, processing and transplantation. FACT's major objective is to promote high-quality patient care and high-quality laboratory performance in the belief that accreditation must assess the clinical aspects of transplantation as well as collection and laboratory practices. FACT standards are comprehensive and include quality management; facility design and operations; policies and procedures; donor evaluation, selection, and management; record keeping; labeling; processing; storage; transportation; the issue and release of HPCs; adverse event reporting; auditing; and outcomes analysis for the purposes of voluntary inspection and accreditation in the field of HPC therapy.

FACT has developed a voluntary inspection program that, if it is successfully completed, leads to a 3-year accreditation in the field of HPC therapy. FACT inspection teams always include a team leader, a physician trained in stem cell transplantation, and professional experts in the areas of stem cell collection and laboratory practices. The inspection team assesses the compliance of a facility with the standards and reports back to an

accreditation board. The accreditation board reviews all facility reports, thus maintaining consistency in the interpretation of the standards. Final accreditation is awarded after approval from the FACT board of directors. This comprehensive process helps to ensure a consistently high quality among facilities. There are currently 130 FACT-accredited HPC transplant facilities in the United States. FACT currently has 160 trained and active inspectors.

In 2002 FACT joined forces with NetCord to develop international standards for maternal donor screening and cord blood collection, processing, testing, banking, selection, and release. The standards are modeled after, but independent of, the HPC-related standards to ensure that they address the specific and sometimes different issues related to cord blood. The FACT/NetCord collaboration was intended to ensure consistently high- quality cord blood units for transplantation not only in the United States but also internationally. FACT/NetCord recognizes that global standardization of cord blood banking will facilitate the availability of quality cord blood units for a greater number of U.S. recipients of all ethnic backgrounds. The FACT/NetCord standards have since been adopted by socie-ties in a large number of countries outside the United States, including countries in Europe and Canada, Asia, and Australia. FACT/NetCord standards for cord blood are comprehensive and were developed with the same philosophy as the HPC-related standards: that the assessment of the quality of clinical transplantation of cord blood is as important as the assessment of collection and laboratory practices. Inspection teams include a physician team leader knowledgeable about cord blood transplantation and experts in collection and laboratory practices. Inspections generally occur over a 2-day period, and a FACT/NetCord accreditation board reviews all inspection reports. Three-year accreditation is awarded following after approval by the FACT and NetCord boards of directors. Currently, 36 cord blood banks around the world have applied for FACT/NetCord accreditation. Of those, 11 banks have been inspected and 5 have been awarded accreditation.

All accredited programs should have in place a quality management program, including quality audits; a system for detecting, evaluating, and reporting errors, accidents, and suspected reactions; documentation; review and reporting; and safety.

Recognizing the importance of developing consensus graft processing standards, in 1994 the North American Task Force (NATF) was formed, consisting of all the major professional organizations interested in hematopoietic cell therapy, including International Society for Hematotherapy and Graft Engineering (ISHAGE), ASBMT, and FACT. There was general consensus that the FACT standards were of sufficiently high quality to serve as

a template for the other organizations involved in this field. Thus, there should be no conflict between the FACT Standards and those of other standard-setting organizations that had joined the NATF. The first edition of the FACT Standards was published in September 1996. The first inspections began in September of 1997.

NMDP Standards

In July 2004, NMDP published a revised edition of its standards, intended to outline the most basic guidelines for facilities involved in the transplantation of HPCs (NMDP, 2004). These guidelines were not intended to be a comprehensive list encompassing all requirements; rather, they were intended to serve as a standard of care for patients in such facilities. They apply to all activities related to donor screening, collection, processing, release, and transplantation of bone marrow, peripheral blood, and cord blood progenitor cells facilitated through the NMDP network of banks and transplant centers.

Recommended Direction

In contrast to adult marrow and peripheral blood donors, who can be examined immediately prior to harvest, the umbilical cord blood donor is not available for additional testing. For this reason, it is critical that the transplant physicians be assured that a thorough screen for genetic and infectious diseases has been performed and be aware of any risk factors prior to final selection and shipment.

Because cord blood transplantation is a dynamic area of clinical research, standards should be stringent yet flexible enough to allow for the incorporation of new advances in the field. Many issues in the methodology of cord blood banking and transplantation are not fully resolved and require ongoing investigation, including procedures for processing, storage, and thawing. Numerous steps in the transplantation process ought to be considered, including:

1. donor selection and consent;
2. collection of units;
3. processing, testing, and storage of units;
4. selection of units for transplantation;
5. release and shipment of units to transplant centers;
6. thawing and infusion;
7. transplantation; and
8. outcomes monitoring by the transplant site.

Each of these steps should be optimized to ensure the success of the transplant. As part of the accreditation process, cord blood banks and collection sites should be considered an integrated unit. Centers performing transplants should also be accredited to ensure proper unit selection, infusion, follow-up, and outcomes reporting. Ideally, all four components should be accredited by the same organization to ensure consistency.

Cord blood banks are responsible for providing high-quality, HLA-typed units for transplantation to patients in need. The quality of the cells is critical, since the transplant must restore hematopoiesis and immunity in the recipient. Patients have a very low chance of achieving long-term survival if the cells do not engraft.[8]

Collection Site

The collection process represents the first step in ensuring a high-quality supply of cord blood units. The collection facility should meet minimum standard requirements; that is, it must routinely provide units that are of adequate volume and that test negative for bacterial, viral, or fungal contamination. A designated medical director should be responsible for overseeing the activities of the collection facility.

The collection facility staff should be trained in all aspects of the collection procedure and this training should be documented. The personnel collecting cord blood should be trained in screening and obtaining informed consent from the donors and in the proper methods of effective, sterile collection. Personnel should receive regular evaluation of their performance as well as ongoing training.

A quality management plan that incorporates all aspects of the collection facility's operations, including personnel training, deviations, adverse event reporting, and internal audits to document compliance with standards, should be in place. The facility should maintain standard operating procedures to ensure an effective sterile collection process, including procedures for the collection, storage, and transportation of units.

Cord Blood Bank

Cord blood units are transferred from the collection site to the cord blood bank where they are processed, tested, and cryopreserved for long-term storage until they are retrieved for transplantation. Each step in this process must be performed properly to ensure a satisfactory outcome for

[8]Though if the patient does manage to survive in the short-term without engraftment, subsequent transplants or autologous recovery may ensure long-term survival.

the transplant recipient. The standards should be flexible and allow the incorporation of new advances in the field; however, cord blood banks must always be able to provide units that meet established minimum standards. Like the collection sites, banks should have a designated director and a medical director who are suitably qualified to supervise all operations and oversee a quality management program that includes scientifically validated methods for processing, storage, thawing, and transportation of the cord blood units. The thawing method should be provided to the transplant facility before or at the time that the unit is shipped. The cord blood bank personnel should be trained in unit receipt, processing, storage, and shipment; and competency assessments should be conducted on an ongoing basis. To ensure adherence to standards, internal audits should be performed at regular intervals. Deviations and adverse events should be monitored and reported appropriately to regulatory and oversight boards. In order to provide another layer of safety and supervision, all banks providing units for allogeneic transplant should have an IND on file with FDA. The IND annual report should be shared with the accrediting agency and oversight board.

Transplant Facility

Transplant centers that receive cord blood units from the proposed national program should be accredited and should adhere to standards. They should demonstrate competency in the selection, handling, thawing, and transplantation of cord blood units. Facilities should have appropriately trained physicians, nurses, and staff, as well as a qualified, appropriately trained medical director. The transplant center should have a demonstrated quality management program for ongoing monitoring of the facility itself, the clinical unit, the experience and training of transplant center personnel, policies and procedures, patient evaluation and selection, administration, data management, and record keeping. Facilities should have a proven record of successful cord blood transplantation or, at a minimum, demonstrated competence with marrow and peripheral blood and a willingness to participate in a mentoring process in order to gain familiarity with cord blood. The time to engraftment after cord blood transplantation should be monitored, and engraftment failures and infections should be reported to the appropriate regulatory agencies. Transplant facilities should report patient outcomes to the accrediting agency, and patient outcomes should also be shared with the cord blood bank and the collection facilities that provided the unit.

Accrediting Organization

Cord blood collection facilities, banks, and transplant centers should be accredited by a central accrediting organization to participate in the proposed National Cord Blood Program. The central accrediting agency should adopt or develop consensus standards and establish a program of inspection and accreditation. This agency should monitor ongoing compliance with standards and the outcomes of transplants. The accrediting agency should report to the policy board of the proposed National Cord Blood Stem Cell Bank Program. Collection centers, banks, and transplant centers should maintain their accreditation and should report the required data to continue to participate in the National Cord Blood Stem Cell Bank Program. The accrediting agency should have a policy in place to detect facilities that become noncompliant in the interim between inspections. The accrediting agency should have a mechanism to withdraw the accreditation for any facility that is found to be noncompliant.

FDA recently issued standards for current good tissue practice which address general issues related to cellular therapies but which are not specific to cord blood banking or transplantation. At present, FDA does not license cord blood.

As mentioned above, two existing organizations, AABB and FACT/NetCord, have developed standards and are accrediting cord blood banks in the United States. In addition, NMDP, while not an accrediting organization, has developed a process to define the minimum acceptable criteria for units to be stored by member banks and listed in their search databases. These criteria do not address all of the quality management issues described above.

The Health Resources and Services Administration should issue a request for proposals to select or create the proposed accrediting body. The organization should meet the standards for the functions for ensuring quality in cord blood collection centers, banks, and transplant centers described above. The organization should demonstrate that it has a comprehensive process, documented by standard operating procedures for standards development and implementation, thorough on-site evaluation of facilities, consistent and comprehensive review of inspection reports, board or oversight committee approval for accreditation, and follow-up procedures throughout the accreditation period. The organization should demonstrate the expertise of the inspectorate, the mechanism for training and competency of the inspectors, ongoing quality control of inspectors, a mechanism for investigating problems uncovered during an inspection, and criteria for retaining or dismissing inspectors. The accrediting organization should define a mechanism for assessing foreign cord blood banks that is comparable to the mechanism for assessing U.S. facilities to guarantee quality and allow those inventories to be available to U.S. recipients.

PRIVATE BANKS

Private cord blood banks have inherently different objectives from public banks, and most of this report is focused on the public banks that might become a part of a national program. However, the committee was explicitly asked whether the standards developed for a national program should also apply to private banks. Although the committee did not want to explicitly address the differences between the two systems of banking or the merits of one over the other, there was no question that individuals storing units with private banks should be assured of the quality of the banks. For this reason, all quality standards adopted by the proposed National Cord Blood Stem Cell Bank Program should apply to both public and private cord blood banks.

Recommendation 4.5: The committee strongly recommends that all cord blood banks, regardless of public or private status or participation in the national program, adhere to the established quality standards.

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5

Ethical and Legal Issues

The collection of tissue from one individual for therapeutic use in another individual involves not only technical and medical issues, but also ethical and legal issues. Donors of cord blood are not merely depositing the leftover by-products of the birth process with interested researchers and physicians; rather, they are making a choice to do something that may potentially benefit either unknown beneficiaries or members of their own families. Pregnant women receive a great deal of information—sometimes conflicting—about the donation process and the consequences of different types of banking. It is crucial to disclose several kinds of information to the potential donor, including who has access to the cord blood once it is donated, where it is stored, how it is stored, and how the donor's privacy is protected.

From the perspective of the recipient, some patients with high-risk diseases known to respond poorly to conventional therapies may consider pursuing experimental HPC interventions. These patients might be willing to take greater risks than less severely ill patients when they are pursuing treatment. As experimental treatments become available, some patients may be willing to undergo them even if the risks and side effects are not fully known. It is crucial to disclose to the potential recipient all available information about risks and probable benefits of experimental interventions, as well as uncertainties, so that he or she can make an informed decision.

Because uses of cells from umbilical cord blood are not yet considered routine medical practice, and because of the need for informed decision making, this therapy currently falls within the legal framework of an investigational new drug (IND) application with the Food and Drug Administra-

tion (FDA). This well-established mechanism allows for the use of experimental drugs or biological products in studies with humans via a registration process.

This chapter focuses on: (1) issues surrounding the procedures used to obtain informed consent from potential cord blood donors; (2) concerns about disclosure to donors of significant clinical information discovered during the donor screening process; (3) and points to consider in the research use of cord blood, including protection of donor confidentiality. In addition, brief mention is given to the potential impact of patent litigation on cord blood banking practices.

INFORMED CONSENT OF DONORS

Until recently, cord blood was considered one of the many biological waste materials discarded after the birth of a baby (Fernandez, 1998; Gluckman, 2000). The possibility of using cord blood as a source of stem cells for transplantation altered this view and introduced different rules and regulations for appropriate decision making, handling, and use of this biological material. It is ethically important to obtain informed consent for the donation of any cord blood unit, regardless of the timing of collection or the potential use of the unit (see Table 5-1 for descriptions of consent practices among several agencies). Informed consent procedures for the donation of cord blood should follow a consistent set of protocols that educate the donor about the various options for cord blood use. The requirements should be modeled on already established criteria for transfusion of whole blood and other unfrozen blood products (Fernandez, 1998).

Who Provides Consent?

The need for consent from the mother, father, or both varies according to the individual circumstances of the potential donors. If the cord blood is removed while the placenta is still in the uterus, generally the mother's consent is sufficient because it is an extension of her body. If the cord blood is removed after the placenta has been taken from the mother's uterus, however, an argument could be made that the father's wishes are also relevant—just as both the mother and the father would be decision makers about their child's care. Few cord blood banks or collection centers obtain consent from both parents (Institute of Medicine bank survey; see Table 5-1 and Appendix C). Because the father may not be available at the moment of delivery, it would be difficult for a cord blood bank to obtain the both paternal and maternal consent within the time frame needed to begin processing. The majority of women polled in a recent study (86 percent) believed that cord blood was a valuable resource and should be collected,

TABLE 5-1 Consent Practices for Agencies Currently Involved with Cord Blood

Consent Parameter	FACT/NetCord	AABB	NMDP
Timing	Before or within 7 days of delivery; consent should be obtained before the collection procedure when the cord blood is collected with the placenta in utero	The consent process should begin before collection and should be completed within 48 hours	Consent should not be undertaken after the onset of active labor and should be postponed until the mother has sufficiently recovered from the delivery process
Surrogate pregnancy	Consent should be obtained from both the surrogate and the biological mother	Consent should be obtained from the biological birth mother	Not addressed
Minor	Not addressed	Applicable informed-consent requirements and regulations shall be met	Not addressed
Specific elements to be included in the consent	• If for an allogeneic transplant, the donation will be made available to other individuals and may not necessarily be available to the donor or donor's family at a later date • If intended for a related allogeneic or autologous transplantation, the release of the cord blood will be limited to the specific family recipients or donor • An interview for personal and family history will be undertaken • A review of the medical record of the mother and infant will be performed • A description of the cord collection procedure • Collection of blood from the mother and infectious	• Description of cord collection procedure • Sample collection and storage for possible future testing • Testing for infectious diseases and genetic disorders • Notification of abnormal results • Review of medical history and family genetic history • Possible dispositions of cord blood unit • Discussion of confidentiality • Ownership	Specific document currently under development

TABLE 5-1 Continued

Consent Parameter	FACT/NetCord	AABB	NMDP
	and genetic testing on the cord blood unit and maternal sample will be performed Maintenance of linkage for the purpose of notifying donor/family of infectious or genetic diseases • Use of cord blood for research, quality control or validation studies • Disposal of cord blood units not meeting criteria for bankingts		

NOTE: FACT = Foundation for the Accreditation of Cellular Therapy; AABB = American Association of Blood Banks; NMDP = National Marrow Donor Program.

since the risks to the mother and fetus were extremely low (Fernandez et al., 2003). When asked who should decide about making the donation, two-thirds believed that the partner should be included in the decision to donate, but in the case of a disagreement, 77 percent held the opinion that the decision should ultimately be left up to the mother (Fernandez et al., 2003). A father informed at some point after collection may have questions or objections. Thus, while the committee does not advocate requiring the father's consent, cord blood collection centers should have a plan in place to address paternal objections to the donation of cord blood.

Recommendation 5.1: Cord blood collection centers should have clear policies about who must provide consent for donation and a plan in place to address paternal objections to the donation of cord blood.

Some have questioned whether minors can appropriately consent to donation. In the committee's site visits, only one bank collected cord blood from mothers who were under 18 years of age. In those situations where the mother was 16 or 17 years old and was otherwise not exempt from donating for health reasons, the consent was obtained from the baby's maternal grandmother. The committee believes that situations regarding nonadult consent should be dealt with on a case-by-case basis, after review of the policies and procedures for obtaining minority consent have been reviewed

and approved by a local Institutional Review Board (IRB). State law regarding age of consent for health services associated with pregnancy should also be taken into account.

When Should Consent Be Obtained?

Optimally, to promote and ensure respect for a pregnant woman's autonomous choice, her informed consent for the collection, storage, and use of her cord blood should be given late in the pregnancy but before labor and delivery and after adequate disclosure of information on the potential uses of the donated cord blood. This is especially important in the realm of public banking, in which the parents often do not initiate the donation process. Almost all the women polled in a recent study expressed the opinion that the information about the collection of cord blood should be presented before the third trimester of pregnancy and could be included in the informational packets that are given to mothers during prenatal visits (Sugarman et al., 2002).

A significant roadblock to donation could develop if women were subjected to the lengthy taking of an extensive family and personal medical history and extensive physical examination, resulting in the signing of multiple consent forms, leading to 1) either failure to collect the cord blood because of lack of staffing, or 2) inability to bank the blood following collection (Sugarman et al., 1998). Historically, a few banks have addressed these concerns issue by approaching women only after the unit has been collected and deemed potentially usable. Thus, women are not asked to engage in an unnecessary decision-making process while they are under the stress of labor, especially if the unit is ultimately deemed unusable after it is collected (or is unable to be collected for a variety of reasons). However, it is important to note that the women interviewed in the previously mentioned study believed that it was important that they be kept informed throughout the process, especially in light of the additional time and testing required of them as donors (Fernandez et al., 2003).

In the course of site visits, the committee learned that a majority of banks require consent prior to labor and delivery, with two variations. One bank obtained consent when the mother enters the hospital, and the other routinely collected cord blood after delivery from mothers who were not registered with private banks and subsequently requested consent for banking units that were bankable. Notably, these two banks also had a great deal of success in banking units from otherwise underrepresented populations. Thus, while informed consent procedures must be designed to protect the interests of the donor family, they may also need to take into account practicality and demographic realities of the donor communities without

compromising donor autonomy. Further, banks should consider routinely translating the informed consent document and other information into languages other than English that are common in their collection areas, as this will help achieve the goal of a diverse inventory.

Recommendation 5.2: Informed consent for the collection, storage, and use of cord blood should be obtained before labor and delivery and after the adequate disclosure of information.

Given the realities of labor and delivery, this ideal approach to consent may not always be feasible. At a minimum, the donor's consent for the collection of cord blood should be given prior to delivery, and the donor should be informed that no steps other than the collection of the cord blood and samples for testing of the mother will be taken until the mother (and, if present, the father) can participate in a full informed consent discussion.

Clarifying Potential Options and Outcomes of Donation

In obtaining informed consent it is important to address any assumptions or motivations the donors might have. The attitudes of mothers toward the collection of cord blood units generally reflect their level of knowledge of the process (Sugarman et al., 1998; Fernandez et al., 2003). Misconceptions about the collection process, the associated risks, and the availability and access of units, should they be needed in the future, are common among cord blood donors. In one recent study, women failed to appreciate their alternatives to donating cord blood to a public bank. Almost one-third did not understand that they had the option of discarding their cord blood at delivery, whereas just over half were aware of the option of placing cord blood unit in a private bank (Sugarman et al., 2002).

Some donors reportedly view public banking as a less expensive way to preserve and gain access to their children's cord blood in the future rather than contracting with a private bank. In one survey, almost one-half of the respondents indicated that the reason they chose to donate their cord blood to a public bank was to protect their child's future health (Sugarman et al., 2002). Sugarman et al. assert that potential donors should be informed that they will not have a property claim to the unit after donation and that if the family were to have a need for the unit in the future it would not necessarily be available.

Recommendation 5.3: The information provided to a donor must include a balanced perspective on the different options for banking. The information disclosed for allogeneic donation should not include language that gives the donor an impression that the unit will be available to the family after donation.

In addition to meeting the major informational concerns discussed above, collectors of cord blood may elect to provide donors with the option to restrict the use of the cells to clinical transplantation. These collectors, who are themselves health care providers, have an obligation to convey in clear and unequivocal language to potential donors that no matter what their decision about donation, their care will not be affected.

Standards for Obtaining Informed Consent of Donors

Because cord blood transplantation is considered an experimental procedure, review and approval of the design and implementation of the informed consent process is the responsibility of the IRB[1] designated by the collection center. Cord blood collectors must be able to tailor the informed consent process to accommodate the local population, which may have specific cultural, religious, and historical attitudes toward the donation of the body or any of its parts. They should present to IRBs an informed-consent process that engenders confidence that use of the donated cord blood will not conflict with personal beliefs or practices. Further, the IRB must adequately assess the methods proposed to maximize the collection of cord blood to be certain they do not conflict with the steps needed to protect the donor's rights and welfare.

DISCLOSURE OF INFORMATION REGARDING SCREENING AND OTHER RISKS

One of the major responsibilities of the collection staff and the storage facility is to screen the donated cord blood units in order to provide units that are safe for the transplant recipient. (A more extensive discussion of safety and quality issues can be found in Chapter 4). The extensive screening and testing of the donor's mother is similar to that required of blood donors and is required by the FDA regulations addressing human cells, tissues, and products (21 CFR 1271, effective May 2005). Because no screening or testing program can eliminate all risks, donors should be informed that they will be notified if abnormal conditions are detected when the cord blood itself is tested.

Screening includes the process of obtaining the donor's extensive social, medical, and genetic history. This information may or may not be linked to the unit for future reference. Health questionnaires designed to determine

[1]IRB review of research protocols, unless otherwise exempt, is required for all human subjects research conducted or supported by the Department of Health and Human Services, 16 other federal agencies, or subject to FDA regulations (see 45 CFR part 46 and 21 CFR parts 50 and 56).

certain characteristics of the donor's history often include questions about sexual and other behaviors and risk factors that then become part of the record. The questionnaires currently in use in allogeneic banks are designed to solicit this information. However, the record may be incomplete because volunteers for allogeneic cord blood donation are not generally motivated by the threat of the immediate loss of a family member and may therefore be less inclined to provide intimate personal information to anyone beyond their personal physician (Zilberstein et al., 1997)

The additional testing of the cord blood unit could reveal unanticipated information about the mother or her child's health that would have otherwise gone unnoticed. These new revelations could result in future emotional, social, and physical hardship to the donor, the donor's child, or the donor's family. For example, the discovery of a genetic predisposition to a disease such as cancer could make health insurance difficult for the family to obtain. Or, to take another example, the discovery of carrier status for certain recessive diseases could lead to stigmatization.

Banks that provide blood for transfusion have been guided by principles of beneficence and autonomy in the testing and notification of their donors of abnormal conditions (Haley, 1999). Extensive disclosure and discussions, both before and after donation, are ways to implement these principles by ensuring that the donor fully comprehends the medical, legal, and ethical issues that arise from the donation of the cord blood units. Test results carry information not only about the child's health, but also about the genetic health of both parents and the infectious disease status of the mother. Although cord blood banks have the duty to notify a donor of abnormal test results, especially in light of the regulations regarding reportable infectious diseases, the information must be kept confidential and also be delivered to the donor in a manner that is not only appropriate relative to the severity of the abnormality, but that is also sensitive to the possible social and economic repercussions of the disclosure.

Hirschhorn et al. (1999) suggest that the patient's general practitioner, if he or she is available, may often be the best person to contact the donor after abnormal genetic testing results. Health care providers unfamiliar with the donor could be perceived as more distant and may not understand the cultural and familial needs of the patient as well as a primary physician who has had a long-standing relationship with the donor and her family (Burgess et al., 1998; Hirschhorn et al., 1999). If this is to become the normal practice, however, primary care physicians may need additional education or training on appropriate methods of genetic counseling.

Additional testing of the mother might also result in the detection of a disease that laboratories have a legal obligation to report to state health departments, and the informed consent materials need to include this possibility. FDA has declared that records that link the donors and the donated

human cells, tissues, and cellular and tissue-based products must be secure to ensure the safety of the transplantable products as well as the safety of the patients receiving transplants. It has also declared that the records must be retained for 10 years to ensure the prevention of communicable disease transmission (FDA, 2004). Given that cord blood units can be stored for long periods, this record retention period might need to be extended.

Sugarman et al. (2002) suggest that women who have volunteered to donate cord blood should be given materials that allow them to easily contact the cord blood bank if the child's health or their personal contact information changes. The follow-up assessment of cord blood donation needs to be bidirectional. However, in a recent study almost 25 percent of 170 women reported that they did not know how to contact the bank if their child developed an illness that would render the donated cord blood unusable.

This risk is extremely low because of the screening for genetic and infectious diseases that takes place prior to storage. However, there is a chance that the child may develop a malignancy or be affected by a metabolic or genetic disease that is undetected at the time of storage. Anecdotal evidence offered the committee suggested that such a unit was likely to be identified as a 6/6 match at the time the child-donor needed a transplant, and DNA testing would reveal the unit to be the one donated by the child, at which point it would be removed from the inventory.

MAINTENANCE OF DONOR RECORDS/PATIENT PRIVACY

Patient care and research rely on the efficient acquisition, analysis, and transfer of data that are accurate, readily accessible, and maintained with integrity. Protecting the privacy of individual patients and the confidentiality of the data is the responsibility of all data users and is necessary to protect individual rights and public expectations. Many groups have focused on privacy concerns related to medical information and medical research and recently enacted regulations aim to improve privacy protections.

Korn (2000) identifies two different types of public concern over the field of bioinformatics: (1) pragmatic (e.g., loss of health insurance or discrimination); and (2) ideological (e.g., strong, deeply held beliefs regarding privacy). Pragmatic concerns about the information gained about the donor's health status can be mitigated—at least in part—by a set of statutes or regulations outlining the appropriate uses of personal data as well as methods to prevent inequity. Ideological concerns, however, are not so effectively mitigated (Korn, 2000).

The privacy of donor medical records is a major concern in cord blood banking. Because most units are frozen for future use and, in order to be

cost-effective, the required tests are done sequentially, the most expensive tests are done only on units that have otherwise met the bank's requirements. Thus, there is need to maintain a linkage between the cord blood unit and the donor's social and medical histories for the benefit of the donor, the donor's child, and the donor's family (in the case of genetically inherited diseases), as well as for the safety of the recipient and his or her family.

The Privacy Rule of the recent Health Insurance Portability and Accountability Act (HIPAA) legislation was an attempt by legislators to create a set of standards to protect patients' privacy and alleviate some pragmatic concerns. Specially, it set limits on who can look at and receive patients' medical records and other health information. The standards are intended to provide patients with more control over how their health information is used. The regulation covers health plans, health care clearinghouses, and health care providers that conduct financial and administrative transactions electronically (HHS, 2002, 2003a, 2003b). This has specific applications to cord blood banks as they will be collecting identifiable health information to ensure the safety of the cord blood unit and ultimately transmitting some of that information to transplant centers and/or researchers. The Privacy Rule generally requires authorization from individuals to use their protected health information in research, unless an exception applies. This authorization is distinct from informed consent, which is a separate process.

When cord blood units are collected for research, even future unspecified research use, donors must be informed of risks that might ensue, including violations of confidentiality. In its 1999 report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (NBAC, 1999), the National Bioethics Advisory Commission noted that a great deal of the research that is conducted with human biological materials should be considered minimal risk research. Even so, risks to privacy and confidentiality must always be considered in research involving specimens and/or the associated data. Donors need to be informed of the potential uses of their cord blood samples and should be aware of the implications of their use in research, even after the removal of identifiers linking the sample to the donor's medical record (Clayton, 1995; Meslin and Quaid, 2004).

Several models exist for protecting individuals whose biological material and associated health data are collected by repositories and used for research. The Office for Human Research Protections (OHRP) has included a model and additional guidance for repositories on its Web site.[2] In this model, the repository's IRB reviews and approves the repository's operat-

[2]See http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm.

ing procedures and policies for protecting donors including the informed consent process. IRB review and informed consent is required at the collection site, unless the IRB has approved a waiver of informed consent. In this model, investigators who are not receiving identifiable data need not obtain IRB review and approval if they sign a human use agreement form documenting that they will abide by the human subjects regulations and not to try to identify donor subjects. Thus, OHRP does allow the research use of coded samples if an agreement exists between the researcher and the bank that the source of the samples will remain inaccessible to the researchers.[3] That is, the cord blood bank will not provide the identities of the donors to the researcher. A complete description of the limits of deidentification should be included in the informed-consent process.

The use of a number that cannot be traced without going into the cord blood bank records is considered sufficient. Public banks operating under an IND can request a statement of confidentiality from the FDA for research subjects. This is good practice for cord blood banks aiming to protect the confidentiality and assure privacy of their donors.

Often, however, it will be critical to research goals to retain identifiers to materials so investigators can continue to gather clinical information about the donors (e.g., diagnoses, outcomes). These secondary data (i.e., data gleaned from sources that were originally collected for another purpose) are critical to advancing the understanding of health and health care practices (Black, 2003). Cord blood units could provide useful data—especially as genetic testing becomes more practicable—on the correlation of early development and health issues later in life. Because, theoretically, cord blood units can be stored indefinitely, the data obtained from tests performed at the time of the initial collection might be useful if the donor later develops a disease. Retrospective analyses can often answer many questions about health conditions, as long as test results are still linkable to the patient-donor. Thus, for the most part, cord blood units will retain identifiers, primarily for transplant safety. It is likely that future research use will increasingly rely on the availability of some clinical information. If that information can be retained in a manner that protects the identity of the donor (e.g., through a coding scheme or use of an honest broker), then it is likely that risks can be minimized, and in most cases the need for informed consent to research can be waived.

Recommendation 5.4: Secure links between the medical records of the donor and the banked cord blood unit must be established to ensure the safety of transplantable products and the patients receiving the trans-

[3]See *Guidance on Research Involving Coded Private Information or Biological Specimens*, OHRP/DHHS, Aug. 10, 2004.

plants. These records must be kept confidential and afforded the full protection of the law. If an abnormality is discovered during testing, the results must be delivered to the donor in a manner that is appropriate in relation to the severity of the abnormality.

CORD BLOOD RESEARCH

Cord blood units are banked primarily for use for transplantation, but, as the previous section notes, some are used as a source of stem cells for research purposes. Throughout this report, the committee has used the term "research" in reference to laboratory research and "clinical use" in reference to the transplantation of the cord blood product into a patient. However, as noted above, as of the writing of this report, most cord blood collection and banking is performed under an FDA IND application, even though the unit is being transplanted into human patients in a clinical setting. Significant laboratory research is also being conducted with cord blood units but not necessarily under an IND.

Although the harvesting of embryonic stem cells from surplus embryos obtained from infertility clinics is controversial, cord blood units offer a relatively noncontroversial source of stem cells, although the versatility of cord blood cannot match that of embryonic stem cells (see Chapter 1). Research uses trigger the need for an ethics review of the research protocols by an IRB (if identifiers are maintained), the need to protect the confidentiality of the associated medical information, and the requirements that donors be informed of and consent to the possible use of the material for research. In addition, the commercial development of stem cell lines could generate significant income for the research facility, a possibility that should be disclosed to donors and that relates to broader debates about ownership of the cord blood and its associated medical information. Identifiers or labeling of cord blood units provides yet another set of legal and ethical challenges. The units are initially linked to the donor's medical and social histories for the purposes of identifying the usability of the unit for transplantation. For cost reasons, human leukocyte antigen testing of cord blood units is generally performed as the final test before listing the unit for search. The removal of donor identification will not be possible under the FDA regulations that will become effective on May 25, 2005 (21 CFR 1271). In addition, the current rules and regulations for DNA banking stipulate that any unidentifiable material may be used for research purposes without obtaining specific consent from the donor.[4] Similarly, HIPAA legislation, while imposing stricter rules for de-identification, allows for the

[4]45 CFR 46. 102(f).

such de-identified material to be exempted from its coverage (Clayton et al., 1995; Clayton, 1995; Bradburn, 2001; OHRP, 2004; Clayton, 2004).

While the de-identification may clear the institution of any obligations under HIPAA or the need for an IRB-approved informed consent procedure, Clayton (2004) explains that public opinion is different, and that most patients still believe they should be informed of all potential research uses of their biological materials and retain some autonomy over their use. Thus, she concludes that research institutions would be best served by working with patients collectively and individually to ensure appropriate oversight.

Recommendation 5.5: Those who collect cord blood for public banks should disclose to potential donors all possible clinical and research uses of the cord blood and, furthermore, that donation will terminate a prospective donor's ability to direct the use of the cells.

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6

Inventory of a National Cord Blood Stem Cell Bank Program

One of the most compelling questions in the establishment of the proposed National Cord Blood Stem Cell Bank Program is the number of units needed in the inventory among all participating banks. On the basis of a preliminary analysis of all existing outcomes data and an economic analysis of the costs and benefits of various inventory sizes, the Institute of Medicine committee has identified preliminary estimates of an efficient inventory size. As more data are collected and as match probabilities and relationships between human leukocyte antigen (HLA) mismatch and cell dose are reevaluated, the final inventory size will need to be determined by an oversight board (see Chapter 7). The final inventory size should take into account clinical, policy, and economic interests.

The field of hematopoietic progenitor cell (HPC) transplantation continues to evolve, and for this reason, the definition of a clinically suitable unit may continue to evolve. As technologies for ex vivo expansion, multiunit cord blood transplants, and other innovations are developed, it is likely that the oversight board proposed in Chapter 7 may need to reconsider the definition of a clinically transplantable unit. In all cases, this definition should take into consideration the need to ensure the best possible outcome for the greatest number of people.

When the question of inventory size is viewed through an economic lens, principles of both efficiency and equity should be considered. Efficiency requires that the inventory of a national cord blood stem cell bank program balance the benefits of storing additional units to enhance the length and quality of life of patients against the costs. This should be done

within the constraints of the available resources as well as the constraints of the differences in the degree of difficulty in finding suitably histocompatible cord blood units.

The goal of efficiency will thus need to be balanced against concerns of equity. Equity is a way of describing the potential differences in the benefits received from HPC transplantation among identifiable subgroups in the population (e.g., different racial or ethnic groups).

The efficiency of the cord blood inventory should be assessed in terms of the ability of the inventory—as one potential source of allogeneic HPCs—to increase the benefits in terms of the length and quality of life of potential transplant recipients, again given the constraints of the available resources and the various degrees of difficulty in finding suitably histocompatible cord blood units.

An inventory created to maximize efficiency within the bounds of the definitions given above would require the expenditure of an amount equal to the unit of benefit gained. Addressing equity concerns would produce variation in this cost per unit of benefit across racial and ethnic groups. It is not clear what level of variation across such groups would best promote increases in equity. The Cord Blood Center proposed in Chapter 7 should thus routinely collect and evaluate data on the distribution of benefits and the cost per unit of benefit across different groups of the population. These results should be reported routinely to the proposed national oversight board to inform decision making about the tradeoffs between equity and efficiency in the proposed National Cord Blood Bank Program.

The inventory should consist of cord blood units that meet consistent standards for regulatory compliance and thus ensure that clinical transplant physicians are confident of the quality of those units used for clinical transplantation. As discussed in Chapter 4, these standards should be flexible enough to accommodate advances in the field of cord blood transplantation, and thus, the cord blood inventory policy will need to have flexibility built into it.

The following list reflects specific principles that will allow the proposed national oversight board to balance the principles of efficacy and efficiency. The inventory, therefore, should:

- Reflect the current needs and indications for clinical hematopoietic stem cell transplantation and retain flexibility to accommodate and address emerging and evolving trends in and technologies for cord blood unit selection, ex vivo expansion, and transplantation of cord blood units.
- Ensure the availability for research purposes of cord blood units that are not (or that are no longer) suitable for clinical use.
- Be appropriately balanced with regard to the diversity of the units from different ethnic and racial groups represented in the inventory and the

differences in characteristics (including cell dose) of the cord blood units from those populations as well as the potential diversity of HLA types.

The committee recognizes that issues related to minority recruitment are very complex and will require a well-organized well-directed effort coordinated with leaders within minority communities. The design of such an effort should be under the direction of the National Cord Blood Policy Board (see Chapter 7), rather than this committee.

The total number of units needed for the National Cord Blood Stem Cell Bank Program is a policy decision that will have to be made by the governance of the program after the goals of the program are set and after it is ascertained how much money can be allocated toward inventory expansion.

The following are other questions that will need to be answered before that target number can be set:

- What is the current total number of units—both domestically and internationally?
- What proportion of those units is clinically useful (i.e., what proportion possesses the adequate volume, cell count, and viability)?
- How realistic is it to use units from the international inventory?
- What level of confidence do the end users (i.e., clinical transplanters) have in the current population of units?
- What is the current representation of cord blood units from various racial and ethnic groups within the current inventory?
- What level of donor-recipient matching is desirable, and what is the likelihood that a suitable match by racial and ethnic groups can be found?

The following sections present the initial estimates that the committee computed after review of the existing data.

EXISTING CORD BLOOD INVENTORY

As of January 2005, Bone Marrow Donors Worldwide (BMDW) lists within the U.S. inventory 87,333 cord blood units from unrelated donors available for transplantation. Of those, however, many units may not be considered usable by today's clinical standards.[1] Others may be housed in

[1]Most banks set thresholds for what they consider to be a bankable unit. Based on Institute of Medicine (IOM) survey results, mode minimum total nucleated cell count is 1.1×10^9 (mean 9.6×10^8) and the mode volume is 40 mL (mean volume 52 mL). The thresholds for private banks are lower, and more information can be found in Appendix C.

banks that are not routinely searched by transplant physicians and thus may not be considered reliable for clinical transplant purposes.[2]

Outside the United States, BMDW lists 99,686 units available from 28 banks in 20 countries. However, both the quality and the accessibility of these units can vary drastically. Thus, before policy makers can determine how many units are needed, they must first ascertain how many units are actually available and useful.

Total Number of Usable Units

By taking into account the fact that a substantial portion of the 87,333 units that BMDW lists as available may not be suited to clinical transplantation, a more realistic number for the currently available U.S. inventory may be as low as 44,000 units (Howard et al., 2005) (see Appendix E). The useable international inventory may be as low as 49,000 units.

Likelihood of Finding a Match

As discussed in Chapter 2, HLA match is an important criterion when a transplant physician is choosing a potential adult donor or cord blood unit. In the current domestic inventory of approximately 87,333 units, the likelihood of finding a match of six of six HLA markers (referred to as a 6/6 HLA match) is about 8 percent. When the search is broadened to include potential marrow donors, this probability increases to about 66 percent. However, as noted in Chapter 1, the attrition rate of those marrow donors is very high, and a potential match in the adult donor database does not mean the immediate availability of a graft source. If the cord blood inventory is increased to 300,000 units, the likelihood of finding a match of either cord blood or bone marrow remains the same, but the likelihood of finding a cord blood match increases to 17 percent. However, patients unable to find an unrelated adult donor with a 6/6 HLA match are unlikely to find a perfect cord blood match, regardless of the inventory size (Howard et al., 2005) (see Appendix E). As will be discussed later in this chapter, however, a 6/6 match for umbilical cord blood, while preferable, is not always necessary.

The committee notes that detection of a suitable HLA match is only one part of the selection process. HLA match requirements also depend, in part, on the cell dose of the cord blood unit. The committee's analysis of the

[2]The committee heard anecdotal evidence from both bankers and transplant physicians about reluctance to use units from banks with which the transplant physician is unfamiliar. Thus, until a bank has developed a reputation of reliability, many transplant centers are reluctant to search or reserve a unit from them.

existing data reveals that to ensure a 90 percent probability of a unit with a match of 4/6 HLAs and with a minimum cell dose of 2.5×10^7 total nucleated cells per kilogram of body weight (TNC/kg), at least 100,000 units are required. Increasing the minimum cell dose to 3.0×10^7 TNC/kg increases the minimum number of units needed to 200,000. This preliminary analysis reveals that the relatively small changes to the minimum system requirements that are needed to maximize efficiency can lead to dramatic increases in the inventory size. In either case, substantial increases to the existing usable inventory are required, as are new criteria for what constitutes an acceptable cord blood unit. (For more information on HLA typing, see Appendix F.)

Racial and Ethnic Representation

The likelihood of finding a 4/6 or a 5/6 HLA match greatly exceeds the likelihood of finding a 6/6 HLA match. Finding a match is even more difficult within the African-American population, for which the likelihood of finding a 5/6 HLA match is only 50 percent, whereas the likelihood is 80 percent likelihood for the population as a whole (Howard et al., 2005) (see Appendix E). In addition, individuals of mixed race make up an increasing proportion of the population and may have particular difficulties in finding HLA-matched donors. A 3/6 HLA match can always be found, but no published data support the routine use of a 3/6 HLA match in clinical cord blood transplantation.

PRACTICAL CONSIDERATIONS

The transplant center must weigh several different competing interests when it chooses a unit for a patient in need. Often the "best available" unit can get lost in pursuit of the "ideal" unit.

Different approaches to unit selection also exist, depending on differing transplant center philosophies and emerging information regarding outcomes. The level of HLA match required, the cell dose, and the particular interplay between these two measures are under constant scrutiny by transplant physicians and banks. Using data provided by the New York Blood Center, the National Marrow Donor Program, and the National Heart, Lung and Blood Institute, the committee conducted an outcomes analysis to better understand these measures.

In an analysis of data for first transplants, it became very clear that the rate of survival after the transplantation of cord blood units with low cell doses ($<2.5 \times 10^7$ TNC/kg) and matched for 4/6 or 5/6 HLAs is substantially lower than that after the transplantation of units matched for 6/6 HLAs with low cell doses. As the cell dose increases, the adverse effects of

HLA mismatching are progressively ameliorated, although transplantation of a cord blood unit matched for 4/6 HLAs never attains the survival benefit of transplantation of a unit matched for 5/6 or 6/6 HLAs. However, for units with the highest cell doses (>5 × 10^7 TNC/kg), the long-term survival benefits of transplantation of units with 5/6 and 6/6 HLA matches are virtually identical (see Appendix G).

This analysis was limited both in the size of the data set and in the inability to consider some newer approaches to transplantation, particularly the use of multiple units for a single transplant. It is worth noting, as discussed in Chapter 2, that banks use different levels of HLA typing, and at this point the data are unclear on whether the high-resolution typing that has proven beneficial in marrow matches is necessary in cord blood. Should it be found clinically necessary to make matches at higher resolution, the probability of finding a match will decrease. At the same time, it is conceivable that given the pain and time involved in bone marrow collection, cord blood may overtake bone marrow in unrelated transplants, as it has already done in pediatric cases. Thus, policy makers may need to reconsider the number of units required to support a national program, should demand increase. All of these factors illustrate the need for continued vigorous analysis of outcomes data.

In the development of a national inventory of units, the data do support the need to pay attention not only to HLA diversity but also to the TNC counts of the units to ensure that the cell doses for patients unable to find a perfectly HLA-matched unit are adequate.

Costs Associated with Increasing the Inventory

As mentioned at the beginning of this chapter, the proposed National Cord Blood Stem Cell Bank Program will need to balance the competing interests of efficiency and equity. One effective way to evaluate efficiency is by analyzing the costs associated with the program.[3]

By modeling the life years gained against the cost per cord blood unit by taking into account such measures as overhead and discard rate, the break even reimbursement rate for a 50,000-unit inventory would be $15,336 per unit. This is in line with the cost recovery charged by most banks as determined in the committee's survey (see Appendix C).

The costs associated with placing more cord blood units in the inventory are mainly those associated with replacing transplanted units and units that have reached an the expiration date (which for the purposes of the study is assumed to be 20 years). The benefits of storing additional units—

[3]The committee commissioned David Howard and colleagues to write such an analysis, which can be found in full in Appendix E.

TABLE 6-1 Model of Inventory Costs

	Cord Inventory				
	50,000	100,000	150,000	200,000	300,000
Cord blood transplants	617	643	655	662	670
Annual cord collection (U)	6,234	11,287	16,310	21,324	31,340
Costs (millions)					
Annual bank costs (C)	$10	$17	$25	$32	$47
Direct treatment costs (cTN)	$136	$142	$144	$146	$147
Start-up costs (C_0)	$0	$100	$200	$300	$500
Total costs (TC)	$146	$162	$175	$187	$210
Break-even per cord fee (f)	$15,336	$31,107	$46,613	$62,014	$92,675

expressed in terms of life years—depend on the likelihood of finding a matched unit, which increases with inventory size, albeit at a decreasing rate. Taking the incremental benefits and costs of cord blood inventory into account, Howard et al. (2005) (see Appendix E) conclude that inventory levels above about 150,000 units are not cost-effective, if it is assumed that the economic willingness to pay for a life year is $160,000 (Vigdor, 2003).

It is worth noting that these costs are estimates based on the current state and standard of care associated with cord blood transplantation and are for that reason conservative and should serve as a starting point only. Should the rate of transplant increase (e.g., for children), or should costs of recruitment for lower-represented ethnic groups be higher than average, it may be necessary for the national policy board to revisit this model.

Table 6-1 shows one model of the costs associated with inventory and different transplant levels. It becomes very clear that with increasing inventory, costs also increase drastically.

RECOMMENDATIONS

Recommendation 6.1: Forecasts of the required size of a national inventory of cord blood should be based on the principles of efficiency and equity for identifiable groups of patients. The program should regularly examine data on

- **ways in which increases in cord blood inventory would benefit the length and the quality of life among potential transplant recipients;**
- **the benefits and costs per unit for identifiable groups of patients; and**
- **the effects of inventory policy on the financial viabilities of hematopoietic progenitor cell collection, storage, and distribution systems for hematopoietic progenitor cells.**

These assessments should be used by the Policy Board to respond to changes in need, indications, and technology for hematopoietic progenitor cell transplantation and future applications for cord blood cellular therapy.

This assessment of efficiency should be done by taking into account constraints in resources (e.g., costs), and by recognizing that cord blood is only one source of HPCs. In addition, it should be recognized that there is variation in the degree of difficulty in finding suitably histocompatible stem cells among identifiable groups of patients.

The equity of the availability of suitably histocompatible stem cells should be assessed for identifiable groups of patients, for example, by race and ethnicity; but such an assessment does not need to be limited to race and ethnicity. For example, the availability of suitably histocompatible stem cells could also be assessed by age, treatment indication, gender, and socioeconomic status.

Recommendation 6.2: Continue to conduct outcomes research. The Health Resources and Services Administration and the National Institutes of Health should support further research directed toward understanding the relationships among inventory size, human leukocyte antigen match quality, cell dose, multiple-unit transplants, and the benefits of hematopoietic progenitor cell transplantation to the length and quality of life.

On the basis of an analysis of the U.S. data, the committee has learned that both the quality of the HLA match and cell dose exhibit a complex interaction with respect to their effects on both short-term engraftment rates and long-term patient survival rates. New ways of increasing the cell dose, particularly for adults, should be rigorously studied in the future At the same time, approaches to bring down the costs—particularly of multiunit transplants which can be more than twice as expensive as a single unit transplant—should also be considered.

Recommendation 6.3: Expand the current inventory. Because an increased inventory size would increase the potential benefits of transplantation, the Health Resources and Services Administration should support inventory growth while it assesses the current inventory and establishes the optimal size of a cord blood unit inventory.

- The quality of the existing inventory should be reviewed in the context of the standards that have yet to be established; some units may not be suitable for clinical use.
- The present inventory should be assessed in the context of the global inventory, and harmonization of international standards will better allow this to be done.

- The principles articulated in this report should be used to determine the optimal inventory size; current evidence suggests that additional units would generate health benefits at an acceptable cost.

SUMMARY

Increases in the size of the national cord blood unit inventory would result in increased access to units appropriate for clinical use, which is associated with improved patient outcomes. The characteristics of what constitutes an acceptable unit for transplantation should be reevaluated by simultaneously considering both cell dose and HLA match.

REFERENCES

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Vigdor ER. 2003. Coverage does matter: The value of health forgone by the uninsured. *Hidden Costs, Value Lost: Uninsurance in America*. Washington, DC: The National Academies Press.

7

Recommended Structure of a National Program

The committee's central charge was to advise the Health Resources and Services Administration (HRSA) on how a National Cord Blood Stem Cell Bank Program should be structured. The committee believes that the primary goal of any program structure created should be able to provide transplant physicians the assurance that when they determine that a hematopoietic progenitor cell (HPC) transplant from an unrelated donor is appropriate, the process for locating the best available cells is accurate and timely; that the procured cells are of high quality; and that information on the clinical experience of the transplant recipient is subsequently collected for ongoing research, quality assurance, and clinical improvement. It is clear to the committee that, at present, umbilical cord blood banks operate under various standards, that the outcomes of a significant proportion of cord blood transplants are not reported either to the bank from which the unit was obtained or to the transplant community in general, and that the economic status of cord blood banking is fragile. The structure that is ultimately identified should address all three of these issues.

Throughout its discussion the committee was aware that current participants in cord blood collection, banking, and transplantation hold strong views about the ideal structure of a national program (summarized in Chapter 1). In addition, the committee recognized that some activities and components of a comprehensive structure already exist, such as a good patient education and advocacy system; however, what is in place is not sufficient to meet for present needs and any structure identified now should be responsive to emerging knowledge about HPC transplantation and should

have the capacity to adjust its procedures and structure as necessary and appropriate to incorporate that emerging knowledge.

The committee also considered lessons learned in the process of building a network for facilitating solid transplantation, which are well documented and the subject of a previous Institute of Medicine (IOM) report, *Organ Procurement and Transplantation: Assessing Current Policies and the Potential of the DHHS Final Rule* (IOM, 1999). The committee attempted to learn from this history, to build on existing strengths and to avoid the previously identified pitfalls.

A single national network for access to all sources of HPCs (whether they be adult bone marrow, peripheral blood, or cord blood) would simplify some aspects of the transplantation process, including search efforts, outcomes data collection and analysis, research, and policy making. In fact, for adult donors (of either bone marrow or peripheral blood stem cells), a national network of donor registries and a process for efficient searches already exists and has been regularly strengthened. The National Marrow Donor Program (NMDP) receives substantial federal funding, maintains an informative Web site, provides access to adult donors (both in the United States and internationally), provides extensive patient and clinician support, and maintains a database to track transplant outcomes. It operates an extensive program and also provides statistical support for making these data, as well as statistical support, available for research. Furthermore, participation in this national network is predicated on adherence to standards of data quality, clinical performance, and responsiveness to inquiries. This network has also extended its activity into the cord blood transplant process.

However, the NMDP, as currently configured, is not a simple solution for cord blood banking. While many aspects to be performed by the proposed National Cord Blood Stem Cell Bank Network have analogs in the NMDP (e.g., searching, outcomes tracking, patient support) not all U.S. and few non-U.S. cord blood banks participate in the NMDP network,[1] and the procurement and banking of donated cord blood are processes very different from those used to recruit and track potential adult donors.

The committee also heard anecdotal evidence that the NMDP's infrastructure, while comprehensive, can also be unwieldy. Of particular concern to the committee were the reported delays some banks encountered when trying to get their inventory listed in the NMDP's registry, both because of lack of compatibility from system to system, and because of lack of bank personnel to do the data entry and provide the information in a

[1]Among the domestic cord blood banks that remain independent are the New York Blood Center, Michigan Community Blood Centers, and the University of Colorado Cord Blood Bank.

manner specific to the NMDP's search system. This means that in spite of a centralized search, many transplant centers may have to still search banks specifically to get the most up-to-date information on units.

Furthermore, the committee has heard concerns that the NMDP's focus on adult donors would prevent it from paying adequate attention to cord blood's development, though others felt that such concerns were overstated given evidence of substantial investment by NMDP in its cord blood program in recent years.

Even without a national cord blood program, there has been movement toward the use of more uniform methods of reporting of search results, which allows transplant center personnel to more easily evaluate and choose among the available units. However, the lack of a complete, coordinated network for assessing the national inventory and evaluating the outcome of transplants using units from various banks have made it difficult for the committee to accurately assess the status and quality of the available cord blood units and their current use in transplantation.

Given all of these considerations, the committee sought to incorporate the following elements into the final structure of the network:

- assured clinical access through substantial increases in the current inventory,
- maximal efficiency of processes,
- minimal redundancy of systems and investment,
- guaranteed cord blood unit quality,
- protected patient and donor confidentiality,
- timely data collection and outcome reporting,
- transparent policies and procedures,
- the long-term financial viability of cord blood banks,
- enhanced communication among all parties,
- adherence to ethical standards.

In moving toward the structure described below, the U.S. Department of Health and Human Services (DHHS) is urged to make transparent to the transplant community, banks, patients, and the public the process for establishing, implementing, and evaluating a national program.

Table 1-1 in Chapter 1 compares two perspectives on what an ideal national cord blood program would look like. Table 7-1 reviews the elements presented in that table and briefly describes how these might be developed if the structure recommended in this chapter is adopted. The committee did not choose elements from either of the two main parties but rather created its own ideal. For this reason, it is important for readers of this report to refrain from any attempt to develop a scorecard on the relative strengths of either reported perspective.

TABLE 7-1 Key Functions of a National Cord Blood Program, as Envisioned by the Institute of Medicine Committee

Governance	A National Cord Blood Policy Board should establish policies and regularly monitor all issues related to cord blood uses. Day-to-day management should be done by a National Cord Blood Center, identified by HRSA through a competitive process.
Search Database	Data on both cord blood units available for transplantation and patient outcomes after the transplant are needed. As these two types of data serve different purposes, it is not necessary for them to be available in a single integrated database.
Unit Selection	The National Cord Blood Center should facilitate coordinated searches while allowing transplant centers to customize reports according to local selection practices and to work directly with cord blood banks. Search support should provide guidance or information on the selection of adult donor versus cord blood graft sources.
Source of Transplanted Material	The choice of the source for HPCs must be driven by the patients' needs and the best available evidence about the different sources of material for transplantation. This evidence about uses of all sources of material for transplantation must be regularly updated and made available.
Finances	Federal funds for support of cord blood banking should be allocated to the expansion of the inventory of banked units with some funds reserved for the national infrastructure that will be needed.
Cord Blood Bank Selection	Banks wishing to participate in the National Cord Blood Program should meet the standards to be established by the National Cord Blood Policy Board and must meet all data requirements of the national program.
Standards	Quality standards for banks, donor centers, and transplant centers will be set by an accrediting agency that is independent of the National Cord Blood Center. The accrediting agency will be chosen by a competitive mechanism.
Outcomes Data	The National Cord Blood Policy Board should have ready access to comprehensive data that allow for analysis of all transplants in which HPCs are used and that can be used to establish the desired inventory size and readily update the policies of the National Cord Blood Program.

NATIONAL OVERSIGHT

Recommendation 7.1: The Secretary of U.S. Department of Health and Human Services (DHHS) should establish a National Cord Blood Policy Board to set policy and advise the Secretary of DHHS and the Health Resources and Services Administration on policy regarding the donation, collection, and uses of umbilical cord blood, as well as on

research needed to improve and augment the uses of the cells in cord blood. The National Board should routinely review outcomes data for all clinical uses of umbilical cord blood and develop policy on changes in inventory size, procedures, and standards, as experience and emerging science indicate. The National Board should ensure active interactions among the various organizations involved in adult donor peripheral blood and bone marrow transplantation and umbilical cord blood transplantation.

Relating directly to the earlier mentioned goal of transparent policies and procedures, this new National Board should be established by the Secretary of DHHS. As a chartered body subject to the Federal Advisory Committee Act (96 Stat. 1822), the charter and all appointments should be publicly announced in the *Federal Register*, and meetings of the National Board should be open to interested parties. The National Board should include experts in cord blood transplantation; cord blood collection, storage, and distribution; clinical transplantation; ethics; epidemiology; statistics; informatics; health care services; and other relevant areas. In addition, the National Board should have representation from the public. The members of the National Board should be objective and free of financial and professional conflicts of interest.

The committee urges the National Board to play an active role in ensuring that the lessons learned during the development and growth of NMDP, Cord Blood Banking and Transplantation Study, and solid-organ transplant program are appropriately applied to all funding and policy decisions regarding the National Cord Blood Program. For example, all policy-setting activities should be the purview of the National Cord Blood Policy Board and not the coordinating center, as described below. This arrangement contrasts with the blending of policy and day-to-day management within the Organ Procurement Transplantation Network, in which the role of the DHHS Scientific Advisory Committee for Organ Transplantation is solely advisory; that committee has no policy-making function.

The National Board should meet no less frequently than three times a year to remain abreast of the developments in the fields of cord blood transplantation and banking and to set policy accordingly. The IOM committee assumes that more frequent meetings may be essential during the formative period to develop a clear perspective on the field of HPC transplantation and to establish the initial policies.

STRUCTURE AND GOVERNANCE

Recommendation 7.2: The Health Resources and Services Administration should use an open, competitive process to establish and fund a

National Cord Blood Coordinating Center (the Cord Blood Center). The Cord Blood Center would have day-to-day responsibility for carrying out the policies promulgated by the National Board, including:

- **managing a national network linking participating transplant centers with participating cord blood banks;**
- **collecting data on the outcomes of subsequent cord blood transplants; and**
- **ensuring that data regarding banked cord blood units and the outcomes of cord blood transplants are available to policy makers (including the National Board) for decision making, the participating banks and transplant centers for quality assurance purposes, and researchers seeking to better understand and expand the uses of cord blood.**

In soliciting proposals for the Cord Blood Center, there should be no requirement that all of the program components be centrally managed, provided that satisfactory mechanisms for coordination are proposed, nor should the central management of all program components be prohibited. The request for proposal (RFP) should require that applicants specify a mechanism that ensures efficient access to the available units and that also fosters the evolution of best practices. In line with the above mentioned goal of efficiency, members of the IOM committee are concerned that a requirement to force all aspects of cord blood activity into a single, central organization might slow the matching process and might stifle the creativity of the participating banks and transplant centers and their ability to search for improved practices; responses to the RFP should specifically address this concern. In line with the goal of enhanced communication between the parties, proposals should describe mechanisms for fostering meaningful links between and among transplant centers and banks, a means for achieving appropriate standardization, and methods that provide clinicians with access to the information needed for clinical decision making.

With regard to the goal of minimal redundancy, the committee envisions not the creation of something new, but rather the development of an appropriate mechanism for coordinating the elements that already exist. While the committee does not believe that any single party is currently performing all the functions that coordinating centers would perform, the committee does hold the opinion that the elements exist and need a means by which they can be brought together, or conversely, that a single party could develop the mechanisms necessary to support the bank program—bearing in mind the aforementioned goals of efficiency and the need to support cord blood in its infancy.

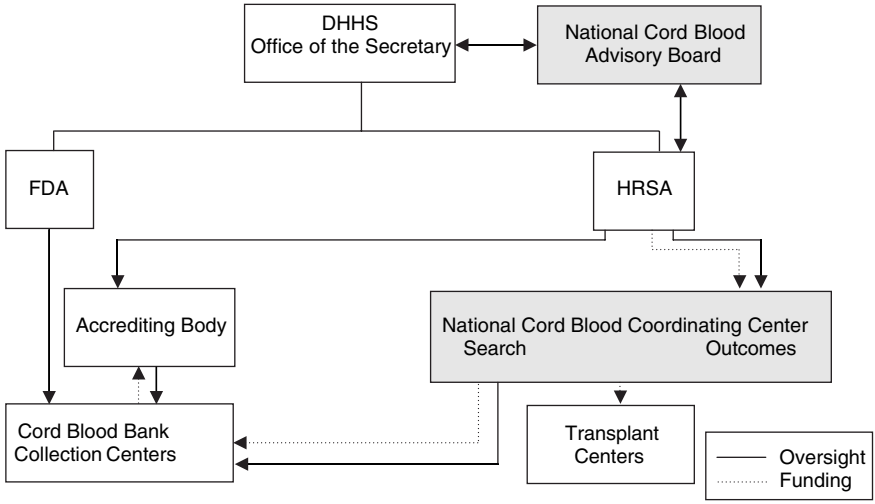

FIGURE 7-1 The relationships that the IOM committee envisions under the governance structure described in its recommendations.

Figure 7-1 illustrates the relationships that the committee envisions under the governance structure described in these recommendations.

Source of Transplanted Material

The National Board should set policy and the Cord Blood Center should perform its functions with full recognition that cord blood, peripheral blood, and bone marrow are complementary, alternative sources of HPCs. The source chosen must be driven by the patients' needs and anticipated outcomes on the basis of the best available evidence rather than on an a priori selection of the source. Thus, every effort should be made to collaborate, as appropriate, with NMDP and other bone marrow donor registries. However, IOM committee members heard a number of expressions of anxiety that NMDP might, because of its resources, unduly influence national decisions about HPC transplantation. For that reason, it is essential that the National Board should assure all parties that policy decisions are made in a fair and unbiased way and that cord blood transplantation is supported in its emergence as a therapeutic option in the complicated world of HPC transplantation.

Inventory Database and Unit Selection

The Cord Blood Center should work to explore the best possible methods for transplant physicians to search the database of the cord blood inventory, obtain confirmatory human leukocyte antigen (HLA) typing, and reserve and select cord blood units for transplantation on the basis of the best available evidence. These protocols will need regular review, as the field is changing rapidly. These methods should include a format for reporting search results that provides a coherent summary of all units available through the national program and that incorporates flexibility to allow transplant centers to customize reports to meet the needs of local selection practices. For clinical purposes, a central database of all available units is not essential (but also not precluded), as long as current information on the inventory in all participating banks is accessible at the time of a search. The data system and policies should allow individual participating transplant centers to work directly with participating banks to locate a unit, if desired. In addition, the Cord Blood Center should work to facilitate efficient access to units collected internationally, as long as they fulfill the quality requirements set by the national system and are compliant with Food and Drug Administration (FDA) regulations.

The committee heard from many sources regarding the desirability of "one-stop-shopping" for all sources of HPC. As mentioned in Chapter 1, this is not currently a realistic goal. However, upon the development of a comprehensive outcomes database (see Recommendation 7.3), and evaluation of the data therein, the National Cord Blood Policy Board should consider working toward the development of a mechanism by which all sources of HPCs can be concurrently searched.

Outcomes Data

Recommendation 7.3: The National Board should support the development of an outcomes database that can guide decisions on inventory size and track cord blood bank quality and other policies as well as assist with the assessment of outcomes from *all* sources of hematopoietic progenitor cells.

This recommendation is directly linked to the goal of timely data and outcomes reporting. Collection of outcomes data by the Cord Blood Center should follow a standardized format and capture the appropriate clinical information that is required by cord blood banks to meet their quality assurance, accreditation, and regulatory requirements. This might be achieved internally by the new Cord Blood Center or, perhaps more economically, by contracting with an existing organization having appropriate capacity. Any transplant center desiring to participate in the national pro-

gram should agree to supply timely data on the immediate and long-term outcomes for patients receiving cord blood units supplied by the national program. The format for this data-reporting process should be consistent with that used for adult donor transplantation and, as mentioned earlier, to foster the development of algorithms to identify the optimal graft source for diverse patient groups, a single outcomes database for adult donor and cord blood HPC transplants should be considered, building on existing efforts if possible. This information would not only ensure that complete data on the clinical outcomes following transplantation are collected but would also provide data to qualified researchers as well as policy makers and clinicians interested in overall analysis of both national adult donor and cord blood resources. Because these data requirements will impose a burden on the participating organizations, and because the collection and submission of high-quality data are time-consuming activities, some financial support will be needed to assist transplant centers with their data collection and data transfer activities.

Finances

Recommendation 7.4: The national program should provide the participating banks with the financial support that they need to achieve an inventory sufficient to provide as many potential recipients as possible with a high probability of a therapeutically effective cord blood unit when one is clinically indicated.

Finding 7.1: At present, if it is assumed that an effective cord blood unit should have a minimum cell dose of $>2.5 \times 10^7$ nucleated cells per kilogram of recipient body weight with *two or fewer* human leukocyte antigen (HLA) mismatches at HLA-A, HLA-B (intermediate resolution), and HLA-DRB1 (high resolution), the committee estimates that at least 100,000 new, high-quality units need to be added to the current inventory to achieve the inventory size recommended in Recommendation 7.4.

The committee believes that expansion of the current inventory with units that meet the established standards should receive the highest priority in the near future to facilitate enhanced patient access. As discussed in Chapter 6, the National Board should offer support to participating banks that are designing expansion plans for their inventories to include racially and ethnically diverse sources of cord blood, thus enhancing access to cord blood by individuals in racial and ethnic minority groups. Participating banks should be reimbursed for the units that they supply for transplantation through health care payment systems in a manner that allows them to become self-sufficient by the end of the period of federal funding.

Recommendation 7.5: Some portion of the funds dedicated to the establishment of the national program should be reserved to support the infrastructure described in this chapter.

The national program will require an infrastructure that supports the outcomes database, as well as the Cord Blood Center and the National Board. The ongoing program of accreditation of participating centers should be supported by the common method of participant fees. To ensure that the available cord blood units are used to the greatest advantage for patient care, federal funds should be provided for start-up and ongoing costs for the development of mechanisms for the sharing and publication of outcomes data; verification that the participating banks and transplant centers meet quality assurance standards; and encouragement of innovation and improvement in banking, matching, and related processes.

Though as mentioned earlier, the committee does not envision the necessity of creating completely new components for the national program, the means to coordinate the program will require support initially.

Cord Blood Bank Selection

Recommendation 7.6: The National Board should establish minimum criteria for quality standards and data sharing for banks participating in the national program. The Cord Blood Center should monitor and manage the implementation of those standards and coordinate a competitive process for the distribution of funds to qualifying banks for inventory growth.

In order to support the goal of guaranteed quality, banks should be selected on the basis of published criteria and demonstration of the quality of their operations (e.g., accreditation and licensure) by their responses to a formal RFP issued by HRSA and subsequent selection by a specially appointed, independent expert panel. Public cord blood banks not receiving funds directly for inventory growth may be linked to transplant centers via the Cord Blood Center search mechanism, should they meet the other participation standards. Although accredited foreign cord blood banks should not be eligible to receive federal funds for inventory expansion, they should be encouraged to participate in other aspects of the program, including provision of access to their cord blood units, data sharing, and the provision of clinician and patient support. Although the committee did not expect participation in this network to be a requirement for all public banks, given the financial and logistical advantages network participation will bring, the committee believes that most banks will choose to take part in the program.

Standards

Quality standards for participating banks, collection sites and centers, and transplant centers should be established and overseen by an accreditation body. The specifics of the quality standards are more fully discussed in Chapter 4. This independent accreditation body should be independent of the Cord Blood Coordinating Center and should be identified through a competitive process open to the several existing groups, as well as any other group(s) that may emerge. The final decision on the body to be recognized by the national program should be made by an expert panel. Only those banks and transplant centers accredited by this body should be able to participate in the National Cord Blood Stem Cell Bank Program. Furthermore, as recommended in Chapter 4, FDA should move quickly to license all blood banks units. At this point, FDA licensure of units would be required of any bank participating in the national program.

Patient Support

Support services, in the form of counseling and assistance with insurance and financial matters, are needed for patients searching for either an adult donor or a cord blood unit, as are educational activities to increase understanding of the transplant process. These elements are essential to a national program and are suggested as a part of the structure. These activities are being conducted well by NMDP and should be adapted and built on as part of the national program. The committee encourages the NMDP to continue their efforts at minority outreach and in making this information about transplantation and the search process available in multiple formats and languages.

REFERENCE

IOM (Institute of Medicine). 1999. Organ Procurement and Transplantation: Assessing Current Policies and the Potential Impact of the DHHS Final Rule. Washington, DC: National Academy Press.

APPENDIXES

A

Methods Section: Data Collection and Analysis

Introduction

As part of its statement of task, the Health Resources and Services Administration charged the Institute of Medicine Committee on Establishing a National Cord Blood Stem Cell Bank Program to "make recommendations for the optimal structure for the cord blood program and address pertinent issues related to maximizing the potential of this technology (e.g., collection, storage, standard setting, information sharing, distribution, reimbursement, research, and outcome measures)."

To answer the questions posed to them in the statement of task, the committee members used their own technical expertise supplemented by various methods of information gathering. These methods are described below.

Literature Search

The committee used an extensive literature search to compile the relevant data on research on cord blood published to date in the EMBASE, PreMedline, and Medline databases of medical literature. The search was conducted in two parts. The first focused on cord blood banking issues limited to human subjects, using the keyword terms: ("blood banks" OR "blood donors" OR "Blood blood preservation" OR "preservation, biological" OR "cryopreservation" OR "freeze drying") AND ("fetal blood" OR "hematopoietic stem cells"). This search generated 1,274 articles. The second search looked specifically at cord blood in hematopoietic progenitor

cell (HPC) transplantation and at HPC transplantation in general, using the key terms "fetal blood [transplantation]" OR "cord blood stem cell transplantation" OR ("fetal blood" AND "stem cell transplantation") OR ("umbilical cord blood" AND ("bone marrow transplantation" OR "hematopoietic stem cell transplantation" OR "peripheral blood stem cell") OR ("umbilical cord blood" AND "stem cell transplantation"). This search was also limited to research with human subjects and provided 870 articles. The breakdown of human subjects described in the articles by age showed that fewer articles described research with adults than research with children and adolescents. The exact number of articles found for each category was: adults, 455 articles; adolescents, 200 articles; children, 271 articles; infants, 130 articles; and infants and newborns, 311 articles. Because cord blood transplantation is a relatively new therapy, the search was not limited by year. Of the 2,144 records in the list, however, only 48 articles dated from before 1980.

Site Visits

At the first meeting, the members of the committee decided that to best characterize the current state of cord blood banking in the United States, they would need to see cord blood banks firsthand. The committee chose a variety of banks with different affiliations, sizes, and objectives to best represent the diversity of the cord blood banking industry. The committee saw both private and public banks, as well as banks that focused on directed donations. Committee representation varied for each visit to allow each committee member to see some banks.

At each bank, members of the committee asked the staff of the bank to guide them through the path of a cord blood unit from the moment that it arrives at the bank, through all processing, to the moment that the unit is frozen in storage. Specific attention was paid to the individual banks' approaches to

- consent,
- collection processes,
- decisions about minimum levels for storage and for transplant,
- labeling and identification,
- processing,
- informatics and databases,
- matching, and
- shipping.

A list of the sites visited is in Box A-1.

BOX A-1
Site Visits Conducted by the Committee (by date of visit)

1. CyroBanks International (July 26, 2004) with Dwight Brunoehler and others
2. New York Blood Center (August 3, 2004) with Pablo Rubinstein, Cladd Stevens, Melissa Penn, Kathleen Reichert, and others
3. Children's Hospital Oakland (August 20, 2004) with Bert Lubin and others
4. Cord Blood Registries (August 23, 2004) with Tom Moore and others
5. St. Louis Cord Blood Bank (September 13, 2004) with Michael Creer, J. Mario Alonso, Donna Regan, and others
6. J.P. McCarthy Cord Stem Cell Bank (October 13, 2004) with Voravit Ratanatharathorn, Louisa Serafimovska, and Jan Keersmaekers
7. Michigan Community Blood Centers Cord Blood Bank (October 14, 2004) with Mary Banfill and others

Survey

No comprehensive data were available about indicators such as the racial makeup of cord blood donors or the cost of storage of each unit in the cord blood inventory in the United States. For this reason, the members of the committee set about gathering these data themselves.

To gather these more quantitative data, the members of the committee asked cord blood banks for information in the form of a questionnaire, which was sent to 40 cord blood banks in the United States. The questions asked for:

- general background information;
- collection and storage;
- inventory size and composition;
- cost, either for storage or as reimbursements from a transplant facility; and
- the procedures used to search for matches and use of cord blood units (completed only if services include public banking).

In addition to mailing the survey to 40 banks, the survey was also made available online (see Appendix B). The surveys were sent with prestamped, return-addressed envelopes, and second and third follow-up letters were sent to thank the banks that had responded and to request responses from those that had not yet done so. As of November 18, 2004, the committee had received 21 partially or fully completed surveys. The information gathered helped the committee make its recommendations.

Raw Data Analysis

Although most public banks attempt to maintain more or less complete sets of outcomes data and follow up with recipients of cord blood months and years after the transplant, many are not able to obtain the information; and even among those that can, the data are not usually shared among the different cord blood banks. The committee was given access to the outcomes data from the National Marrow Donor Program cord blood transplants, the results of the COBLT study, and the data from the New York Blood Center and did its own analysis (see Appendix G).

Commissioned Papers

The committee selected several areas in which it wanted analyses to be conducted by experts: human leukocyte antigen typing, the racial make-up and diversity needs of a national inventory, economic issues associated with cord blood banking, and future prospects for cord blood use. These papers were written by Karen Ballen, Margaret Goodell, David Howard, and Carolyn Hurley, respectively. Some of those papers can be found in Appendixes D to F.

Committee Meetings

The committee held two information-gathering meetings before commencing with the writing of the final report.

The first meeting, held on June 2 and 3, 2004, in Washington, D.C., included speakers involved in creating the legislation relevant to the committee's charge and speakers from selected federal agencies and professional organizations, as well as a speakers presenting the clinical perspective on cord blood transplantation.

At the second meeting, held August 18 and 19, 2004, in Irvine, California, the committee heard from speakers on the topics of informatics and matching algorithms, cord blood bank accreditation, cord blood collection and preservation issues, ethical and legal considerations, outcomes data, and patient support issues. Speakers were chosen for their expertise in their fields.

In addition, periods for participants to make open comments were included during each of the first two meetings. These allowed members of the public representing various constituencies and interested groups to address the committee.

The third and fourth meetings, held September 29 and 30, 2004, in Woods Hole, Massachusetts, and December 15 and 16, 2004, in Washington, DC, respectively, were deliberative and writing meetings, during which

the committee developed and refined its recommendations and the members of the committee worked together to draft the report. The committee also kept in close contact by telephone and electronic communication.

Invited Participants and Guests

The following individuals were invited participants and guests at meetings of the committee.

James Burdick, M.D.
Health Resources and Services Administration

Shelly Carter, Sc.D.
The EMMES Corporation

Jeffrey Chell, M.D.
National Marrow Donor Program

Phil Coelho
Thermogenesis Corporation

Dennis Confer, M.D.
National Marrow Donor Program

Jeff Couglin
American Society for Hematology

Michael Fitzpatrick
America's Blood Centers

Captain Robert Hartzman
Director, Department of Defense Marrow Program, Navy

Liana Harvath, Ph.D.
National Institutes of Health

Valerie Hurt
National Institutes of Health Office of the General Counsel

Brent Jaquet
Congressman William Young's Office, Florida

Naynesh Kamani, M.D.
Children's National Medical Center

Joanne Kurtzberg, M.D.
Duke University Pediatric Stem Cell Transplant Center

Ellen Lazarus, M.D.
Food and Drug Administration

David Leitch
Illinois House of Representatives

Pam Murph, LCSW
Association of Oncology Social Workers

Sudip Parikh
Senator Arlen Specter's Office, Pennsylvania

Pablo Rubenstein, M.D.
National Cord Blood Program of the New York Blood Center

Karen Shoos-Lipton
American Association of Blood Banks

Edward Snyder, M.D.
American Association of Blood Banks

Cladd Stevens, M.D., MPH
National Cord Blood Program of the New York Blood Center

Susan Stewart
BMTInfonet

Elizabeth Wagner
National Heart, Lung, and Blood Institute

Phyllis Warkentin, M.D.
Foundation for the Accreditation of Cellular Therapy

Jill Warner, Esq.
Food and Drug Administration

Thomas Weigand
Operations Manager, Caitlin Raymond International Registry

B

SURVEY*

Committee on Establishing a National Cord Blood
Stem Cell Bank Program

Please answer the following questions as completely as possible and provide the indicated materials.

Contact Information

Name of individual filling out this survey

_____

Cord Blood Bank Name

_____

Title/Position _____

Phone Number _____

Fax _____

Address _____

_____

General Background

1. What type of banking service(s) do you offer? (check all that apply):

☐ Public ☐ Private (Directed Donation)

If both, what percentage of business is private? _____

*Note the survey as it appears in this appendix is as it was sent to the banks.

2. Please fill out the following table:

	Public Bank	Private Bank (Directed Donation)
Date of 1st Unit Cryopreservation		
Date of 1st Unit Released for Transplant		

3. What accreditation(s) does your bank have?

☐ FACT ☐ Other _____
☐ AABB

4. Please provide the following:

Number of Individuals Consenting to Collection: _____
Number of Units Collected: _____
Number of Units Banked (after testing and screening for low volume) in Total: _____
Number of Units Available for Transplant
completed review): _____
Number of Units in Searchable Registry: _____
Number of Units Used for Transplant to Date: _____

5. Is your bank currently actively recruiting new units for storage (circle one)?
Yes No

6. Is there a scientific board to review things such as collection procedures and outcomes data? What exactly do they review?
_____

Inventory

1. Is the donor identifying information linked to the banked units at your facility?_____

If so, who has access to the information linking the donor and the unit?
_____

How is that information stored (e.g., separate donor and recipient databases)?

Can recipients obtain access to their donor's information? _____

2. Please fill out the following table:

Ethnicity	# of Units Banked	# of Units Available
Asian		
African American		
Hispanic		
Native American		
Middle Eastern		
Caucasian		
Unknown/Missing Information		
Multi-racial		
Other		

3. What criteria are used to determine which units are suitable for banking (e.g., testing negative for certain conditions during health screening)?

☐ Threshold of nucleated cell dose _____
☐ Volume _____
☐ Bacterial contamination
☐ Level of HLA resolution _____
☐ Other?

4. What is done with units that are not usable for transplant?

☐ Research – Internal
☐ Research – External
☐ Discarded or Destroyed
☐ Investigator Charged
☐ No Charge

5. Are units bar coded and tracked electronically? If not, how are they tracked?

6. What informatics does your bank use? In what format is unit information stored?

☐ Database System
  ☐ Excel Spreadsheet
  ☐ Access Database
  ☐ Other Database _____
☐ Data Entry
☐ Quality Assurance Program
☐ Other

Collection and Storage

1. Please discuss in detail the procedure for cord blood collection and storage, including but not limited to:

a. Who collects the blood

- ☐ Obstetrician/Midwife
- ☐ OB Nurse
- ☐ Designated collector from the CBB
- ☐ Researcher
- ☐ Other _____

b. Where the cord blood is collected

- ☐ In the Obstetrician Suite (site of delivery)
  - ☐ In Utero
  - ☐ Ex Utero
- ☐ Designated Collection Room
- ☐ Other _____

c. Can more than one unit be 'in process' by one technician?
Yes / No

d. At what time point are aliquots removed for infectious disease testing? (Please check all that apply)

- ☐ On whole blood (before any processing)
- ☐ On red cell depleted or mononuclear cell product
- ☐ On cryopreserved aliquot
- ☐ Other_____

e. At what point are aliquots removed for HLA typing? (Please check all that apply)

- ☐ On whole blood (before any processing)
- ☐ On red cell depleted or mononuclear cell product
- ☐ On cryopreserved aliquot
- ☐ Other_____

f. At what point are aliquots removed for hemoglobinopathy testing? (Please check all that apply)

- ☐ On whole blood
- ☐ On red cell depleted or mononuclear cell product
- ☐ On cryopreserved aliquot
- ☐ Other_____

g. How is the unit stored?

☐ As whole blood without manipulation
☐ As whole blood but with volume reduction only
☐ As red cell depleted or mononuclear cell product
☐ Other_____

☐ Anticoagulant used _____
☐ Cryoprotectant used _____

h. Steps in storage and freezing

2. How many collection sites does your bank have? Where are they located?

3. What training, if any, is required of collection sites? Is there documentation or training certification kept by your bank? Do you maintain files of collection procedures for each of the collectors? How are collectors re-certified? How often are they re-certified?

4. Please attach any advertisements/materials used for recruitment of donors.

5. Please provide a copy of your bank's donor consent forms. Please detail:

a. Timing of Consent
☐ Prior to Labor
☐ After Delivery
☐ Other _____

b. Consent Obtained from
☐ Mother
☐ Father
☐ Both

c. Consent Obtained by
☐ M.D.
☐ Nurse
☐ Trained Official
☐ Other _____

d. Is consent taken more than once (e.g., a preliminary consent followed by a final consent signed later)?
_____

e. Public Banks ONLY: What do you tell the patient about finding her infant's unit at a later date if it is needed?

f. Background and training requirements for obtaining consent:

6. When is the patient health screening and medical history obtained? Who performs this function? What items of the patient's or family's medical history would exclude them as a donor?

7. Is there follow-up in neonatal health status? If yes, when is this undertaken?

   How is this follow-up performed?
   - ☐ Postcard
   - ☐ Phone call to mother
   - ☐ Other

8. Please indicate which obstetricial/fetal clinic conditions would result in exclusion of a unit (check all that apply):

   - ☐ Multiple gestations
     Gestational age of less than _____ weeks
   - ☐ Chorioamnionitis (Definition at your center: _____)
   - ☐ Meconium
   - ☐ Prolonged rupture of membranes (without chorioamnionitis)
   - ☐ Tear in cord insertion from placenta
   - ☐ Postive group B strept carrier
   - ☐ Active genital herpes
   - ☐ Vulvar or perineal condylomata
   - ☐ Known fetal structural anomalies (e.g., spinal bifida)
   - ☐ Known fetal chromosome abnormalities
   - ☐ Other _____

9. Please check all screening that is completed prior to storage:

   - ☐ Genetic Screening
     - ☐ Hemoglobinopathy
     - ☐ ABO Group
     - ☐ Rh Type
     - ☐ Health Questionnaire
     - ☐ Other _____
   - ☐ Infectious Disease Testing
     - ☐ Alanine Aminotransferase (ALT)

☐ Cholesterol
☐ CMV IgG
☐ CMV IgM
☐ CMV culture/shell vial
☐ Hepatitis B virus
  ☐ HBSAG ☐ HB cord Ag ☐ NAT
☐ Hepatitis C virus
  ☐ Ab ☐ NAT
☐ HIV, type 1
  ☐ Ab ☐ P24 Ag
☐ HIV, type 2
☐ Human T-cell lymphotropic virus, type I
☐ Human T-cell lymphotropic virus, type II
☐ *Treponema pallidum* (syphilis)
☐ West Nile NAT
☐ Other _____

☐ Exclusion using current FDA travel restrictions
If so, are there any recommended travel restrictions that would prevent exclusion of the unit from your bank?

_____
_____
_____
_____

10. Please discuss the HLA typing procedure carried out on cord blood samples prior to storage.

Location of Laboratory _____
Accreditations of Laboratory _____
Level of Resolution
☐ A
☐ B
☐ C
☐ DR

11. Is confirmatory typing required at time of unit release? If yes, where is confirmatory typing performed?

☐ Bank/Designated HLA Lab ☐ Not Required
☐ Transplant Center ☐ Other _____

12. How many units have been collected and shipped up to today for each year of the banking program?

COLLECTED:	SHIPPED:
1993 _____	1993 _____
1994 _____	1994 _____
1995 _____	1995 _____
1996 _____	1996 _____
1997 _____	1997 _____
1998 _____	1998 _____
1999 _____	1999 _____
2000 _____	2000 _____
2001 _____	2001 _____
2002 _____	2002 _____
2003 _____	2003 _____
2004 _____	2004 _____

Search for Matches and Use of Cord Blood Units - To Be Completed Only if Services Include Public Banking

1. What level of HLA typing is considered during searches?

   ☐ A
   ☐ B
   ☐ DR

   What other criteria beyond HLA typing are used in matching? If other criteria are used, please describe your algorithms for matching using multiple results.

2. Please provide a search request form. What is the information system you use for the search process?

3. Please provide a sample search report.

4. What kind of assistance is provided during a search by the bank staff, if any?

   ☐ Rapid confirmatory HLA typing (details: _____)
   ☐ Potential search algorithm (details:_____)
   ☐ Reduced costs under certain conditions (details:_____)
   ☐ Other: _____

5. Please indicate (by checking the relevant boxes) what testing is mandatory at the time of unit selection prior to transplant?

   ☐ Repeat HLA Typing
   ☐ Genetic Disease Testing
   ☐ Other _____

6. Availability of Attached Segments:

   Minimum Number of Segments _____
   If not attached, how is the segment linked (bar code, written identifier, etc.)?

   _____

   What is in the segment?

   ☐ Viable nucleated cells
   If yes, how are they stored (liquid nitrogen, –80ºC freezer, other)?
   _____
   Are they attached within the unit cassette? If not, what are they stored in: nunc vials, other)?
   _____
   How many cells are in each aliquot?
   _____
   How many aliquots (range if variable)?
   _____
   How many units have at least one attached segment within the unit cassette?
   How many do not?
   _____

   ☐ Serum
   If yes, what is the volume in each aliquot?
   _____
   No. of aliquots (range if variable)_____
   How are they stored (liquid nitrogen, –80ºC freezer, –20ºC freezer)?
   _____

   ☐ Plasma
   ☐ DNA
   If yes, how are they stored (filter paper, nunc vials, other)?
   _____

7. What criteria must a unit meet before it is made available to transplant centers?

8. What are the criteria (if any) must a transplant center meet before receiving units from your bank?

   ☐ NMDP Approved Site for Unrelated Marrow Donor Transplant
   ☐ FACT Accreditation
   ☐ Other _____
   ☐ Exceptions allowed based on:

9. How is your bank most commonly accessed by a transplant center?

   ☐ Direct Contact from Individual Transplant Center
   ☐ Via NetCord
   ☐ Via NMDP
   ☐ Other _____

10. Do you collect outcome data? If yes, provide us all the case report forms and outcome data your bank has collected. Please tell us how many cases have complete engraftment and survival data been provided by the transplant center. What is the frequency that updates are requested? How is the data verified? Is it audited? If so, how is the audit done and how frequently?

11. Please indicate:

    Proportion of patients in database for whom there is
    engraftment data at day 42_____
    GVHD data at day 100_____
    survival data at day 100 _____
    survival data at day 360 _____
    Proportion of patients in database who have died _____

12. Is a delivery history of the unit maintained? Are transplant results followed and recorded? What data in particular is collected? Please include post-transplant data collection forms if your bank supplies them.

Cost

1. **Private Banks ONLY:** How much does your bank charge to:

   Collect a unit: _____
   Store a unit: _____
   Obtain a unit for transplant: _____

   Public Banks ONLY:
   What is your current reimbursement per unit? _____

2. **Public Banks ONLY:** How is your bank funded currently and how has it been funded historically?

Currently	Historically
NIH	NIH
Private/Philanthropy	Private/Philanthropy
State-funding	State-funding
Support from Public Bank Revenue	Support from Public Bank Revenue
Other _____	Other _____

Thank you for your time and concern in helping the committee gather needed information!

C

Survey Results

TABLE C-1 Banks That Responded

Bank	State
American Red Cross North Central Blood Services Cord Blood Program	MN
Carolinas Cord Blood Bank	NC
Children's Hospital of Orange County Cord Blood Bank	CA
Cord Blood Registry	CA
Cryobanks International, Inc.	FL
ITxM Cord Blood Services	IL
JP McCarthy Cord Stem Cell Bank	MI
Lifebank USA	NJ
LifeCord	FL
LifeStor	VA
Michigan Community Blood Centers Cord Blood Bank	MI
National Cord Blood Program of the New York Blood Center	NY
New Jersey Cord Blood Bank	NJ
Puget Sound Blood Center and Hawaii Cord Blood Bank	WA
Sibling Donor Cord Blood Program Children's Hospital Oakland Research Institute	CA
South Texas Blood & Tissue Center	TX
St. Louis Cord Blood Bank	MO
StemCyte International Cord Blood Center and Cord Blood Family Trust	CA
The Elie Katz Umbilical Cord Blood Program	NJ
University of Colorado Cord Blood Bank	CO
Viacord	MA

TABLE C-2 Type of Bank

PUBLIC BANKS
American Red Cross North Central Blood Services Cord Blood Program
JP McCarthy Cord Stem Cell Bank
Michigan Community Blood Centers Cord Blood Bank
National Cord Blood Program of the New York Blood Center
New Jersey Cord Blood Bank
South Texas Blood & Tissue Center
St. Louis Cord Blood Bank
University of Colorado Cord Blood Bank

PRIVATE BANKS
Cord Blood Registry
LifeStor
Sibling Donor Cord Blood Program Children's Hospital Oakland Research Institute
Viacord

BANKS THAT OFFER BOTH
Carolinas Cord Blood Bank
Children's Hospital of Orange County Cord Blood Bank
Cryobanks International, Inc.
ITxM Cord Blood Services
Lifebank USA
LifeCord
Puget Sound Blood Center and Hawaii Cord Blood Bank
StemCyte Inc. and Cord Blood Family Trust
The Elie Katz Umbilical Cord Blood Program at Community Blood Services

Totals: 8 Public, 4 Private, 9 Mixed

TABLE C-3 Self-Reported Accreditation[a]

Bank	FACT	AABB	Other[b]
American Red Cross North Central Blood Services Cord Blood Program		X	
Carolinas Cord Blood Bank	X		FACT pending, NMDP
Children's Hospital of Orange County Cord Blood Bank	X		JCAHO, California Tissue Bank License, Seeking FACT Accreditation
Cord Blood Registry		X	
Cryobanks International, Inc.		X	
ITxM Cord Blood Services			Will apply for FACT this fall
JP McCarthy Cord Stem Cell Bank			NMDP
Lifebank USA		X	ISO
LifeCord	X	X	NMDP
Michigan Community Blood Centers Cord Blood Bank		X	FDA Registration
National Cord Blood Program of the New York Blood Center	X		New York State Board of Health
New Jersey Cord Blood Bank			
Puget Sound Blood Center and Hawaii Cord Blood Bank		X	
Sibling Donor Cord Blood Program Children's Hospital Oakland Research Institute	X		California State Biologies, California State Tissue Bank (both current)
St. Louis Cord Blood Bank		X	CAP
StemCyte, Inc. and Cord Blood Family Trust		X	ASHI, NMDP, CAP, California Biologics License, CLIA, FACT pending
The Elie Katz Umbilical Cord Blood Program		X	
University of Colorado Cord Blood Bank	X		
Viacord		X	CLIA, CAP proficiency, NY State, NJ State, KY State, PA State, registered with FDA and IL State, and MD tissue bank permit

[a]The accreditation status of the banks was not independently verified.
[b]The definitions of the acronyms are provided at the end of this appendix.

TABLE C-4 Numbers of Collected, Stored, and Transplanted Units

Bank	Consenting to Collect	Collected	Banked	Available	Searchable	Used for Transplant	Note
American Red Cross North Central Blood Services Cord Blood Program	23,130	18,680	6,069	5,962	5,962	242	8 not transplanted
Carolinas Cord Blood Bank	17,519	17,000	8,300	7,800	7,800	320	
Children's Hospital of Orange County Cord Blood Bank	3390	2,900	1,550	1,375	1,350	7	
Cryobanks International, Inc.	17,741	15,429	9,439	7,485	7,485	5	4 public, 1 private
ITxM Cord Blood Services	9,867	5,280	5,000	2,620	2,513	20	Consenting refers to collection kits requested
JP McCarthy Cord Stem Cell Bank	3323	2,486	600	517	445	4	
Lifebank USA	17,807	17,228	16,264	3,300	3,300	1	
LifeCord	1	7,429	1,975	1,474	1,474	10	
LifeStor	102	96					
Michigan Community Blood Centers Cord Blood Bank	6,665	5,531	1,497	1,386	1,375	6	
National Cord Blood Program of the New York Blood Center	27,328	29,525	25,989	25,989	25,989	1,765	Includes first and second transplantations and multiple-unit grafts
New Jersey Cord Blood Bank		2,621	1,984	1,796	1,796	7	

continues

TABLE C-4 Continued

Bank Name	Consenting to Collect	Collected	Banked	Available	Searchable	Used for Transplant	Note
Puget Sound Blood Center and Hawaii Cord Blood Bank	3,877	2,358	1,097	727	727	5	
Sibling Program Children's Hospital Oakland Research Institute	1,556	1,438	1,378	1,064	0	43	
St. Louis Cord Blood Bank	40,000	40,000	10,000	10,000	10,000	656	10,000 means >10,000. Searches include NMDP, CRIR, and direct searches. Transplants are through June 30, 2004
StemCyte, Inc. and Cord Blood Family Trust	16,777	13,566	8,558	8,331	8,331	78	
The Elie Katz Umbilical Cord Blood Program		3,635	2,473	2,473	1,511	25	
University of Colorado Cord Blood Bank	10,000	9,943	7,017	6,669	6,435	234	Total consenting not known with precision
Viacord	60,000	60,000			0	14	60,000 means >60,000. Every consent resulted in a collection.
Total	259,083	255,145	109,190	62,979	60,504	3,384	

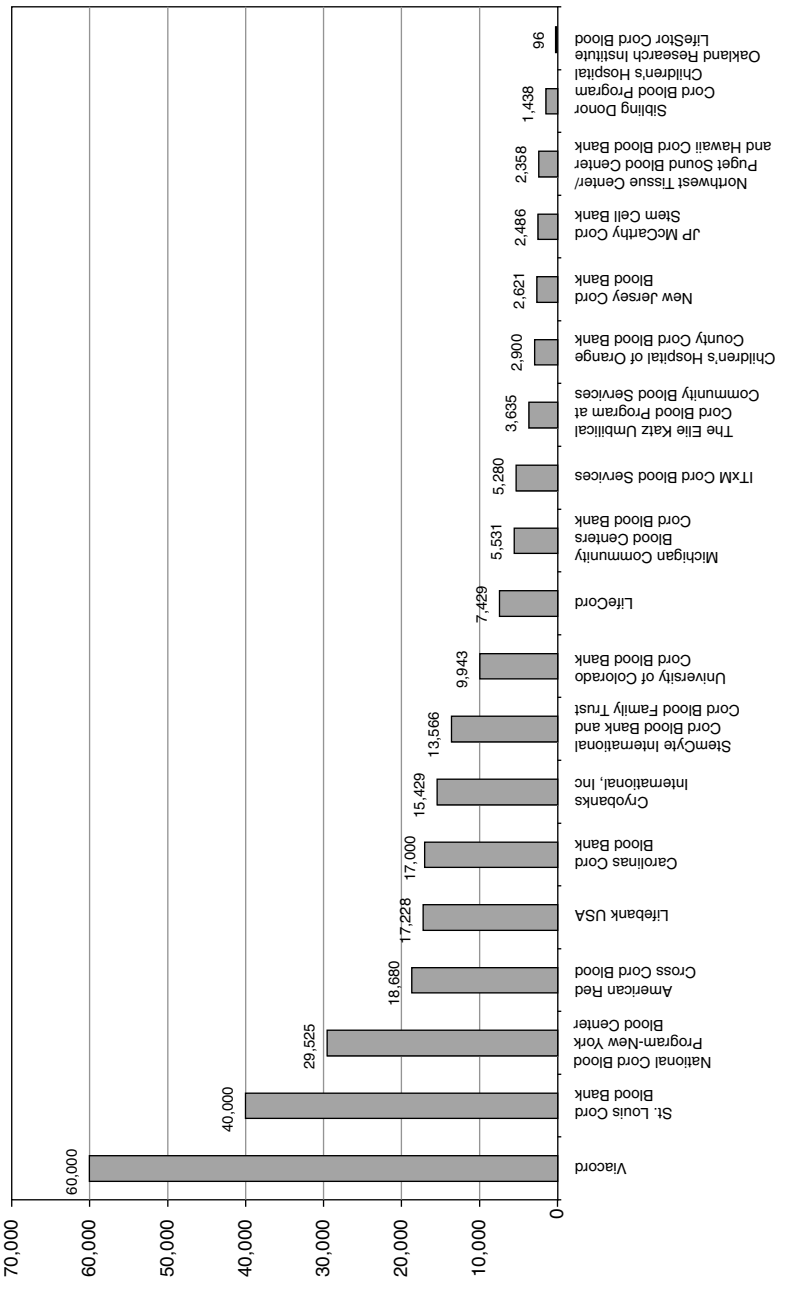

FIGURE C-1 Total units collected, by bank.

TABLE C-5 Banks That Are Currently Collecting Units

Bank
American Red Cross North Central Blood Services Cord Blood Program
Carolinas Cord Blood Bank
Children's Hospital of Orange County Cord Blood Bank
Cord Blood Registry
Cryobanks International, Inc.
ITxM Cord Blood Services
JP McCarthy Cord Stem Cell Bank
Lifebank USA/Anthrogenesis Corp.
LifeCord
Michigan Community Blood Centers Cord Blood Bank
National Cord Blood Program of the New York Blood Center
New Jersey Cord Blood Bank
Puget Sound Blood Center and Hawaii Cord Blood Bank
Sibling Program Children's Hospital Oakland Research Institute
St. Louis Cord Blood Bank
StemCyte, Inc. and Cord Blood Family Trust
The Elie Katz Umbilical Cord Blood Program
Viacord

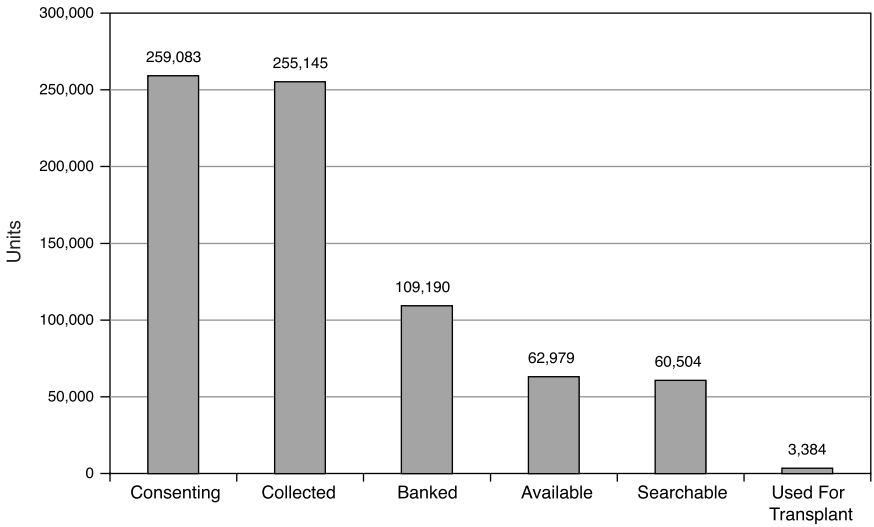

FIGURE C-2 Available units—across all banks.

TABLE C-6 Racial Makeup of Inventory

	Percent Available								
	Asian	African American	Hispanic	Native American	Middle Eastern	Caucasian	Unknown	Multiracial	Other
Averages by total number of units	5.79	11.60	16.81	1.02	0.11	56.08	4.89	3.01	0.69
BY BANK									
American Red Cross North Central Blood Services Cord Blood Program	2.47	6.59	12.03	0.37		64.64	13.90		
Carolinas Cord Blood Bank	2.21	19.52	9.26	0.14	0.00	59.15	0.02	9.21	0.50
Children's Hospital of Orange Country Cord Blood Bank	17.70	0.67	35.40	2.67		43.55	0.00	0.00	0.00
Cryobanks International, Inc.	1.92	8.06	11.16	1.12	0.57	67.24	0.28	9.65	
ITxM Cord Blood Services	3.72	2.16	5.58	1.38	0.00	86.46		0.43	0.26
JP McCarthy Cord Stem Cell Bank	0.45	80.67	2.25	0.22		6.52		9.66	0.22
LifeCord	0.83	3.32	2.76	0.00	0.41	82.72		9.95	
Michigan Community Blood Centers Cord Blood Bank	1.17	2.20	3.03	1.38		64.19	28.03		
National Cord Blood Program of the New York Blood Center	7.70	21.00	21.10			45.60	4.60		
New Jersey Cord Blood Bank	2.17	7.24	0.50	0.89	0.39	61.41			27.39
Puget Sound Blood Center and Hawaii Cord Blood Bank	33.01	1.79	4.54	4.26		56.40			
St. Louis Cord Blood Bank	0.66	1.59	0.28	4.69		84.35	0.94	7.50	
StemCyte, Inc. and Cord Blood Family Trust	14.99	4.00	51.01	0.39		27.00	2.62		
The Elie Katz Umbilical Cord Blood Program	2.02	2.95	10.96	0.08	1.05	42.74	40.19	0.00	0.00
Averages by bank	6.50	11.55	12.13	1.35	0.41	56.57	10.06	5.80	4.73

TABLE C-7 Criteria to Determine Which Units Are Suitable for Banking

Bank	Threshold of Nucleated Cell Dose	Volume	Bacterial Contamination (Negative)
American Red Cross North Central Blood Services Cord Blood Program	Preprocessing TNC of 1.2×10^9	50 ml	X
Carolinas Cord Blood Bank	9×10^8	60 ml	X
Children's Hospital of Orange County Cord Blood Bank	9×10^8	40 ml minimum	X
Cryobanks International, Inc.	Precount $>8 \times 10^8$	60 g	X
ITxM Cord Blood Services		40 ml collection per NMDP IND	X
JP McCarthy Cord Stem Cell Bank			X
Lifebank USA	TNC = 5×10^8	35 ml	X
LifeCord	8×10^8 TNC preprocessing	≥40 ml	
Michigan Community Blood Centers Cord Blood Bank	11×10^8, minority threshold = 9.5×10^8	45 ml	X
National Cord Blood Program of the New York Blood Center	9×10^8		X

Level of HLA Resolution	Other
	Donation is excluded if: • unit is reactive for infectious disease markers • unit has less than 70 percent postprocessing and prefreezing viability • there is a family history of diseases, conditions, and/or genetic disorders that may affect the recipient • the mother has symptoms of or has been diagnosed with certain infectious diseases including West Nile virus, parasitic blood diseases, syphilis, hepatitis, and HIV/AIDs • the mother has engaged in behaviors or received medical treatments that increase the risk of contracting these diseases
Intermediate resolution for Class I HLA, high-resolution DRB1	Tests negative for homozygous hemoglobinopathies; positive CFU growth Negative infectious disease testing on maternal blood
	Negative maternal infectious disease markers, processed within 36 hours of collection
	Maternal and baby health questionnaire eligibility Infectious disease testing, microbiology testing, hemaglobinopathy screen, viability
	Infectious disease markers, ABO and RH type determination of cord blood unit, newborn screening retention samples, maternal medical health questionnaire, review of maternal and newborn medical records
	Virology negative (except for CMV)
	Negative infectious disease test results, lack of family medical history of inherited genetic disorders or diseases, no inappropriate affirmative responses to questions from risk behavior questionnaire
	Negative infectious disease testing, normal genetic screen "We also apply the same deferral criteria as that of whole blood donors for risk factors"
Class I antigen level (molecular test, SSP)	No evidence of viral infection for HIV/HILV-1/11, hepatitis B or C virus, CMV by culture or DNA PCR testing.

continues

TABLE C-7 Continued

Bank	Threshold of Nucleated Cell Dose	Volume	Bacterial Contamination (Negative)
New Jersey Cord Blood Bank	minimum of 1.5×10^8 preprocessing, 1.2×10^8 postprocessing	>40 ml of cord blood	X
Puget Sound Blood Center and Hawaii Cord Blood Bank	9×10^8	40 ml	
Sibling Program Children's Hospital Oakland Research Institute	$\leq 3 \times 10^8$	≤20 cc	
St. Louis Cord Blood Bank	$>8.0 \times 10^8$	45 ml	X
StemCyte, Inc. and Cord Blood Family Trust		50 ml public, 10 ml private	X
The Elie Katz Umbilical Cord Blood Program	4×10^8 TNC for autologous storage and 6×10^8 TNC for allogeneic	if less than 50 ml then check TNC	X
University of Colorado Cord Blood Bank	TNC greater than 10^9*	≥95 ml collected*	X
Viacord	100×10^6 TNC	≥10 ml	

Level of HLA Resolution	Other
HLA-A HLA-B, and DRB1 intermediate resolution	Maternal health history, maternal infectious disease screening, 6-month and 1-year follow-up of child's health
	Complications and/or congenital abnormalities observed
	Since units are all related, we bank as many as possible
	$CD34^+$ and CF4 values, viability
Intermediate-resolution HLA-A and HLA-B, high-resolution DRB1	Infectious disease markers (only positives banked are CMV and Hepatitis B core), maternal health history and family genetic history
	Negative viral marker results
HLA-A, HLA-B serological equivalent, HLA-DRB1 high resolution	Negative infectious disease markers, no risk factors from maternal donor questionnaire, complete consent Criteria with "*" are to be used for qualifying future collections
	CD34, viability <50 percent, positive HIV status of mother, units with other abnormal infectious disease results stored only after a review by medical director

TABLE C-8 Criteria Used to Determine Which Units Are for Transplant

	Criteria for a Transplant Center Before Receiving Units from Bank		
Bank	NMDP Approved Site	FACT Accreditation	Other
American Red Cross North Central Blood Services Cord Blood Program			Evidence of IRB approval (or international equivalent); evidence of NMDP, FACT, or equivalent certification; agreement to provide outcome data
Carolinas Cord Blood Bank	X		Use IRB approved protocols
Children's Hospital of Orange County Cord Blood Bank	X		
Cryobanks International, Inc.	X		Meet WMDA recommendations for transplant center criteria
ITxM Cord Blood Services	X		
JP McCarthy Cord Stem Cell Bank	X		
Lifebank USA			IRB approved protocol, agreeing to provide post-transplant data
LifeCord	X		
Michigan Community Blood Centers Cord Blood Bank			IRB approved transplant protocol
National Cord Blood Program of the New York Blood Center			Must have a recognized track record in BMT, and accreditation by EBMT, JACIE, etc.
New Jersey Cord Blood Bank	X		Written prescription from transplant center
Puget Sound Blood Center and Hawaii Cord Blood Bank	X		Signed agreement and memorandum of understanding
St. Louis Cord Blood Bank			

	How Bank Is Most Commonly Accessed by Transplant Center			
Transplant Center Exceptions	Direct Contact	NET-CORD	NMDP	Other
Exceptions allowed on basis of approval by medical director	X			
Medical director has personal knowledge of transplant center	X		X	parents or referring physician
N/A			X	
Medical director approval				CRIR
Private family units do not need to go to NMDP centers	X		X	
NMDP will permit compassionate-use requests for nonmember transplant centers			X	
				BMDW
			X	
	X			CRIR
	X	X		
			X	
			X	CRIR
	X		X	CRIR

continues

TABLE C-8 Continued

	Criteria for a Transplant Center Before Receiving Units from Bank		
Bank	NMDP Approved Site	FACT Accreditation	Other
StemCyte, Inc. and Cord Blood Family Trust	X		For most non-U.S. transplant centers, this does not apply
The Elie Katz Umbilical Cord Blood Program			IRB, if available, request form
University of Colorado Cord Blood Bank			Must meet WMD recommendations and requirements per Goldman et al., 1994, A special report: Bone marrow transplants using volunteer donors—recommendaions and requirements for a standardized practice throughout the world. *Blood* 84:2833.

	How Bank Is Most Commonly Accessed by Transplant Center			
Transplant Center Exceptions	Direct Contact	NET-CORD	NMDP	Other
			X	CRIR
Foreign countries	X			BMDW
Compassionate use	X			CRIR, various foreign national registries

TABLE C-9 Units That Are Not Usable for Transplant

Bank	Research–External			
	Research/ Internal	Discarded or Destroyed	Investigator Charged	No Charge
American Red Cross North Central Blood Services Cord Blood Program	X	X	X	X
Carolinas Cord Blood Bank	X	X	X	X
Children's Hospital of Orange County Cord Blood Bank	X	X		
Cryobanks International, Inc.	X	X		X
ITxM Cord Blood Services	X	X		X
JP McCarthy Cord Stem Cell Bank		X		X
Lifebank USA	X			X
LifeCord	X	X		X
Michigan Community Blood Centers Cord Blood Bank		X		
National Cord Blood Program of the New York Blood Center	X	X	X	X
New Jersey Cord Blood Bank	X	X		
Puget Sound Blood Center and Hawaii Cord Blood Bank	X	X		
St. Louis Cord Blood Bank	X	X		X
StemCyte, Inc. and Cord Blood Family Trust	X	X	X	X
The Elie Katz Umbilical Cord Blood Program	X	X		X
University of Colorado Cord Blood Bank	X	X	X	X
Viacord	X	X or continue storage		

TABLE C-10 Are Units Bar Coded and Tracked Electronically? If Not, How Are They Tracked?

Bank	Tracking of Units
American Red Cross North Central Blood Services Cord Blood Program	Units are labeled with unique, bar-coded identifiers. All paperwork and corresponding samples are labeled with the unique identifier associated with the unit. A database is used to monitor the location of the unit and inspection and testing status.
Carolinas Cord Blood Bank	Yes. Units are bar coded with the ISBT 128 system.
Children's Hospital of Orange County Cord Blood Bank	Yes, bar coded and tracked
ITxM Cord Blood Services	Bar coded, tracked in database
LifeCord	Yes
Michigan Community Blood Centers Cord Blood Bank	Manual entry into database
National Cord Blood Program of the New York Blood Center	Yes
New Jersey Cord Blood Bank	Yes
Puget Sound Blood Center and Hawaii Cord Blood Bank	Yes; bar coded; also, the location is recorded in the unit chart
Sibling Program Children's Hospital Oakland Research Institute	Units are bar coded and tracked electronically and manually; a written inventory log is kept
St. Louis Cord Blood Bank	Yes
StemCyte, Inc. and Cord Blood Family Trust	Yes
The Elie Katz Umbilical Cord Blood Program	Yes
University of Colorado Cord Blood Bank	Yes (for cord blood unit banked after July 1999, 68 percent of searchable inventory)
Viacord	Bar code from collection of cord blood through transport to receipt at lab. Manual tracking from receipt to storage (and distribution if called on)

TABLE C-11 Informatics

Bank	Excel Spreadsheet	Access Database	Other Database
American Red Cross North Central Blood Services Cord Blood Program	X	X	Oracle Database
Carolinas Cord Blood Bank		X	EMMES
Children's Hospital of Orange County Cord Blood Bank			CordLink NMDP
Cryobanks International, Inc.		X	
ITxM Cord Blood Services		X	NMDP CordLink
JP McCarthy Cord Stem Cell Bank		X	
Lifebank USA	X		Stem Lab Software
LifeCord			Oracle
Michigan Community Blood Centers Cord Blood Bank	X	X	
National Cord Blood Program of the New York Blood Center			Oracle
New Jersey Cord Blood Bank			Sybase and CordLink
Puget Sound Blood Center and Hawaii Cord Blood Bank		X	Cordlink
Sibling Program Children's Hospital Oakland Research Institute	X		SQL database
St. Louis Cord Blood Bank		X	SQL server
StemCyte, Inc. and Cord Blood Family Trust	X	X	
The Elie Katz Umbilical Cord Blood Program	X	X	
University of Colorado Cord Blood Bank		X	
Viacord	X	X	

TABLE C-12 Collection and Storage: Who Does the Collection

Bank	Obstetrician/ Midwife	Obstetrical Nurse	Designated Collector from the CBB
American Red Cross North Central Blood Services Cord Blood Program	X		X
Carolinas Cord Blood Bank	X		X
Children's Hospital of Orange County Cord Blood Bank			X
Cryobanks International, Inc.	X	X	
JP McCarthy Cord Stem Cell Bank			X
Lifebank USA	X	X	
LifeCord	X	X	X
Michigan Community Blood Centers Cord Blood Bank	X	X	
National Cord Blood Program of the New York Blood Center			X
New Jersey Cord Blood Bank	X	X	X
Puget Sound Blood Center and Hawaii Cord Blood Bank	X	X	
Sibling Program Children's Hospital Oakland Research Institute	X	X	
St. Louis Cord Blood Bank	X		
StemCyte, Inc. and Cord Blood Family Trust	X	X	X
The Elie Katz Umbilical Cord Blood Program	X	X	X
University of Colorado Cord Blood Bank	X	X	X
Viacord	X	X	X

NOTE: No banks answered "Researcher" or "other."

TABLE C-13 Exclusion Criteria

Bank	Multiple Gestations	Gestational Age of Less Than ____ Weeks	Chorioamnionitis (Definition at This Center)	Prolonged Rupture of Membranes (Without Chorioamnionitis)	Tear in Cord Insertion from Placenta
American Red Cross North Central Blood Services Cord Blood Program	X	X	Evaluation of infection is performed by the cord blood bank through chart review		
Carolinas Cord Blood Bank	X	34	Inflammation of the chorion and the amnion, the membranes that surround the fetus		
Children's Hospital of Orange County Cord Blood Bank		36			X
Cryobanks International, Inc.					
ITxM Cord Blood Services	X	36	Evidence of infection or odor, pus, temperature >38.5°C		X
JP McCarthy Cord Stem Cell Bank					X
Lifebank USA				X	
LifeCord		36			
Michigan Community Blood Centers Cord Blood Bank	X	36	Per attending physician's determination		

Positive Group B Strept Carrier	Active Genital Herpes	Vulvar or Perineal Condylomata	Known Fetal Structural Anomalies (e.g., Spinal Bifida)	Known Fetal Chromosome Abnormalities	Other
X		X		X	Reactive for infectious disease markers Less than 70 percent postprocessing and prefreezing viability There is a family history of diseases, conditions, or genetic disorders that may affect the recipient The mother has symptoms of or has been diagnosed with certain infectious diseases including West Nile virus, parasitic blood diseases, syphilis, hepatitis, and HIV/AIDS. The mother has engaged in behaviors or received medical treatments that increase the risk of contracting these diseases
X	X	X	X	X	Maternal-fetal shunt
		X		X	Two vessel cord; temperature over 100.4°F in the infant
		X		X	
X	X	X	X	X	Placenta previa, placental abruption, fetal or maternal distress
X		X	X	X	
		X		X	
				X	Mother's temperature is 100.4°F or greater
X				X	Placental abruption, tears, or infection, eclampsia, HELLP syndrome, stillbirth, maternal fever within 24 hours of delivery

continues

TABLE C-13 Continued

Bank	Multiple Gestations	Gestational Age of Less Than ____ Weeks	Chorioamnionitis (Definition at This Center)	Prolonged Rupture of Membranes (Without Chorioamnionitis)	Tear in Cord Insertion from Placenta
National Cord Blood Program of the New York Blood Center					X
New Jersey Cord Blood Bank	X	34			
Puget Sound Blood Center and Hawaii Cord Blood Bank	X				
Sibling Program Children's Hospital Oakland Research Institute		32			
St. Louis Cord Blood Bank	X	35	Placental infection, malodorous placenta		
StemCyte, Inc. and Cord Blood Family Trust	X	34	The presence of foul-smelling, purulent fluid		X
The Elie Katz Umbilical Cord Blood Program		36			X
University of Colorado Cord Blood Bank	X	35	Purulent vaginal discharge with fever		X
Viacord					

NOTE: no banks answered "meconium."

Positive Group B Strept Carrier	Active Genital Herpes	Vulvar or Perineal Condylomata	Known Fetal Structural Anomalies (e.g., Spinal Bifida)	Known Fetal Chromosome Abnormalities	Other
X					
X		X		X	Stillborn infant
					Known to be affected by a genetic disease
		X			Maternal or infant temperature >102°F
X				X	Only vaginal deliveries with active genital herpes are deferred; also exclude tumor within or attached to placenta; abruptio placenta
		X		X	Temperature >38.5°C, maternal eclampsia and/or maternal HELLP syndrome
X	X	X	X	X	Caesarean section
			X		Customer choice to store or not

TABLE C-14 Screening Completed Prior to Storage

Genetic Screening

Bank	Hemoglobinopathy	ABO Group	Rh Type	Health Questionnaire	Other
Carolinas Cord Blood Bank	X	X	X	X	X
Children's Hospital of Orange County Cord Blood Bank	X	X	X	X	
Cryobanks International, Inc.		X	X	X	
ITxM Cord Blood Services	X	X	X	X	
JP McCarthy Cord Stem Cell Bank	X	X	X	X	
Lifebank USA				X	
LifeCord	X	X	X	X	X
Michigan Community Blood Centers Cord Blood Bank	X	X	X	X	X
National Cord Blood Program of the New York Blood Center	X	X	X	X	
New Jersey Cord Blood Bank	X	X	X	X	
Puget Sound Blood Center and Hawaii Cord Blood Bank		X	X	X	
Sibling Program Children's Hospital Oakland Research Institute	X	X	X	X	
St. Louis Cord Blood Bank	X	X	X	X	
StemCyte, Inc. and Cord Blood Family Trust		X	X	X	
The Elie Katz Umbilical Cord Blood Program		X	X	X	
University of Colorado Cord Blood Bank	X	X	X	X	
Viacord		X	X	X	

TABLE C-14 Continued

Bank	Infectious Disease Testing																		
	Alanine Aminotransferase (ALT)	Cholesterol	CMV IgG	CMV IgM	CMV Culture/Shell Vial	Hepatitis B Virus—HBsAg	Hepatitis B Virus—HB Core Ab	Hepatitis B Virus—NAT	Hepatitis C Virus—Ab	Hepatitis C Virus—NAT	HIV, Type 1—Ab	HIV, Type 1—P24 Ag	HIV, Type 2	Human T-cell Lymphotropic Virus, Type I	Human T-cell Lymphotropic Virus, Type II	*Treponema pallidum* (Syphilis)	West Nile Virus NAT
American Red Cross North Central Blood Services Cord Blood Bank	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Carolinas Cord Blood Bank			X	X		X	X	X	X	X	X		X	X	X	X	X
Children's Hospital of Orange County Cord Blood Bank			X	X		X	X		X	X	X	X	X	X	X	X	X
Cryobanks International, Inc.					X				X		X	X	X	X	X		
ITxM Cord Blood Services			X		X	X	X	X	X	X	X	X	X	X	X	X	X
JP McCarthy Cord Stem Cell Bank			X	X	X				X		X		X	X	X	X	X

continues

TABLE C-14 Continued

Infectious Disease Testing (continued)

Bank	Alanine Aminotransferase (ALT)	Cholesterol	CMV IgG	CMV IgM	CMV Culture/Shell Vial	Hepatitis B Virus—HBsAg	Hepatitis B Virus—HB Core Ab	Hepatitis B Virus—NAT	Hepatitis C Virus—Ab	Hepatitis C Virus—NAT	HIV, Type 1—Ab	HIV, Type 1—P24 Ag	HIV, Type 2	Human T-cell Lymphotropic Virus, Type I	Human T-cell Lymphotropic Virus, Type II	*Treponema pallidum* (Syphilis)	West Nile Virus NAT
Lifebank USA	X		X	X		X	X	X	X	X	X		X	X	X	X	X
LifeCord	X	X	X	X		X	X		X	X	X		X	X	X	X	X
Michigan Community Blood Centers Cord Blood Bank			X	X		X	X		X	X	X	X	X	X	X	X	X
National Cord Blood Program of the New York Blood Center	X			X	X	X			X	X	X		X	X	X	X	
New Jersey Cord Blood Bank			X			X	X		X		X		X	X	X	X	
Puget Sound Blood Center and Hawaii Cord Blood Bank			X			X		X	X		X		X	X		X	X

Sibling Program Children's Hospital Oakland Research Institute		X	X				X	X			X	X		X		X	X	
St. Louis Cord Blood Bank				X		X	X	X	X		X	X		X		X	X	
StemCyte, Inc. and Cord Blood Family Trust	X	X	X	X	X			X	X		X	X		X		X	X	
The Elie Katz Umbilical Cord Blood Program		X	X	X	X		X	X	X		X	X		X		X	X	
University of Colorado Cord Blood Bank	X	X	X	X	X		X		X	X	X	X		X		X		
Viacord		X		X	X		X	X	X		X	X		X		X		

TABLE C-14 Continued

Other Exclusions: Other Infectious Disease Testing and Travel

Bank	Other	Current FDA Travel Restrictions
American Red Cross North Central Blood Services Cord Blood Bank		Yes
Carolinas Cord Blood Bank		Yes
Children's Hospital of Orange County Cord Blood Bank	HIV 1 and 2 NAT	Yes
Cryobanks International, Inc.	HBV Ab and CMV, total by PCR	Yes
ITxM Cord Blood Services		Yes
JP McCarthy Cord Stem Cell Bank	HIV and HCV NAT; HBV NAT	Yes
Lifebank USA		Yes
LifeCord	HIV NAT	Yes

Any Other Recommended Travel Restrictions That Would Prevent Inclusion of the Unit?
Mother lived in any area where malaria is endemic within the past 3 years or traveled to those areas in the past 12 months. Mother spent a total time from 1980 to 1996 that adds up to 3 months or more in the United Kingdom (UK) from 1980 to 1996 or she received a blood transfusion in the UK in this time frame. Mother was born or lived in Cameroon, Central African Republic, Chad, Congo Equatorial Guinea, Gabon Niger, Nigeria, or Ivory Coast since 1977 or been the sexual partner of a person who was born in or lived in these countries in this time frame. Note: all time frames relate to date of infant's delivery.
No
Immigrants, refugees, or citizens coming from a country in which malaria is considered endemic will be deferred for 3 years after departure from the area if they have been free from unexplained symptoms suggestive of malaria. If after their arrival in the United States they visit any region where malaria is endemic, a deferral of 3 years applies. Other donors who have traveled to a country where malaria is considered endemic will be deferred for 12 months after returning from that area, regardless of whether or not they took antimalaria prophylaxis. Also deferral if since 1980 the mother spent 5 years or more in Europe, 3 months or more in the UK from 1980 to 1986; member of military from 1980 to 1996 and spent more than 6 months in Belgium, The Netherlands, or Germany (1980 to 1990), or Spain, Portugal, Turkey, Italy, or Greece (1980 to 1996).
All exclusions applicable to whole-blood donors, e.g. malaria, vCJF, and SARS.
Mothers who have traveled to areas where malaria is endemic are deferred for 1 year after return. Immigrants from countries where malaria is endemic are deferred for 3 years after leaving the country. Persons who have lived for 5 or more years in countries where malaria is endemic are deferred for 3 years after returning to the United States. Travel to Cameroon, Central Africa Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, Nigeria, and Cote d'Ivoire since 1977 would restrict donation due to possible HIV exposure. Travel to the United Kingdom from 1980 to the present for 3 months or Europe for 6 months would restrict donation due to possible CJF.
Travel to high-risk area • Travel outside of United States or Canada in the past 3 years • Born in Africa • Lived in Europe since 1980 • Spent more than 3 months since 1980 in UK • Member of military from 1980 to 1996 • Spent more than 6 months between 1980 and 1996 in Belgium, The Netherlands, Germany, Spain, Portugal, Turkey, Italy, or Greece

continues

TABLE C-14 Continued

Other Exclusions: Other Infectious Disease Testing and Travel (continued)

Bank	Other	Current FDA Travel Restrictions
Michigan Community Blood Centers Cord Blood Bank	HIV NAT has replaced p24 Ag since fall 2003. Other genetic tests performed include for CAH, hypothyroidism, galactosemia, maple syrup urine disease, PKU, MCAD, biotinidase deficiency	Yes
New Jersey Cord Blood Bank		Yes
Puget Sound Blood Center and Hawaii Cord Blood Bank	HIV NAT antibody screen	Yes
Sibling Program Children's Hospital Oakland Research Institute	HIV type 1 NAT	No
St. Louis Cord Blood Bank	CMV total Ab, HIV NAT	
StemCyte, Inc. and Cord Blood Family Trust	HIV type 1 and type 2 NAT	Yes
The Elie Katz Umbilical Cord Blood Program		Yes
University of Colorado Cord Blood Bank	Future collection testing will include HIV and HCV NAT, WNV NAT	Yes
Viacord	Antibody screen HIV NAT	

Any Other Recommended Travel Restrictions That Would Prevent Inclusion of the Unit?
Malarial deferrals will result in quarantine of unit until follow-up phone call and/or other testing is performed after the deferral period. Travel areas affected by SARS would result in exclusion.
The CDC Health Information for International Travel 2003–2004 is used.
Exclusion for travel to malaria risk areas within the past 3 years (is possible to reduce the time restriction to the past 12 months). Exclusion for vCJF risk and SARS as advised by the FDA.
These are evaluated on a case-by-case basis by staff in conjunction with the medical director.
No
Defer for travel areas where malaria and SARS areas are endemic within the last 14 days, extended stay in UK (for CJF).
Collections from 1996 to 2001 utilized the then-current FDA guidelines for donor exclusion based on travel to foreign countries. However, short-term travel did not warrant exclusion.
Questions on travel history were asked and documented on health history questionnaire.

TABLE C-15 Number of Units Collected and Shipped by Year 1993–2004

Bank	Status	1993	1994	1995	1996	1997
American Red Cross North Central Blood Services Cord Blood Bank	Collected					1,350
	Shipped					0
Carolinas Cord Blood Bank	Collected					
	Shipped					
Children's Hospital of Orange County Cord Blood Bank	Collected	0	0	0	0	0
	Shipped	0	0	0	0	0
Cryobanks International, Inc. (Pr = private, Pu = public)	Collected	Pr: 0 Pu: 0	Pr: 0 Pu: 0	Pr: 9 Pu: 23	Pr: 127 Pu: 397	Pr: 143 Pu: 268
	Shipped	Pr: 0 Pu: 0	Pr: 0 Pu: 0	Pr: 0 Pu: 0	Pr: 0 Pu: 0	Pr: 0 Pu: 0
ITxM Cord Blood Services	Collected	0	0	3	63	226
	Shipped	0	0	0	0	0
JP McCarthy Cord Stem Cell Bank	Collected					
	Shipped					
LifeCord	Collected					122
	Shipped					0
Michigan Community Blood Centers Cord Blood Bank	Collected					
	Shipped					
National Cord Blood Program —New York Blood Center	Collected	943	1,739	1,615	920	763
	Shipped	2	16	100	214	256
New Jersey Cord Blood Bank	Collected					
	Shipped					
Puget Sound Blood Center and Hawaii Cord Blood Bank	Collected	0	0	0	0	0
	Shipped	0	0	0	0	0

1998	1999	2000	2001	2002	2003	2004
2,155	175	2,579	5,062	6,511	3,092	522
10	11	9	22	50	81	59
960	4,136	2,147	1,851	2,326	2,325	1,164
0	9	36	68	76	75	52
0	44	370	510	666	528	375
0	0	0	1	1	1	3
Pr: 251	Pr: 156	Pr: 126	Pr: 159	Pr: 220	Pr: 241	Pr: 75
Pu: 671	Pu: 316	Pu: 337	Pu: 1,168	Pu: 3,983	Pu: 5,256	Pu: 3,010
Pr: 0	Pr: 0	Pr: 0	Pr: 0	Pr: 0	Pr: 1	Pr: 0
Pu: 0	Pu: 0	Pu: 0	Pu: 0	Pu: 0	Pu: 491	Pu: 2
289	1,149	1,740	1,145	388	30	188
0	0	0	2	9	8	1
			211	922	921	432
					2	2
337	345	287	333	288	168	95
0	0	0	2	0	6	2
	124	604	1,086	1,301	1,477	880
	0	0	1	1	3	1
255	1,395	2,530	3,301	4,322	4,333	2,884 (as of 8/31/04)
174	174	200	115	168	214	133 (as of 8/31/04)
		12	462	1,114	797	237
		0	0	1	5	1
0	154	402	415	477	492	418
0	0	0	0	0	1	2

continues

TABLE C-15 Continued

Bank	Status	1993	1994	1995	1996	1997
Sibling Donor Cord Blood Program	Collected					4
	Shipped					1
St. Louis Cord Blood Bank	Collected				1,487	4,708
	Banked				695	1,544
	Shipped				0	9
StemCyte, Inc. and Cord Blood Family Trust	Collected	0	0	0	0	0
	Shipped	0	0	0	0	0
The Elie Katz Umbilical Cord Blood Program	Collected	0	0	0	4	162
	Shipped	0	0	0	0	0
University of Colorado Cord Blood Bank	Collected				4	569
	Shipped					
Viacord	Collected			67	524	383
	Shipped				1	2

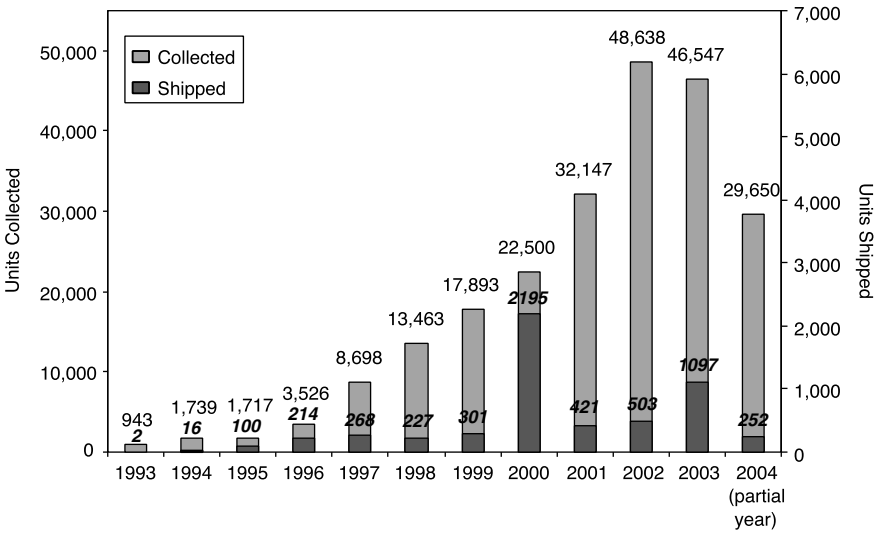

FIGURE C-3 Units collected and shipped, by year.

1998	1999	2000	2001	2002	2003	2004
33	160	251	252	307	312	123
2	2	7	5	11	17	2
5,969	5,334	4,237	4,117	5,082	5,377	3,280
1,447	1,188	1,059	1,023	1,286	1,546	843
38	74	96	151	129	110	49
			Pu: 4,198	Pu: 7,748	Pu: 1,519	Pu: 101
0	0	0			Pr: 33	Pr: 147
0	0	0	Pu: 2	Pu: 9	Pu: 30	Pu: 37
632	1,066	916	134	157	220	344
0	6	3	5	3	6	4
1,161	1,779	3,935	2,495			
3	24	42	44	43	45	33
750	1,560	2,027	5,248	12,826	19,426	18,259 (as of 10/04)
	1	2	3	2	1	2

TABLE C-16 Costs

	Private		
Bank	Collection	Storage	Release
American Red Cross North Central Blood Services Cord Blood Program			
Carolinas Cord Blood Bank			
Children's Hospital of Orange County Cord Blood Bank	$1,700	$0	$0
ITxM Cord Blood Services			$18,000 on release
LifeCord	$0	$0	$15,500
Michigan Community Blood Centers Cord Blood Bank			
National Cord Blood Program of the New York Blood Center			
New Jersey Cord Blood Bank			
Puget Sound Blood Center and Hawaii Cord Blood Bank	$655 (processing and first unit of storage $1,000)	$210/ 5 years	shipping charges only, in addition to any requested testing
Sibling Program Children's Hospital Oakland Research Institute	$0	$0	$19,600
St. Louis Cord Blood Bank			
StemCyte, Inc. and Cord Blood Family Trust	$1,450	$95/year	No cost
The Elie Katz Umbilical Cord Blood Program	$1,350 ($1,500 if paid in installment, $900 at specified hospitals)	$100/year	$0
University of Colorado Cord Blood Bank			
Viacord	$1,800	$125/year	$0

Public Reimbursement
$18,000
Pending $18,500
$15,500
$15,000 per NMDP
$15,500
$25,000
$22,490—includes patient CT-negative unit CT-positive Unit DNA for transplant center CT, unit shipment in the United States
NMDP provides $15,500 for a unit when it is transplanted.
$15,000
$15,000 before 2004, $21,500 after 1/1/04
$0
$17,000

TABLE C-17 Funding of Public Banks

Bank	When	NIH	Private/ Philanthropy	State Funding
American Red Cross North Central Blood Services Cord Blood Program	Currently			
	Historically		X	
Carolinas Cord Blood Bank	Currently			
	Historically	X	X	
Children's Hospital of Orange County Cord Blood Bank	Currently		X	
	Historically		X	
ITxM Cord Blood Services	Currently		X	
	Historically		X	
LifeCord	Currently			
	Historically			
Michigan Community Blood Centers Cord Blood Bank	Currently		X	
	Historically		X	
National Cord Blood Program of the New York Blood Center	Currently		X	
	Historically	X	X	
New Jersey Cord Blood Bank	Currently			X
	Historically		X	X
Puget Sound Blood Center and Hawaii Cord Blood Bank	Currently		X	
	Historically		X	
Sibling Program Children's Hospital Oakland Research Institute	Currently	X	X	
	Historically	X	X	
St. Louis Cord Blood Bank	Currently		X	
	Historically		X	
StemCyte, Inc and Cord Blood Family Trust	Currently		X	
	Historically		X	
The Elie Katz Umbilical Cord Blood Program	Currently			
	Historically			
University of Colorado Cord Blood Bank	Currently			
	Historically			

Public Bank Revenue	Other
X	
X	Support From ARC
	X
	ARC
	By participating entities, UF, Shands, LifeSouth
	By participating entities, UF, Shands, LifeSouth
X	
X	
X	NYBC
X	NYBC
X	
X	
X	
X	
X	Fund raising
X	Fund raising
	Private bank revenue
	Private bank revenue
	Self-supporting from reimbursement fees
	University of Colorado Hospital

TABLE C-18 Neonatal Health Status Follow-Up

Bank	If There Is Follow-Up in Neonatal Health Status, When Is It Done?
American Red Cross North Central Blood Services Cord Blood Bank	Delivery data are assessed 24 hours or more after delivery. In addition, donors are reminded in a follow-up letter/survey mailed 60 days after delivery and in a birthday card sent at 1 year, to ask the family to report on any changes in infant's health.
Carolinas Cord Blood Bank	Yes, 24-hour review of pediatric exam/neonatal history 6 months or more, computer system; mom's age > 35 years and no amniocentesis follow-up unit at time of request
Children's Hospital of Orange County Cord Blood Bank	None
Cryobanks International, Inc.	No follow-up of neonatal health status is done at present
ITxM Cord Blood Services	Yes, before release for transplantation; not always able to locate the mother
JP McCarthy Cord Stem Cell Bank	No follow-up after the baby has been discharged from the hospital
Lifebank USA	No
LifeCord	No. However, the mother is asked to call if a health problem arises; the bank receives notification of leukemia in an infant whose cord blood was donated.
Michigan Community Blood Centers Cord Blood Bank	(1) No formal follow-up. (2) Donor moms are given a card to keep in baby's book asking for notification if child becomes seriously ill.
National Cord Blood Program of the New York Blood Center	No
New Jersey Cord Blood Bank	Follow-up from the donor is requested at 6 months and 1 year
Puget Sound Blood Center and Hawaii Cord Blood Bank	Yes, prior to transplant (when a cord blood unit has been selected for use)
Sibling Program Children's Hospital Oakland Research Institute	Hemoglobinopathy screening is performed on the cord blood unit. Clinical status of donor is reviewed before release of the unit for transplantation

How Is Follow-Up Performed?		
Postcard	Phone Call to Mother	Other
		X
X		Review of medical record from pediatrician office
	X	
X		
	X	
		X

continues

TABLE C-18 Continued

Bank	If There Is Follow-Up in Neonatal Health Status, When Is It done?
St. Louis Cord Blood Bank	Yes, 2 weeks postdelivery and when confirmatory typing is requested on a cord blood unit
StemCyte, Inc. and Cord Blood Family Trust	The mother is asked to notify the bank of any change in the health status of the child. A letter with a SASE requesting a response regarding the health of the child is sent between 6 months and 1 year postdelivery.
The Elie Katz Umbilical Cord Blood Program	No for public units; yes for private units
University of Colorado Cord Blood Bank	No
Viacord	Not proactive, at customer request

How Is Follow-Up Performed?		
Postcard	Phone Call to Mother	Other
	X	
		X

TABLE C-19 How the Units Are Stored

Bank	Stored as		
	Whole Blood	Volume Reduction Only	RRC Depleted/ Mononuclear Cell Product
American Red Cross North Central Blood Services Cord Blood Bank			X
Carolinas Cord Blood Bank			X
Children's Hospital of Orange County Cord Blood Bank			X
Cryobanks International, Inc.			X
ITxM Cord Blood Services	X		X
JP McCarthy Cord Stem Cell Bank			X
Lifebank USA			X
LifeCord	X (<50 processed this way)		X
Michigan Community Blood Centers Cord Blood Bank			X
National Cord Blood Program of the New York Blood Center			X
New Jersey Cord Blood Bank			X
Puget Sound Blood Center and Hawaii Cord Blood Bank			X
Sibling Program Children's Hospital Oakland Research Institute		X	
St. Louis Cord Blood Bank			
StemCyte, Inc. and Cord Blood Family Trust			
The Elie Katz Umbilical Cord Blood Program			
University of Colorado Cord Blood Bank			X
Viacell			X

Other	Anticoagulant Used	Cryoprotectant Used
	CPD	DMSO/dextran
	X	X
	X	X
	CPD solution USP	Stemsol-DMSO, 99% purity, USP grade
X	CPD	DMSO-dextran
		X
	X	X
	CPD-Adenine	DMSO 10%, HES 1%, dextran40 1%
	X	X
	ACD-A	DMSO
	CPD	DMSO-dextran 40, (unit nos. 668 to present) DSMO-pentastarch-plasma (unit nos 1 to 667)
Buffy coat (RBC and plasma reduced)	CPD	DMSO
Plasma depleted, non-red-cell-depleted product	CPD solution	DMSO-Gentran
Red cell depleted with volume reduction	CPD	10% DMSO
	CPD	DMSO
	CPD	DMSO

ACRONYMS AND ABBREVIATIONS

AABB	American Association of Blood Banks
ACD-A	Anticoagulant Citrate Dextrose Solution, formula A
ARC	American Red Cross
ASHI	American Society for Histocompatibility and Immunogenetics
BMDW	Bone Marrow Donors Worldwide
BMT	bone marrow transplant
CAH	congenital adrenal hyperplasia
CAP	College of American Pathologists
CBB	cord blood bank
CLIA	Clinical Laboratory Improvement Amendments
CMV	cytomegalovirus
CPD	citrate-phosphate-dextrose
CRIR	Caitlin Raymond International Registry
DMSO	dimethyl sulfoxide
EBMT	European Group for Blood and Marrow Transplantation
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
g	gram(s)
HbcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	haemolysis, elevated liver enzymes, low platelets
HES	hetastarch
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IgG	immunoglobulin G
IND	investigational new drug
IRB	institutional review board
ISBT	International Society of Blood Transfusion
ISCT	International Society for Cellular Therapy
ISO	International Organization for Standardization
JACIE	Joint Accreditation Committee ISCT EBMT

JCAHO	Joint Commission for Accreditation of Healthcare Organizations
MCAD	medium-chain acyl-CoA dehydrogenase
ml	milliliter(s)
NAT	nucleic acid test
NIH	National Institutes of Health
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
PCR	polymerase chain reaction
PKU	phenylketonuria
RBC	red blood cell
SARS	sudden acute respiratory syndrome
SASE	self-addressed stamped envelope
SQL	structured query language
SSP	split spectrum processing
TNC	total nucleated cell count
UCLA	University of California, Los Angeles
UF	University of Florida
USP	United States Pharmacopeia
vCJF	variant Creutzfeldt-Jakob disease
WMDA	World Marrow Donor Association
WNV	West Nile virus

D

COMMISSIONED PAPER

POTENTIAL NONHEMATOPOIETIC USES FOR STEM CELLS IN CORD BLOOD

An analysis prepared for the Committee on Establishing a National Cord Blood Stem Cell Bank.

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ABSTRACT

Regeneration of nonhematopoietic tissues using hematopoietic stem cells has been a focus of research over the past 5 years, with the hope that the application of bone marrow and cord blood transplantation could be greatly expanded. However, basic research in this area has been controversial, and many reports are contradictory. A consensus view is emerging that progeny of hematopoietic stem cells can indeed become incorporated into nonhematopoietic tissue, but that this occurs with extremely low efficiency, and via a cell fusion mechanism, likely between myeloid and nonhematopoietic

tissues. The low efficiency indicates that, in the short-term, bone marrow and cord blood transplantation are unlikely to be optimal sources for regeneration of nonhematopoietic tissues. However, a number of strategies are being developed to improve the efficiencies with the long-term aim of using hematopoietic cell sources in therapy of nonhematopoietic disease.

INTRODUCTION

The stem cell field has witnessed an explosion of interest in the past 5 years, due to the tandem discoveries of human embryonic stem (hES) cells and reports of the potentially broad differentiation capacity of adult stem cells. In particular, the differentiation capacity of hematopoietic stem cells (HSC), primarily derived from the bone marrow (BM), has been a focus of interest. If, indeed, HSC can differentiate outside of hematopoietic lineages, then BM or cord blood (CB) transplantation could potentially be used for therapeutic applications far beyond those currently used, which are almost exclusively hematologic disorders.

In this analysis, I will discuss the evidence for and against the concept that HSC may generate nonhematopoietic tissues. At this point in time, the literature in this general area is extensive. I will not attempt to review it comprehensively, as there are a number of excellent reviews in the field. Instead, I will endeavor to concisely summarize the data, using a few key papers as examples for the field. Because the majority of the work has been performed with HSC derived from BM, these will be the basis of the majority of the discussion. However, I will also discuss possible differences between BM- and cord CB-derived HSCs toward the end of this appendix.

POTENTIAL NONHEMATOPOIETIC DIFFERENTIATION FROM BONE MARROW CELLS

After Bone Marrow Transplantation

One of the first reports to suggest that hematopoietic cells could generate nonhematopoietic tissue came from the observation that when a whole BM transplant was given to lethally irradiated recipient mice, and skeletal muscles of those animals were subsequently acutely injured, donor-derived cell nuclei were found incorporated into the regenerated skeletal muscle at a frequency of around 0.01 percent [1]. The donor BM was derived from a transgenic mouse strain that expressed *lacZ* under a nuclear-localized muscle-specific promotor, and the evidence for bona fide incorporation of BM cells into differentiated skeletal muscle was extremely convincing. A number of other studies, using BM transplants in mice, rats, and humans,

similarly indicated that donor-derived cells could be found in such diverse tissues as heart, liver, gut, brain (Table D-1). While the cumulative evidence suggested some degree of nonhematopoietic differentiation from some BM-derived cell, the prevalence of these so-called "transdifferentiation" events varied sometimes by two to three orders of magnitude (Table D-1), and the markers used to track BM progeny and the photomicroscopy evidence presented were not always equally persuasive. In addition, almost all of the initial studies involved transplantation of whole BM, leaving open the possibility that generation of nonhematopoietic progeny was derived from any number of cell types present in the BM, including potentially mesenchymal stem cells, differentiated hematopoietic cells, or conceivably tissue-specific stem cells "lost" in the BM.

Nonhematopoietic Differentiation from HSCs

In order to refine these observations and determine whether HSCs or their direct progeny were contributing to these diverse tissue types or whether a nonhematopoietic (circulating?) stem cell within BM was involved, several groups examined the engraftment activity of small numbers of purified HSCs. HSC preparations of 30 to 2000 cells were transplanted into recipients and shown to generate, in addition to peripheral blood, skeletal muscle cells [2], cardiac muscle and endothelial cells [3] and hepa-

TABLE D-1 Donor Cell Contribution to Nonhematopoietic Tissues After Whole Bone Marrow Transplantation in Animal Models

Species	Target Tissue	Approximate Frequency (%)	Reference
Mouse	Macro and Microglia	0.5–2	[34]
	Skeletal muscle	Minimal	[35]
	Skeletal, cardiac muscle	Not given	[36]
	Skeletal muscle	3.5	[16]
	Endothelial cells	Not given	[37]
	Neurons	0.2–0.3	[38]
	Neurons	0.3–2.3	[39]
	Neurons	0	[21]
	Hepatocytes	2.2	[40]
Dogs	Endothelial cells	n/a	[41]
Rat	Oval cells/hepatocytes	0.14	[42]

tocytes [4]. The caveat to all of these studies is that even these highly purified populations could have included multiple stem cells: some stem cells in the preparations could have accounted for the hematopoietic activity, while other stem cells, or impurities, could have accounted for the nonhematopoietic activity. Thus, the next refinement was to examine generation of nonhematopoietic progeny from HSC at a clonal level, to determine whether one cell could generate both hematopoietic and nonhematopoietic progeny in the same animal.

This has begun to be addressed. After BM transplantation with single HSC, extremely rare donor-derived hepatocytes and Purkinje cells were observed [5]. The generation of endothelial cells from single transplanted HSC was reported in a retinal neovascularization model using single HSC marked with green fluorescent protein (GFP) fluorescence [6]. And, in principle, this was examined in epithelial tissues, where HSCs transplanted by limiting dilution were shown to generate epithelial cells in liver, lung, and gut [7]. Surprisingly, in lung, HSC-donor progeny, tracked using in situ hybridization to donor Y-chromosome-positive cells in female recipients, were reported to generate nearly 20 percent of pneumocytes. While in a landmark paper, these data are not widely accepted, although a plausible alternative explanation (other than as technical artifacts) for the data has never been put forth, and the authors are well respected and have vigorously supported their claims.

More recently, additional studies with single HSC transplantation have shown that HSC progeny can become incorporated into regenerating skeletal muscle both after acute injury and when transplanted into genetic models of skeletal muscle degeneration (specifically, the *mdx* mouse, a model of Duchene muscular dystrophy) [8], and of liver regeneration [9]. In both of these studies, the incorporation of HSC-progeny into the tissues was an exceedingly rare event (around 0.03 percent of recipient cell nuclei in the given tissue). However, in the liver, a powerful selection system, in a mouse model of familial tyrosinemia, allowed HSC-derived hepatocytes to repopulate up to around a third of the liver. Moreover, the HSC-derived hepatocytes provided full function and rescued the mice from an otherwise lethal condition. These data unequivocally showed that HSC progeny could become incorporated into nonhematopoietic tissues, albeit at a low efficiency.

Human Transplantation Data

In addition to the studies in animal models, a number of groups have looked at clinical specimens for evidence of similar "plasticity" of cells derived from human BM. All of these studies used samples from patients with organ or BM transplants that were sex mismatched (Table D-2). For

TABLE D-2 Circulating Cell Contribution to Nonhematopoietic Tissues in Clinical Specimens

Tissue Transplanted	Donor Cells Observed	Approximate Frequency (%)	Reference
Bone marrow	Osteoblasts	1.5–2	[43]
Bone marrow	Hepatocytes	2.2	[10]
Bone marrow	GI tract epithelia	0–4.6	[14]
Bone marrow	Stroma	0	[19]
Mobilized peripheral blood	Keratinocytes	0	[20]
Mobilized peripheral blood	Hepatocytes	0–7	[15]
	GI[a] tract and skin epithelia	0–7	[15]
Heart	Cardiomyocytes	20	[12]
	Endothelium	15	[12]
Heart	Cardiomyocytes	0.04	[11]
	Endothelium	25	[11]
Heart	Cardiomyocytes	0.2	[13]
Heart	Cardiomyocytes	0	[18]
Heart	Cardiomyocytes	0	[17]

[a]GI = gastrointestinal

NOTE: In the BM or peripheral blood transplants, male donor cells were transplanted into female recipients. In the heart transplants, female hearts were transplanted into male recipients.

example, hearts from females transplanted into males that showed evidence of male-derived cardiomyocytes or endothelial cells suggest that circulating male cells (potentially derived from BM) could give rise to these cell types. Likewise, in patients who had sex-mismatched BM transplants, the contribution of the donors' cells to nonhematopoietic organs could be assessed. When tissue specimens from such patients have been examined using in situ hybridization for the Y chromosome, evidence of chimerism was found in multiple cell types, including hepatocytes [10], cardiomyocytes [11–13], and skin and gut epithelium [14, 15]. While the data imply that a circulating cell is engrafting into nonhematopoietic tissues, the data do not demonstrate that the phenomenon is related to the stem cell, nor even that the donor cell is restricted to the hematopoietic lineage, since many cell types could potentially circulate to some degree. Furthermore, in situ hybridization for the Y chromosome is not the most reliable technique; so, while the data are important, they are not all widely accepted.

Prevalence of "Transdifferentiation"

While the animal model and clinical data suggest that HSCs can generate nonhematopoietic cells, one of the major discrepancies of the field is the wide variance reported in the prevalence of such events. For example, in studies of BM-derived engraftment into the heart, the reported frequencies of engraftment vary by four orders of magnitude—a difference that in itself raises serious concerns about the technologies used and the conclusions drawn. In three studies where male Y-chromosome-positive host cells were followed in recipients of female heart allografts, one group reported that up to 20 percent of cardiomyocytes were host-derived [12], one group reported that 0.2 percent were host-derived [13], and one group that 0.04 percent were host derived [11]. This final figure is closest to that seen in similar studies in the mouse using the *lacZ* marker, where engraftment was observed to be around 0.02 percent [3]. Likewise, frequencies of BM-derived engraftment into skeletal muscle in mouse models vary by three orders of magnitude in the literature, from 0.01 percent [1] to over 3 percent [16]. Variations in engraftment frequencies could be due to a variety of factors, such as duration of the graft, tissue type, or degree of graft versus host disease (GVHD). Indeed, it was observed that the level of cardiomyocyte engraftment correlated with the degree of GVHD within a group of patients [12]. However, GVHD would also bring higher numbers of BM-derived inflammatory cells into affected tissues, which, when closely adhered to the target tissue, could potentially be mistaken for "transdifferentiation" events.

Lack of Engraftment Also Reported

Some laboratoriess have looked for BM-derived contribution to specific tissues and failed to see it at all. Two groups have looked in human specimens for BM-derived engraftment in human cardiomyocytes and failed to observe any [17, 18]. Karotinocyte stem cells and stromal cells were not found to be generated from the BM in clinical specimens [19, 20]. And in the mouse, attempts to observe neural differentiation from BM cells failed in some studies [21]. Also in the mouse, when marked hematopoietic cells were introduced via a parabiotic mouse model, no engraftment into any tissue was observed [5], although for most tissues, no injuries were induced, which is thought to play an important role in recruitment and differentiation of stem cells.

Mechanism of HSC-Derived Incorporation in Nonhematopoietic Tissue

In the most recent studies using single transplanted HSCs, the mechanism of HSC-derived incorporation was also examined, and this has direct bearing on the potential therapeutic use of BM and CB for nonhemato-

poietic disease. Work with embryonic stem cells had suggested the possibility that cell-cell fusion events could be accounting for some of the apparent "transdifferentiation" of adult stem cells into new tissue types [22, 23]. Using lineage tracing strategies, fusion between hematopoietic cells and nonhematopoietic regenerating target tissue has now been shown to be a likely mechanism explaining at least some incorporation of HSC-progeny into liver and skeletal muscle [8, 9]. Moreover, it is likely that the fusogenic cell is not a circulating HSC, but, instead, a myeloid cell, most likely a macrophage, derived from the HSCs [9, 24]. This interpretation of the data has to be further corroborated, and extended to other tissues, but is now becoming a prevailing view in the field.

SUMMARY OF EVIDENCE

Overall, the evidence overwhelmingly indicates that HSC-derived cells can, at least at low levels, become incorporated in nonhematopoietic tissues. Most studies, however, indicate that this occurs with *extremely low efficiency*, far too low to likely be of therapeutic benefit in most disease states. Moreover, these studies have shown that injury of the target tissue is essential for incorporation. Finally, the recent studies showing that the majority of incorporation is due to fusion with HSC progeny, most likely with a myeloid cell, appear to be widely accepted, and a number of investigators are using these concepts as a basis to harness the phenomenon for development of therapeutic modalities (see below).

The end result is that incorporation of the HSC-derived nuclei into regenerating nonhematopoietic tissue can indeed occur. The HSC-derived cells are essentially donating a wild-type genome, via fusion, to the recipient tissue. In the case of the *mdx* mouse, rare muscle fibers, previously negative for the dystrophin protein (lacking in Duchene muscular dystrophy), could be identified which now expressed the wild-type protein [8]. In the case of the mouse model for familial tyrosinemia, a severe liver disease, selection for the rare HSC-incorporation events enabled a complete "cure" of this otherwise fatal disease [9, 24], a truly remarkable result of cell-cell fusion. These studies, while not leaving a clear path toward therapeutic application of the phenomenon (see below), do justify some of the initial excitement for the concept of using BM or CB for therapy of nonhematopoietic disease. Nevertheless, serious caution, in the face of the major discrepancies in efficiencies and mechanisms is also warranted.

Major Discrepancies Cloud the Field

While I have described a consensus view, there is no doubt that this field remains highly polarized with other conflicting opinions. There are

several excellent laboratories that have published their findings recently in high-profile journals that contradict the idea that the phenomenon is rare [7, 16], due to fusion [25, 26], requires severe injury (other than BM transplantation) [7, 16], or involves a differentiated myeloid cell [27].

Furthermore, clinical studies of BM cell infusion into infarcted hearts are reporting modest improvements in function [28–30], even though animal studies are unable to show functional improvements using similar strategies, and show no evidence that BM-derived cells are even incorporated into the injured hearts at appreciable frequencies [31, 32].

IMPLICATIONS FOR CELL THERAPY USING CB OR BM TRANSPLANTATION

With the inefficiencies that I have described, we are unlikely to be able to use, at this time, BM or CB transplantation broadly for treatment of nonhematopoietic diseases. Diseases such as muscular dystrophy would very likely require contribution of wild-type cells to muscle at much higher levels than 0.05 percent or so of all nuclei. Likewise, most liver diseases are not amenable to selection for the rare HSC-liver incorporation events, preventing immediate application of BM transplantation for most liver diseases. These are clear limitations with the existing technology.

However, it is possible that the efficiency of incorporation could be improved, and several laboratories are investigating this. How to improve the efficiency depends on the major bottlenecks, which are currently poorly understood but likely include some of the following. First, tissues that tolerate a polyploid state are likely to be the best targets. Skeletal muscle, for example, exists as a syncitium, and is postmitotic. Therefore, fusion of a nonhematopoietic cell into a muscle fiber is unlikely to cause deleterious events downstream, such as neoplastic transformation. Likewise, hepatocytes typically persist as highly polyploid cells, and this does not appear to affect their function or regenerative capacity. Second, cell-cell fusion is likely an inefficient process. Strategies to improve the efficiency of fusion, particularly in a manner targeted to specific cell types, may enhance the usefulness of the technology. The technology then becomes one of a gene delivery strategy using a hematopoietic cell to provide a wild-type or otherwise therapeutic gene. Third, once cells fuse, the interactions between the different cellular programs are completely unexplored. Presumably, the entire muscle program needs to be activated in a macrophage that is fusing with a muscle fiber, in order to activate muscle-specific and therapeutic genes from the macrophage genome. The efficiency of this reprogramming and potential strategies to manipulate or bias it are not understood. Finally, if macrophages are indeed the only cell type that mediates these fusion events, strategies based on macrophage transplantation, rather than whole

BM or CB, could prevail. These research areas could certainly bear fruit and lead to the expanded application of BM or CB transplantation for therapy of nonhematopoietic disease, but this is likely a long-term prospect.

What Needs to Be Established to Determine Usefulness of CB in Nonhematopoietic Repair?

As stated above, with current data and discrepancies in the field, it is difficult to definitively argue that BM or CB transplantation could not be used for therapy of nonhematopoietic disease, although in my opinion this will not be feasible in the short term. What needs to be established to answer this more definitively?

Some of the discrepancies in the field are due to poor-quality studies. Therefore, additional clonal analyses such as those described above with muscle and liver, and tracking of cells with ideal markers need to be performed. Better evaluation of the potential of human cells is needed. Unfortunately, there is an enormous gap in the ability to test the potential of human cells due to lack of good animal models that will support the growth of human cells. It is possible that data from other large animal models could assist. Finally, if the efficiency of HSC-derived incorporation could be improved, using excellent models and markers, with some of the strategies mentioned above, the therapeutic usefulness of hematopoietic cell transplantation may increase.

ARE THERE DIFFERENCES BETWEEN STEM CELLS IN CORD BLOOD AND BONE MARROW?

There is a wide perception in the lay press, and even among scientists not expert in the field, that stem cells in CB are somehow more primitive than those in BM. To some extent, this view is currently being exploited in the advertising from the private CB banking companies to persuade parents to bank their baby's CB in order to have the potential to generate a wide variety of tissues. While there is certainly some weak support for this notion in the literature, this view is not widely supported by most clinical hematologists. The HSC in CB may be more plentiful than those in adult blood. CB is certainly a source enriched for HSCs, but there is little or no convincing evidence that CB contains any "embryonic" stem cell that has a differentiation capacity beyond that of normal BM HSCs. CB has been reported to contain mesenchymal-like stem cells [33], that could conceivably have some broad differentiative potential, but this remains to be substantiated by additional laboratories, and such cells are unlikely to *also* have HSC potential. Furthermore, there is little evidence that any non-HSC type is capable of reaching wide distribution via the circulation. This area could certainly

benefit from some additional high quality research, but at this point, the prevailing view among basic HSC biologists as well as clinicians is that there is no significant difference between CB and BM that would warrant a special focus on CB as a source of nonhematopoietic stem cell potential.

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

As indicated above, in my opinion, it appears unlikely at this point that wholesale replacement or repair of nonhematopoietic tissues by circulating stem cells in CB or BM is possible; nevertheless, there is not complete consensus in the field. With the current observed inefficiencies and uncertainties, it is difficult to use the potential for nonhematopoietic differentiation as a justification for a national CB banking program for the short-term. Of course, the advent of new technologies, which a number of laboratories are actively working toward, could change this potential. In addition, one might envision that if regeneration of nonhematopoietic cells from HSCs were improved to the point that hematopoietic transplantation could be used as a therapeutic modality for treatment of nonhematopoietic disease, gene-engineered autologous HSC sources would likely be favored over allogeneic banked sources.

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E

COMMISSIONED PAPER

A COST-BENEFIT ANALYSIS OF INCREASING CORD BLOOD INVENTORY LEVELS

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INTRODUCTION

In establishing a national cord blood bank program, the Health Resource and Services Administration will have to decide how many cord blood units to place in inventory. The larger the inventory, the greater the likelihood that transplant candidates will match to a stored unit. Processing new cord blood units is costly, however, so the access benefits must be weighed against the storage costs. The purpose of this study is to estimate the benefits and costs associated with increasing the cord blood inventory. We express the results in terms of the incremental cost per life year gained for inventory sizes in the range of 50,000 to 300,000 cord blood units. Creation of a national banking program is partly motivated by a desire to increase access for minority patients, so we also consider the impact of bank size and racial and ethnic composition on disparities in match probabilities between groups.

Previously, several studies have used quantitative models to explore the costs and benefits of increasing the number of marrow donors (Beatty et al., 2000; Kollman et al., 2004) and cord inventory (Sirchia et al., 1999). We build on these analyses by modeling patients' preferences over adult unre-

lated donor versus cord blood stem cell sources and explicitly modeling the cost structure of a cord blood bank.

PATIENT SURVIVAL TIME

Match Probabilities

Cord blood inventory size affects patient survival times through its impact on the likelihood that a transplant candidate matches a stored unit. The first step in estimating the benefit associated with various inventory levels is to determine the corresponding match probabilities by match level (six of six, five of six, or four of six human leukocyte antigen [HLA] matches [referred to as 6/6, 5/6, and 4/6 matches, respectively]). These were calculated by (1) estimating the population frequency of HLA types by racial/ethnic group ("racial groups" for short, hereafter), based on the distribution of HLA phenotypes in the National Marrow Donor Program registry, (2) calculating separately for each HLA type the likelihood of matching to an adult unrelated donor or cord unit, assuming that the HLA types in the registry and cord bank are the same as in the general population, and (3) summing over HLA types separately for each racial group (Kollman et al. [2004] provide a detailed description of the algorithm). We calculated nationally representative estimates by taking a weighted sum of the racial group-specific probabilities based on the racial distribution of patients conducting searches of the National Marrow Donor Program registry in the second half of 2001, as reported in Kollman et al. (2004). These are shown in Table E-1. Matching is defined at the antigen level for HLA-A and B and at the allele level for HLA-DRB1.

For marrow match probabilities, the model assumes that only a fraction of matched donors will be available and willing to donate, based on historical patterns among each racial group. For cord unit match probabilities, the model uses the cell count distribution of cord units in the National Marrow Donor Program database and the empirical weight distribution of transplant candidates to estimate probabilities for a given minimum cell dose threshold. In the baseline analysis, we assume a threshold of 2.5×10^7 total nucleated cells per kilogram of body weight (TNC/Kg) and that cord units are collected from each racial group in proportion to the number of births among each group in 2002 (Martin et al., 2003). We further assume that transplants occur with one and only one cord unit. In some cases, heavier transplant candidates may receive more than one cord unit to achieve the minimum cell dose, but this is not standard practice.

Table E-1 displays estimated match probabilities for patients ≥20, averaged over weight deciles and racial groups, for cord blood inventories in the range of 50,000 to 300,000 units. Table E-2 displays probabilities for

TABLE E-1 Match Probabilities for Adults Age ≥20

	Cord Inventory				
Transplant Type	50,000	100,000	150,000	200,000	300,000
LR 6/6 Bone marrow	0.66	0.66	0.66	0.66	0.66
HR 7/8 Bone marrow	0.37	0.37	0.37	0.37	0.37
HR 8/8 Bone marrow	0.17	0.17	0.17	0.17	0.17
LR 5/6 Bone marrow	0.99	0.99	0.99	0.99	0.99
HR 7/8 Bone marrow	0.24	0.24	0.24	0.24	0.24
6/6 Cord blood	0.07	0.10	0.12	0.14	0.17
6/6 Cord blood or 6/6 bone marrow	0.66	0.66	0.66	0.66	0.66
6/6 Cord but no 6/6 bone marrow	<0.01	<0.01	<0.01	<0.01	<0.01
6/6 or 5/6 Cord blood	0.40	0.49	0.55	0.59	0.65
6/6 or 5/6 Cord blood or 6/6 bone marrow	0.70	0.72	0.74	0.75	0.77
6/6 or 5/6 Cord blood but no 6/6 bone marrow	0.04	0.06	0.08	0.09	0.11
6/6, 5/6, or 4/6 Cord blood	0.84	0.90	0.93	0.94	0.96
6/6, 5/6, or 4/6 Cord blood or 6/6 bone marrow	0.89	0.92	0.94	0.95	0.97
6/6, 5/6, or 4/6 Cord blood but no 6/6 bone marrow	0.23	0.27	0.28	0.29	0.31

NOTE: Bone marrow match probabilities assume a fixed registry size of 2,267,366. Bone marrow match probabilities incorporate donor availability. The probabilities of obtaining a 8/8 or 7/8 high-resolution match for HLA-A, -B, -C, and DR conditional on having a 6/6 or 5/6 low-resolution match for HLA-A, -B, and DR are based on data presented in Flomenberg et al. (2004). Cord blood match probabilities represent the likelihood of finding a matched cord unit for a minimum cell dose of 2.5×10^7 TNC/Kg, averaged across the empirical weight distribution of transplant candidates' age ≥20. LR: low resolution. HR: high resolution.

patients <20. Differences in match probabilities between adults and children reflect differences in the underlying weight distributions. Because younger patients are lighter, they are more likely to match to a cord unit with a volume of at least 2.5×10^7 TNC/Kg.

The current inventory of cord units in the United States is about 80,000, but the effective inventory may be much lower because many units were not collected and stored properly. We believe results for a 50,000-unit inventory most closely approximate the current situation. Going from a 50,000-unit inventory to a 300,000-unit inventory increases the likelihood that an adult patient will match to a cord blood unit at 6/6 antigens from 7 to 17 percent, the likelihood of matching on 5/6 antigens from 40 to 65 percent, and the likelihood of matching on 4/6 antigens from 84 to 96 percent.

TABLE E-2 Match Probabilities for Pediatric Patients Age <20

	Cord Inventory				
Transplant Type	50,000	100,000	150,000	200,000	300,000
LR 6/6 Bone marrow	0.66	0.66	0.66	0.66	0.66
HR 8/8 Bone marrow	0.37	0.37	0.37	0.37	0.37
HR 7/8 Bone marrow	0.17	0.17	0.17	0.17	0.17
LR 5/6 Bone marrow	0.99	0.99	0.99	0.99	0.99
HR 7/8 Bone marrow	0.24	0.24	0.24	0.24	0.24
6/6 Cord blood	0.23	0.29	0.34	0.37	0.42
6/6 Cord blood or 6/6 bone marrow	0.66	0.67	0.67	0.67	0.68
6/6 Cord blood but no 6/6 bone marrow	<0.01	0.01	0.01	0.01	0.02
6/6 or 5/6 Cord blood	0.76	0.83	0.86	0.89	0.91
6/6 or 5/6 Cord blood or 6/6 bone marrow	0.82	0.87	0.89	0.91	0.93
6/6 or 5/6 Cord blood but no 6/6 bone marrow	0.16	0.21	0.23	0.25	0.27
6/6, 5/6, or 4/6 Cord blood	0.98	0.99	0.99	0.99	1.00
6/6, 5/6, or 4/6 Cord blood or 6/6 bone marrow	0.98	0.99	0.99	1.00	1.00
6/6, 5/6, or 4/6 Cord blood but no 6/6 bone marrow	0.32	0.33	0.33	0.34	0.34

NOTE: Marrow match probabilities assume a fixed registry size of 2,267,366. Marrow match probabilities incorporate donor availability. The probabilities of obtaining a 8/8 or 7/8 high-resolution match for HLA-A, -B, -C, and DR conditional on having a 6/6 or 5/6 low-resolution match for HLA-A, -B, and DR are based on data presented in Flomenberg et al. (2004). Cord match probabilities represent the likelihood of finding a matched cord unit for a minimum cell dose of 2.5×10^7 TNC, averaged across the empirical weight distribution of transplant candidates age <20. LR: low resolution. HR: high resolution.

Given that bone marrow transplantation is the more established therapy, one could argue that the appropriate end point is the impact of an increase in inventory size on the *marginal* likelihood of finding a matched source of stem cells. Rows 8, 11, and 14 of Tables E-1 and E-2 show the impact of increasing inventory size on the proportion of patients who have a 6/6, 5/6, and 4/6 cord unit match but lack a 6/6 adult unrelated donor match, respectively. Moving from a 50,000 to a 300,000 inventory increases the probability of a 5/6 cord match for adults by 7 percentage points and a 4/6 cord match by 8 points. Patients unable to find a perfectly matched (6/6) adult unrelated donor are unlikely to find a perfect 6/6 cord match, regardless of inventory level.

Number of Transplants

Using the match probabilities, we calculated the impact of inventory size on the number of patients who would receive a transplant by match level and transplant type (marrow versus cord). There are several ways to estimate the number of potential transplant candidates. The first is to simply determine the number of patients who initiate formal donor searches with the National Marrow Donor Program. The drawback of this approach is that not all searchers are suitable transplant candidates; many initiate searches early in the course of their disease while they are simultaneously considering other treatment options. The second method is to estimate the number of transplant candidates based on the number of adult related donors. If it is assumed that 30 percent of all transplant candidates have an HLA-matched adult related donor (Kollman et al., 2004) and that there are 3,500 adult related donor transplants annually, then the number of transplant candidates without an unrelated adult donor is 8,200 (= 3,500 $\times$ 0.70 $\div$ 0.30). We prefer this approach because it is based on transplants that actually occur. We assume that one-third of candidates are age <20 years (hereafter referred to as "pediatric" candidates) and that two-thirds are age ≥20 years (hereafter referred to as "adult"candidates), based on a recent analysis of International Bone Marrow Transplant Registry (2004) data reporting the breakdown of allogeneic marrow transplants by age group (≥20 versus <20).

Many patients will match to both adult unrelated donors and cord units. To estimate the number of cord unit transplants, we need to assume how patients (and their physicians) choose among stem cell sources when multiple matches are available. We start by assuming that search strategies differ between adult and pediatric patients, and then by medical urgency within each of these groups (the time from search to transplant is less for cord blood). Search strategies for adult and pediatric patients are depicted graphically in Figures E-1 and E-2, respectively. These strategies are not literal representations of the search and transplant process. Rather, they attempt to capture probabilistically how transplant candidates arrive at the terminal states. We assume that for pediatric patients 4/6 cord blood transplants are preferred to 5/6 adult unrelated marrow donor transplants. The probability that a pediatric patient matches on 4/6 antigens to a cord unit with a sufficient cell dose for an inventory of 50,000 cord units is very high (>99 percent), so we do not explicitly model the number of pediatric patients who, failing to obtain a 4/6 cord match, seek a 5/6 adult unrelated marrow donor.

We assume that 25 percent of patients are urgent, based on an unpublished National Marrow Donor Program survey of transplant centers. However, the figure may be as high as 40 percent (General Accounting Office

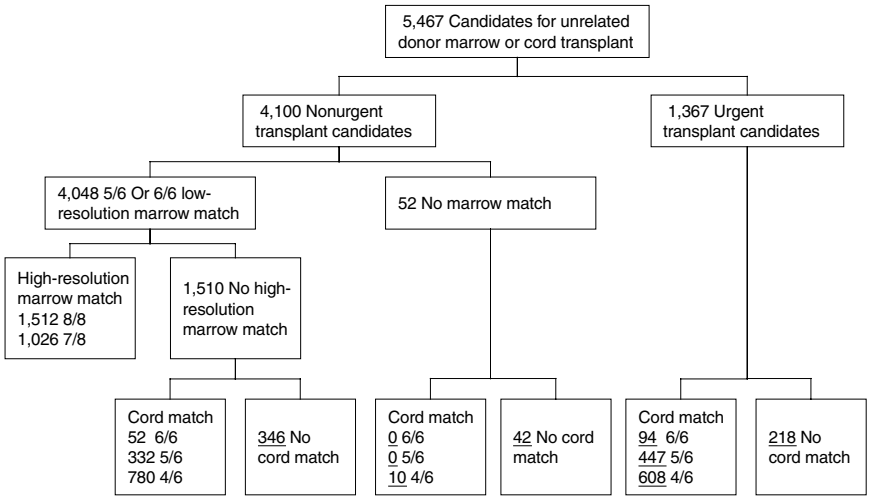

FIGURE E-1 Search strategy for patients age ≥20.
NOTE: Underlined numbers reflect match probabilities for a 50,000 cord unit bank and a minimum cell dose of 2.5×10^7 TNC/Kg. Numbers may not add up to total due to rounding.

2002). As an approximation to the limited options facing urgent patients, we assume they consider cord blood transplants exclusively. The time from search to transplant for cord blood transplants is about one month shorter than for adult unrelated marrow donor transplants (Barker et al., 2002). In reality, urgent patients probably search for both matched cord blood units and adult unrelated marrow donors.

We assume that following an initial low-resolution typing, potential adult unrelated marrow donors undergo a high-resolution typing for the HLA-A, -B, -C, and DR antigens and that adult unrelated donor transplants are considered only if the donor matches to the recipient on at least 7/8 antigens. The probabilities of a 8/8 or 7/8 high-resolution match for HLA-A, -B, -C, and DR conditional on a 6/6 or 5/6 low-resolution match for HLA-A, -B and DR were based on data reported in Flomenberg et al. (2004). For example, the probabilities that a patient has an 8/8 or 7/8 high-resolution match conditional on having a 6/6 low-resolution match are 56 and 26 percent, respectively.

Not all transplant candidates who theoretically match to a bone marrow donor or cord blood unit undergo transplantation. Some never initiate a donor or cord blood search, some die before the transplant occurs, and others select alternative therapies. We have little information with which to estimate the relevant probabilities from historical practice. Instead, we cali-

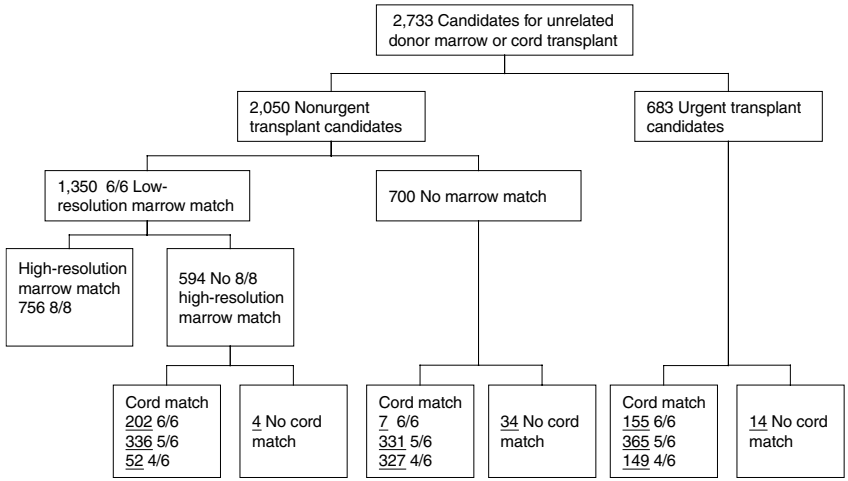

FIGURE E-2 Search strategy for patients age <20.
NOTE: Underlined numbers reflect match probabilities for a 50,000 cord unit bank and a minimum cell dose of 2.5×10^7 TNC/Kg. Numbers may not add up to total due to rounding.

brate these probabilities so that with a 50,000-cord blood-unit inventory the model yields estimates of total bone marrow and total cord blood transplants that are close to the actual figures of around 2,000 bone marrow and 600 cord blood transplants, two-thirds of which occur in pediatric patients. The corresponding transplant probabilities, representing the likelihood of transplant conditional upon obtaining a suitable match, are: 65 percent for marrow matches (adult and pediatric), 10 percent for adult cord matches, and 20 percent for pediatric cord matches. We do not allow transplant probabilities to vary by match strength. Realistically, patients who match to a cord unit on 6/6 antigens are probably more likely to pursue transplantation than patients who match on only 4/6 antigens. However, even with constant transplant probabilities, our estimated distribution of cord transplants by match level for an inventory of 50,000 units is similar to the empirical distribution (Institute of Medicine, 2005).

The numbers in Figures E-1 and E-2 indicate the numbers of patients through the search process for the case of a cord inventory of 50,000 units. For example, of the 5,467 adult transplant candidates without an adult related donor, 4,100 are nonurgent and 4,048 match on at least 5/6 antigens to an adult unrelated donor at low resolution. Of these, 1,512 match at 8/8 antigens and 1,026 match at 7/8 antigens at high resolution, 1,164 do not match at high resolution but do match to a cord unit at 6/6 antigens (52), 5/6 antigens (332), or 4/6 antigens (780), and 346 do not match to an

TABLE E-3 Projected Number of Annual Transplants by Cord Blood Inventory Level

	Cord Inventory				
Transplant Type	50,000	100,000	150,000	200,000	300,000
Patients age ≥20					
8/8 Bone marrow	983	983	983	983	983
7/8 Bone marrow	667	667	667	667	667
6/6 Cord blood	15	21	26	30	36
5/6 Cord blood	78	97	109	117	127
4/6 Cord blood	140	135	129	123	113
No transplant	3,585	3,563	3,554	3,548	3,541
Patients age <20					
8/8 Bone marrow	491	491	491	491	491
7/8 Bone marrow	0	0	0	0	0
6/6 Cord blood	73	95	109	120	136
5/6 Cord blood	206	217	219	218	214
4/6 Cord blood	106	78	64	55	44
No transplant	1,857	1,852	1,850	1,849	1,848
Cord blood total	617	643	655	662	670

NOTE: Results are based on the assumption that the likelihood of proceeding to transplant for patients matching to an adult unrelated marrow donor is 65 percent. The equivalent probabilities for cord transplants are 10 percent (for adults) and 20 percent (for children).

adult unrelated donor or a cord unit. Note that transplant centers use varying criteria for what constitutes an acceptable match, and so these figures may differ from actual experience of a cohort of patients at a specific center. Also note that not all of the patients who match to a marrow donor or cord unit will undergo transplantation. For example, of the 1,512 adult patients matching on 8/8 antigens to a marrow donor, we assume that 983 (= $1,512 \times 0.65$) will be transplanted.

Table E-3 displays the number of patients who would receive cord blood transplants at various cord blood inventory levels. The number of patients receiving bone marrow transplants does not vary, but the number undergoing transplantation with cord blood increases from 617 with an inventory of 50,000 units to 670 with an inventory of 300,000 units. Increasing inventory from 50,000 to 300,000 units also improves match quality; the number of 6/6-matched cord blood transplants increases by 84 and the number of 5/6 cord transplants increases by 57, but the number of

4/6 cord transplants decreases by 88. On net, there are 53 additional transplants.

Life Years Gained

Using data from the International Bone Marrow Transplant Registry on adult unrelated bone marrow transplants occurring between 1988 and 1996 (Flomenberg et al., 2004), we calculated 5-year survival rates by match level and age group. The results are as follows: patients ≥20, 8/8 match, 36 percent [95 percent cumulative incidence (CI): 32 percent, 40 percent]; patients ≥20, 7/8 match, 25 percent [95 percent CI: 20 percent, 30 percent]; patients <20, 8/8 match, 49 percent [95 percent CI: 42 percent, 56 percent]; patients <20, 8/8 match, 41 percent [95 percent CI: 33 percent, 49 percent].

We use two different scenarios to model the degree to which survival rates for cord transplants vary by match level. In the first, we assume that cord blood transplant survival rates vary by match level. Specifically, we assume that 5 year survival rates for 6/6 and 5/6 cord transplants are equal to those for 8/8 and 7/8 marrow transplants, respectively. This assumption is supported by several recent studies of long-term survival rates in adult recipients (Laughlin et al., 2004; Rocha et al., 2004). We assume that survival rates for 4/6 cord transplants are 20 percent in adults and 33 percent in children, based on the relative survival rates reported in the Statistical Report (Institute of Medicine, 2005). In the second scenario, we assume that survival rates for cord transplants do not vary by match level. Instead, we assume that survival rates for all cord transplants are equal to the age group-specific 7/8 marrow transplant rate. These scenarios represent extreme cases. We further assume that the 5 year survival rate for patients who do not undergo transplantation is 15 percent, based on data reported in Appelbaum and Kopecky (1997).

We computed using the International Bone Marrow Transplant Registry data the average survival time for patients who die within 5 years. We assume that average survival time for patients who die within 5 years but do not receive a transplant is 6 months. For patients who live at least 5 years, we computed survival time based on mortality rates in U.S. life tables (Arias, 2004), assuming that adults are transplanted at age 40 and children at age 5 and that relative mortality rates for transplant patients are five times higher than in the general population (Socié et al., 1999) from year 5 through year 20 post-transplant and normal thereafter. Using these conditional survival times and the survival rates, we computed unconditional survival times by transplant and match type. Results are displayed in Table E-4.

TABLE E-4 Life Years Gained from Marrow and Cord Transplantation

	5 year survival rate (%) Scenario		Life expectancy Survival		Total life years Scenario	
Transplant type	1	2	<5 years	≥5 years	1	2
Patients age ≥20						
8/8 Bone marrow	36	36	0.7	25.0	9.5	9.5
7/8 Bone marrow	25	25	0.6	25.0	6.7	6.7
6/6 Cord blood	36	25	0.3	25.0	9.2	6.5
5/6 Cord blood	25	25	0.3	25.0	6.5	6.5
4/6 Cord blood	20	25	0.3	25.0	5.2	6.5
No transplant	15	15	0.5	25.0	4.2	4.2
Patients age <20						
8/8 Bone marrow	49	49	0.6	68.0	33.6	33.6
7/8 Bone marrow	41	41	0.7	68.0	28.3	28.3
6/6 Cord blood	49	41	0.6	68.0	33.6	28.2
5/6 Cord blood	41	41	0.6	68.0	28.2	28.2
4/6 Cord blood	33	41	0.4	68.0	22.5	28.1
No transplant	15	15	0.5	68.0	10.6	10.6

NOTE: Average survival times for patients surviving ≥5 years are based on U.S. life table values (Arias 2004), assuming that patients ≥20 are transplanted at age 40 and patients <20 are transplanted at age 5. Life years gained for an 8/8 high resolution (HR) marrow transplant are $9.5 = (1 - 36\%) \times 0.7 + 36\% \times 25.0$. Calculations for other transplant types are similar.

We computed total life years for each inventory level (including life years for patients receiving unrelated donor marrow transplants and patients who do not receive any transplant) by multiplying the survival times in Table E-4 by the numbers of patients in each category from Table E-3. Results are displayed in Figure E-3. Results differ by scenario. Total life years start out higher for scenario 2, but increase more rapidly under scenario 1. Increasing the cord blood inventory from 50,000 to 300,000 units is associated with a gain of 1,039 life years under scenario 1 and 259 life years under scenario 2. The benefit in life years of expanding cord blood inventory size primarily reflects (1) a greater number of transplants among urgent patients, (2) a greater number of transplants among patients who match to an unrelated marrow donor on 6/6 or 5/6 antigens at low resolution but have more than one mismatch at high resolution, and in scenario 1 only (3) increased longevity among patients who are able to obtain a 6/6 or 5/6 cord match with a large inventory but would receive a poorer match at a low inventory level.

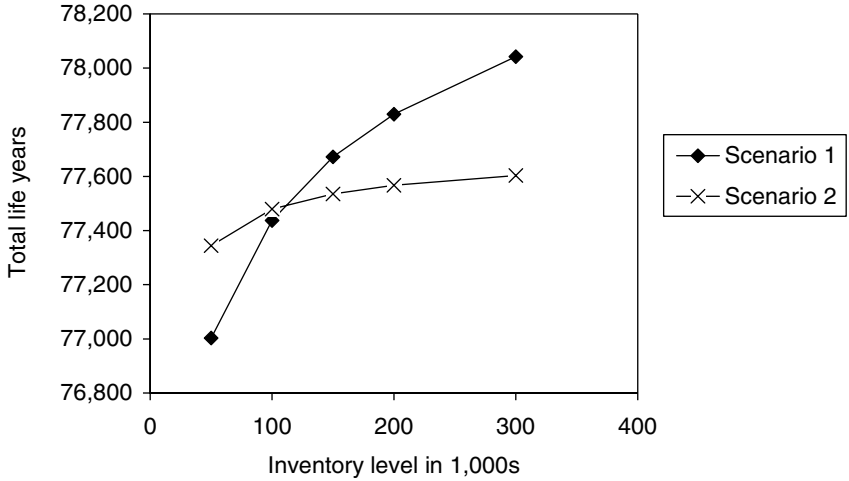

FIGURE E-3 Total life years for 8,200 transplant candidates as a function of cord inventory.
NOTE: Total life years includes survival time following cord and unrelated marrow transplantation and survival time for patients who do not receive transplants of either type. Scenario 1: Survival rates vary by cord match level. Scenario 2: Survival rates do not vary.

COSTS

The Cost Model

A cord blood bank will incur costs for the collection and processing of new cord blood units, the storage of existing units, and administration. Each year, the bank must collect units to replace transplanted units, T, and units discarded from the inventory because they have reached the "expiration date" of y years. A portion of the collected units, λ, are discarded prior to storage because they do not meet the minimum standards. Thus, many more units must be collected than ultimately end up in storage. The total number of units that must be collected, U, to ensure a stable inventory of size N is:

$$U = \frac{\frac{1}{y}N + T}{1 - \lambda}. \quad [1]$$

Note that the number of transplanted units is itself a function of the inventory level, as shown in Table E-2.

By letting c^{PS} represent the cost of processing a stored unit, c^{PD} the cost

of processing a unit that is discarded prior to storage (so that $c^{PD} < c^{PS}$), c^S the annual cost of storing a unit, and A the annual cost of administration, the annual costs for a cord blood bank are:

$$C = \left[(1-\lambda)c^{PS} + \lambda c^{PD}\right]U + c^{s}N + A \quad [2]$$

The bank must incur a one-time expense for the collection of units to bring the current inventory, N_0, up to the target level of N:

$$C_0 = \left[(1-\lambda)c^{PS} + \lambda c^{PD}\right]\frac{N - N_0}{1-\lambda}. \quad [3]$$

We assume that collection occurs instantaneously, although, realistically it would take a few years to reach inventory levels greater than 100,000 units.

For purposes of calculating the incremental cost per life year gained of a cord bank, we calculate total costs, TC, as the sum of annual costs, annuitized start-up costs, and the direct costs of transplantation, c^T:

$$TC(N) = C + rC_0 + c^{T}T, \quad [4]$$

where r is the interest rate. The incremental cost-effectiveness ratio, $ICER$, or the incremental cost per life year gained, associated with increasing inventory from N to N' is then:

$$ICER(N, N') = \frac{TC(N') - TC(N)}{LY(N') - LY(N)}, \quad [5]$$

where $LY(\cdot)$ represents life years as a function of the inventory, as shown in Figure E-3.

Another quantity of interest is the per-cord unit fee, f, that the bank must charge to break even, defined as the fee such that the net present value of revenues plus an initial endowment from Congress, E, minus the net present value of costs equals 0:

$$\frac{f \times T}{r} + E - C_0 - \frac{C}{r} = 0, \quad [6]$$

The fee depends on inventory size through T, C_0, and C.

Parameter Values

The goal of the analysis is to examine how transplants and costs vary with inventory size, N. Parameter values are summarized in Table E-5 and described below in order of appearance in the model.

TABLE E-5 Cost Model Parameters

Parameter	Description	Value	Unit
Inventory parameters			
N_0	Initial inventory	50,000	cord units
λ	Discard rate	0.50	proportion
y	Length of storage before discard	20	years
Cost parameters			
c^{PS}	Cost of initial processing, stored unit	$1,500	dollars
c^{PD}	Cost of initial processing, discarded unit	$500	dollars
c^{S}	Cost of storage, annual	$50	dollars
c^{T}	Cost of transplantation	$220,000	dollars
E	Endowment	$9,000,000	dollars
A	Annual administrative cost	$1,000,000	dollars
r	Discount rate	0.03	proportion

Discard Rate (λ)

In the Cord Blood Banking and Transplantation (COBLT) study 47 percent of collected units were discarded prior to storage. Thus, we assume a discard rate of 50 percent. However, several Institute of Medicine committee members suggested that the discard rate could be much higher than 50 percent, possibly as much as 90 percent. In particular, we would expect the discard rate to increase if the committee recommends a higher minimum transplantable cell dose.

Storage Length (y)

Little is known about the durability of stored cord blood units. In their analysis of Milano Cord Blood Bank costs, Sirchia et al. (1999) assume that units are discarded after 10 years. However, committee members indicated this figure is probably too conservative and that units can be stored for longer periods. In the absence of definitive evidence, we assume that units are discarded after 20 years.

Collection and Storage Costs (c^{PS}, c^{PD}, c^{S})

We assume that c^{PS} = $1,500, c^{PD} = $500, and c^{S} = $50. These figures are based on an informal survey by Institute of Medicine staff of public and private blood banks. Note that c^{PD} is an average processing cost for discarded units and includes units that are discarded prior to HLA-typing as well as those that undergo HLA-typing prior to discard. More stringent

processing requirements will probably lead to increased costs, so we have assumed processing costs toward the higher end of the range reported. We have not adjusted for the impact of economies of scale on the collection costs incurred by a national bank.

Cost of Transplantation (c^T)

We assume that transplanted patients incur costs of $220,000 over a one year period, based on figures reported in Lee et al. (1998). We lack the data to compute net lifetime costs for these patients.

Administrative Costs (A)

The collection and storage cost estimates from the blood bank survey are average costs and thus include overhead costs. However, we assume that a national cord bank will incur additional administrative costs for oversight, research, and analyses such as this one. We assume that A = $1,000,000.

Discount Rate (r)

We assume that $r = 0.03$, based on the recommendation of the Panel on Cost-Effectiveness in Medicine and Health (Gold et al., 1996).

Initial Inventory (N_0)

Based on data listed on www.bmdw.org, there are approximately 80,000 cord blood units currently in storage in the United States. However, the quality of these units is uncertain because many were processed and stored using protocols that would not meet the standards likely to be adopted by the committee. Thus, the existing inventory is below 80,000 units, although it is difficult to say by how much. For this analysis, we assume that the initial, usable inventory is 50,000 units.

Initial Endowment (E)

Congress has appropriated $9,000,000 for establishing a national cord bank.

Cost Estimates

Table E-6 displays the results of the cost analysis. We estimate that the break-even fee for an inventory level of 50,000 units is $15,336. This figure

TABLE E-6 Cost Estimates by Inventory Level

	Cord Inventory				
	50,000	100,000	150,000	200,000	300,000
Cord blood transplants	617	643	655	662	670
Annual cord collection (U)	6,234	11,287	16,310	21,324	31,340
Costs (millions)					
Annual bank costs (C)	$10	$17	$25	$32	$47
Direct treatment costs ($c^{T}N$)	$136	$142	$144	$146	$147
Start-up costs (C^{0})	$0	$100	$200	$300	$500
Total costs (TC)	$146	$162	$175	$187	$210
Break-even per cord fee (f)	$15,336	$31,107	$46,613	$62,014	$92,675

closely matches what public banks currently charge for a transplanted unit. If a national cord bank maintained an inventory of 150,000 units, the break-even fee could easily triple. Total costs range from $146 million for an inventory of 50,000 units to $210 million for an inventory of 300,000 units. Direct transplant costs account for at least 70 percent of total costs in all of the inventory scenarios.

INCREMENTAL COST-EFFECTIVENESS

Table E-7 displays the incremental cost per life year gained for each inventory level and scenario. For example, under scenario 1, an increase in the inventory from 200,000 to 300,000 units is associated with an additional cost of $23 million and a gain of 212 life years. The incremental cost per life year gained is $106,948 = ($23 million ÷ 212). The difference between scenarios 1 and 2 reflects the fact that in scenario 1 much of the gain in life years from expanding inventory is due to a shift toward better-quality cord blood matches among transplanted patients, rather than a greater absolute number of transplants. Failing to take account of how survival rates vary by match level ignores the survival gains from this first effect.

EQUITY

Equity between racial groups is an important motivation behind the establishment of a national cord bank. We examine the impact of increasing cord inventory on equity by comparing match probabilities and life years gained per patient between African Americans and Caucasians. For

TABLE E-7 Cost per Life Year Gained as a Function of Cord Inventory

	Cord Inventory				
	50,000	100,000	150,000	200,000	300,000
Total costs (millions)					
Total	$146	$162	$175	$187	$210
Incremental	NA	$16	$13	$12	$23
Scenario 1: Cord survival varies by match level					
Life years gained					
Total	77,003	77,437	77,672	77,830	78,042
Incremental	NA	434	234	158	212
Incremental cost per life year	NA	$37,667	$55,873	$75,953	$106,948
Scenario 2: Cord survival does not vary by match level					
Life years gained					
Total	77,344	77,479	77,536	77,568	77,603
Incremental	NA	135	56	32	36
Incremental cost per life year	NA	$121,231	$232,680	$376,385	$639,402

this analysis, we use the scenario 1 assumptions for cord blood survival rates. Increasing inventory size reduces the absolute difference between groups in the likelihood of obtaining a 4/6 cord blood match from 20 to 8 percentage points. Life years gained per patient are lower for African Americans at all inventory levels, but the incremental gains from increasing inventory size are larger.

The baseline model assumes that cord units are collected from racial groups in proportion to the number of births within each group. Other collection strategies ought to be considered, however, in light of the goal of reducing disparities. We re-estimated match probabilities under the assumption that cord unit collections from non-Caucasian donors are doubled, with collections among Caucasian donors reduced proportionately. Results are shown in the bottom half of Table E-8. Compared to a proportional collection strategy (i.e., the baseline model), overcollection increases match probabilities among African Americans and decreases match probabilities among Caucasians. The same pattern holds for life years gained per patient. In general, though, differences in match probabilities and life years are surprisingly small. A more thorough analysis of the trade-offs entailed in various collection strategies awaits future research.

TABLE E-8 Match Probabilities by Race

	Cord Inventory				
	50,000	100,000	150,000	200,000	300,000
Baseline model					
African Americans					
Match probabilities					
6/6 Cord	1%	2%	3%	3%	5%
5/6 Cord	20%	28%	33%	37%	43%
4/6 Cord	70%	79%	84%	87%	90%
Life years per patient	8.16	8.24	8.28	8.31	8.35
Incremental life years	NA	0.08	0.04	0.03	0.04
Caucasians					
Match probabilities					
6/6 Cord	12%	16%	19%	22%	25%
5/6 Cord	52%	62%	67%	70%	75%
4/6 Cord	90%	94%	96%	97%	98%
Life years per patient	9.58	9.63	9.66	9.68	9.70
Incremental life years	NA	0.05	0.03	0.02	0.02
Overcollection of non-Caucasian cord units					
African Americans					
Match probabilities					
6/6 Cord	2%	3%	4%	4%	6%
5/6 Cord	24%	33%	38%	42%	49%
4/6 Cord	75%	83%	88%	90%	93%
Life years per patient	8.21	8.28	8.32	8.35	8.39
Incremental life years	NA	0.07	0.04	0.03	0.04
Caucasians					
Match probabilities					
6/6 Cord	8%	11%	14%	16%	19%
5/6 Cord	44%	54%	59%	63%	69%
4/6 Cord	86%	92%	94%	96%	97%
Life years per patient	9.54	9.59	9.62	9.64	9.67
Incremental life years	NA	0.05	0.03	0.02	0.03

NOTE: Life years per patient assume survival rates for cord transplants vary by match level (scenario 1).

SENSITIVITY ANALYSES

We re-estimated incremental cost per life years gained and racial differences in match probabilities under the following assumptions, using scenario 1 assumptions for cord blood survival rates.

- Assume 40 percent of patients are urgent (instead of 25 percent).
- Assume that the 5 year survival rate for patients who do not receive transplants is 30 percent.
- Assume cord blood collections from non-Caucasian donors are doubled, with collections among Caucasian donors reduced proportionately (as discussed in the previous section).

Results are displayed in Table E-9. In general, cost-effectiveness ratios from the sensitivity analyses are qualitatively similar to those from the scenario 1 baseline analysis.

TABLE E-9 Sensitivity Analyses

	Cord Inventory				
	50,000	100,000	150,000	200,000	300,000
Baseline model (scenario 1)					
Break-even per cord fee	$15,336	$31,107	$46,613	$62,014	$92,675
Total life years	77,003	77,437	77,672	77,830	78,042
Incremental cost per life year	NA	$37,667	$55,873	$75,953	$106,948
Proportion of patients who are urgent is 40%					
Break-even per cord fee	$13,882	$27,963	$41,817	$55,583	$82,998
Total life years	74,029	74,502	74,758	74,931	75,164
Incremental cost per life year	NA	$35,723	$51,959	$69,995	$97,931
5 year survival rate without a transplant is 30%					
Break-even per cord fee	$15,336	$31,107	$46,613	$62,014	$92,675
Total life years	108,978	109,285	109,465	109,592	109,769
Incremental cost per life year	NA	$53,206	$72,875	$94,820	$128,329
Overcollection of non-Caucasian cord units					
Break-even per cord fee	$15,523	$31,335	$46,845	$62,239	$92,875
Total life years	76,770	77,224	77,469	77,635	77,858
Incremental cost per life year	NA	$37,757	$54,814	$73,713	$103,025

NOTE: In the baseline model the proportion of patients who are urgent is 25 percent, the 5 year survival rate without a transplant is 15 percent, and cord units are collected proportionately by race. Total life years include life years from bone marrow recipients and patients who do not receive a transplant of any kind. Survival rates for cord transplants vary by match level (scenario 1).

CONCLUSION

The decision about how many cord units to place in inventory entails weighing the benefits in terms of increased transplants and life years against costs. The degree to which cord blood transplant survival rates vary by match level is a key determinant of the benefits of storing additional cord blood units. In the absence of definitive evidence, we estimated cost-effectiveness ratios under two scenarios, representing extreme cases. In the first, cord transplant survival rates vary by match level, mirroring differences in marrow transplant survival rates. The corresponding cost per life year of increasing inventory from 50,000 to 100,000 units is $37,667. In the second, survival rates do not vary by match level. The corresponding cost per life year of increasing inventory from 50,000 to 100,000 units is $121,231. Under either scenario, the fee charged to patients and insurance companies for each transplanted cord unit will have to rise substantially for a national cord bank to break even at larger inventory levels.

Estimates of the economic value of a life year vary widely, from $24,777 to $428,286 (Hirth et al., 2000). However, for purposes of gauging the economic benefits of health interventions, estimates in the range of $100,000 to $160,000 are used most often (Cutler and McClellan, 2001; Vigdor, 2003). Based on these values, this analysis suggests that it is cost-effective to increase the cord blood inventory size beyond current levels. For example, the cost per life year gained of increasing inventory from 50,000 to 100,000 units under scenario 1, $37,667, is well below the $160,000 threshold. However, better estimates of long-term survival with cord blood transplants are necessary to properly evaluate the cost-effectiveness of large-scale increases in cord blood inventory levels.

There is a large degree of uncertainty about most of the parameters in this model, and even those we are fairly confident about are likely to change over time as technology evolves. Many of our assumptions will lead us to overestimate the benefits of increasing cord blood inventory. For example, we assume that survival rates are the same for urgent and nonurgent patients when, realistically, urgent patients will experience poorer post-transplant outcomes. Also, we ignore the availability of cord blood from banks outside the United States. Other assumptions may lead us to underestimate the benefits of storing cord blood. For example, the estimates of the probabilities of a 8/8 or 7/8 high-resolution match for HLA-A, -B, -C, and DR conditional on a 6/6 or 5/6 low-resolution match for HLA-A, -B, and DR were based on a study of transplanted patients (Flomenberg et al., 2004). A sample that also included nontransplanted patients would probably yield lower estimates, thus increasing the role for cord blood as an alternative source of transplantable stem cells. Also, we do not account for the fact that larger inventories will increase the number of patients transplanted with

higher cell volumes, leading to improved outcomes at any given level of HLA matching. Given the uncertainty we face, this analysis should best be seen as a template for an ongoing study of cord bank inventory to be continually updated as circumstances change and new information becomes available.

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F

COMMISSIONED PAPER

HLA OVERVIEW

An analysis prepared for the Institute of Medicine, of the National Academies, for the Committee on Establishing a National Cord Blood Stem Cell Bank.

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January 3, 2005

KEY OBSERVATIONS ON HLA AND HEMOTOPOIETIC STEM CELL TRANSPLANTATION

The following bulleted list is a summary of key facts about HLA that are described in more detail in the paragraphs below.

- Major histocompatibility complex encodes proteins, HLA molecules, that control tissue rejection.
- The genes that encode HLA molecules are highly polymorphic and the majority of nucleic acid substitutions alter the protein sequences in the key functional regions of the resultant HLA molecules.

- Even single amino acid differences between HLA proteins can have a profound effect on their ability to present antigen, interact with T lymphocytes, and stimulate allorecognition (transplant rejection or graft vs host disease).
- The frequencies of specific HLA alleles and haplotypes (alleles on one chromosome) differ in different racial/ethnic groups but approximately two-thirds of the alleles and most theoretical haplotypes are rare.
- HLA typing uses either DNA-based methods to define which potential alleles are carried or serology to define which proteins are expressed by an individual.
  - The ability of DNA-based typing to identify alleles varies depending on the method and reagents used. Typing of new volunteers for a registry is usually at low to intermediate resolution, narrowing down the potential alleles carried by an individual. Typing of a patient for transplant usually defines specific alleles carried by the patient. This is a newer method, and an increasing number of volunteer donors are typed by these methods.
  - Serologic typing is low resolution; it does not define which of many alleles might be carried by an individual. Large numbers of volunteer donor typings on registries were obtained with this method.
- Seventy percent of patients with fatal blood diseases treated with hematopoietic stem cell transplant require an unrelated donor and are served by registry and cord blood banks around the world.
- A registry/bank must possess sophisticated algorithms for storing and matching to address the complexity of HLA assignments received on volunteer donors/cord blood units. Quality control of typing is also critical.
- While transplant centers differ in their definition of a "match," the National Marrow Donor Program, has recommended matching for alleles at 4 HLA loci, HLA-A, -B, -C, -DRB1. When possible, DQB1 matching may provide additional benefit.
- The average patient searching the >5 million NMDP registry has an 85 percent chance of finding a 6 of 6 antigen match. Of the 6 of 6 antigen matches undergoing transplant, the probability of finding a 6 of 6 allele match is about 72 percent, a 10 of 10 allele match is about 50 percent, and a 12 of 12 match is 11 percent. The chance of finding a 6 of 6 antigen match for minorities is lower: 65 percent for an African American patient, and probability of allele matching has not yet been evaluated.
- The probability of match depends on allele and haplotype frequencies.
- Registries should possess the ability to evaluate the HLA characteristics of the database to improve knowledge of the HLA system and to enhance their ability to identify suitable donors for all patients.

THE HLA SYSTEM

MHC-Encoded HLA Proteins

In humans, proteins that controlled tissue compatibility were first detected on the surface of white blood cells using human-derived antibodies and were named human leukocyte antigens (HLA)(4, 13, 39, 76). Genes encoding these cell surface molecules are located in a cluster on chromosome 6 named the major histocompatibility complex (MHC) (Figure F-1). Two types of MHC-encoded (or HLA) molecules have been described, class I and class II. Class I molecules are expressed on the surface of essentially all nucleated cells. Humans express three different class I molecules: HLA-A, HLA-B, HLA-C. The class I molecules each consist of a single polypeptide encoded within the MHC, which associates with beta 2 microglobulin encoded on another chromosome (5). Class II molecules are expressed on the surface of cells of the immune system and they can be induced on some other cell types. Humans express three different class II molecules, HLA-DR, HLA-DQ, HLA-DP. Each class II molecule is comprised of an alpha and a beta polypeptide encoded within the MHC.

Although the class I and class II molecules are composed of different polypeptide chains, they assume a very similar structure on the cell surface. The amino terminal residues of the MHC-encoded polypeptides form two alpha helices and a beta sheet, creating a groove that binds peptides. It is this region of the HLA molecule that performs the functions attributed to these proteins (5).

Antigen Presentation Function

The normal role of MHC molecules is to bind short peptides within their antigen binding grooves and to carry these peptides to the cell surface for recognition by T lymphocytes (40, 41). The peptides are found within the endoplasmic reticulum (endogenous peptides, class I) or in the endocytic pathway (exogenous peptides, class II) and derive from the degradation of normal cellular proteins or from any pathogens encountered by the cell. T cell recognition of peptides from pathogens or malignant cells triggers a cellular immune response. T lymphocytes usually ignore self peptides bound to an MHC molecule.

Each MHC molecule binds a single peptide for transport to the cell surface. The peptides that bind to a particular MHC molecule must share common characteristics to allow the peptide to "fit" within the antigen binding cleft of the MHC molecule. Thus, only a subset of peptides are bound by the set of MHC molecules expressed by an individual. Since only a subset of peptides from any given pathogen will be bound by MHC and

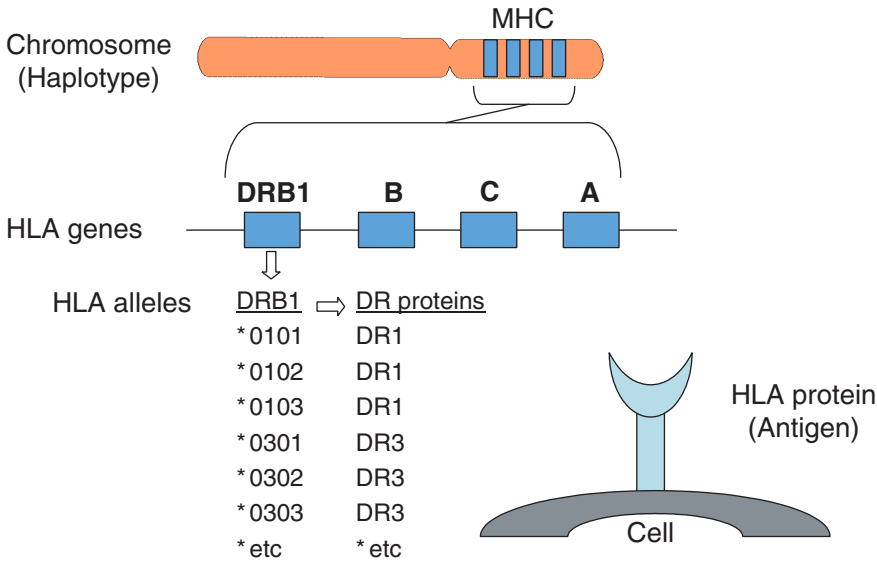

FIGURE F-1 Human histocompatibility genes.

targeted for T cell recognition, individuals may vary in their ability to mount immune responses to pathogens depending on the MHC molecules that they express (11).

HLA Genes

The genes for the HLA-A, -B, -C, -DR, -DQ, and -DP molecules are found next to one another within the MHC on chromosome 6 (68). The alpha (or heavy) chains of the class I molecules are encoded in the MHC; the second class I polypeptide chain, beta-2 microglobulin, is encoded on another chromosome. The genetic information needed to make a class II molecule is found in two different genes, a class II A (alpha) and a class II B (beta) gene. For example, a DQA1 gene and a DQB1 gene together provide the information needed to make a DQ molecule. Other class II A and B gene pairs include: DPA1 and DPB1, and DRA and DRB1. Some versions of chromosome 6 carry a second DRB gene, DRB3, DRB4, or DRB5. Its product can also associate with DRA to form a second DR molecule. Thus some individuals carry a copy of chromosome 6 that encodes two different DR molecules.

TABLE F-1 Alleles Identified at Each HLA Locus as of January 2005 (37)

Gene	Alleles	Gene	Alleles	Gene	Alleles	Gene	Alleles
A	338	DRA	3	DRB4	13	DQB1	59
B	617	DRB1	383	DRB5	18	DPA1	22
C	179	DRB3	41	DQA1	28	DPB1	111

HLA Alleles

HLA loci are the most polymorphic known in man (37). Several hundred alleles have been defined at some MHC-encoded loci (e.g., HLA-A, -B, -DRB1) (Figure F-1, Table F-1). The majority of these alleles carry nucleotide substitutions that change the amino acid sequence of the resultant protein which alters the antigen binding groove and T cell receptor contact residues of the MHC molecule (5). The extensive repertoire of alleles is likely due to the evolution of antigen presenting diversity at the level of the human population (46, 81).

The majority of the polymorphism is hypothesized to have arisen by mutation followed by nonreciprocal exchange of short polymorphic regions among alleles. The latter process, referred to as gene conversion, spread the variations in nucleotide sequence among alleles. As a result, the HLA alleles are patchworks of polymorphic sequences, each sequence shared by some of the other alleles at the locus, embedded in a conserved framework (46).

HLA Haplotypes

Because the HLA genes are clustered on chromosome 6, the alleles on one chromosome are usually inherited as a haplotype. Any two children in a family have a one in four chance of receiving the same two chromosomes from their parents. Children receiving the same chromosome from one parent, but a different chromosome from the other parent, are haploidentical.

The two chromosomes carrying the HLA genes sometimes exchange gene segments to "reshuffle" the HLA-A, -B, -C, -DR, -DQ, and -DP allele combinations that make up haplotypes. The frequency of recombination across the MHC from HLA-A to HLA-DPB1 is 2 to 2.5 percent, although recombination is concentrated in just a few segments in that region (e.g., recombination occurs between B and DRB loci but is unusual between DR and DQ loci) (12).

An HLA typing result provides a genotype (HLA alleles carried) or

phenotype (HLA antigens expressed) but doesn't identify which alleles are linked together on the chromosome as a haplotype. The only way to know for sure is through family segregation analysis. When family data are not available, the EM algorithm has been used to predict haplotypes (45,52).

When two or more genes are on the same chromosome, they are said to be linked. When alleles of linked genes occur in haplotypes more frequently than would be expected on the basis of chance alone, those genes are said to be in linkage disequilibrium. The HLA gene complex is in linkage disequilibrium (7, 10). Apparently high disequilibrium across the DR-DQ subregion coupled with a lack of recombination have resulted in specific associations between DQA1 and DQB1 alleles and between DRB1 and DQ alleles.

These associations may differ among individuals of different racial/ethnic backgrounds. At the level of class I–class II associations, the best known example of linkage disequilibrium is the HLA-A1, -Cw7, -B8, -DR3, -DR52, -DQ2 haplotype, which occurs approximately four times more frequently than would be expected by chance. It is thought that combinations such as this one (often called extended haplotypes) account for at least 30 percent of HLA allele combinations in whites.

Allele and Haplotype Frequencies

The frequencies of HLA alleles and haplotypes found in individuals differ among ethnic/racial groups (9,38,43,77). Some alleles and haplotypes are common to several populations; others may be predominantly confined to one particular population group. Most of the alleles are rarely observed. For example, in the United States, DRB1*03 (or DR3) is carried by 10–23 percent of four U.S. population groups (Table F-2) (77). The allele DRB1*0301 is common to most population groups, but DRB1*0302

TABLE F-2 DRB1*03 Allele Frequencies in Various U.S. Populations

DRB1*03 allele	U.S. Whites	African Americans	U.S. Hispanics	Asian Americans
DRB1*0301	100%	54%	83%	98%
DRB1*0302		46%	15%	1%
DRB1*0304				1%
DRB1*0305			1%	
DRB1*0307			1%	
DRB1*0316			1%	
Other DRB1*03 Frequency	DRB1*03 23%	25%	17%	10%

NOTE: The 22 other DRB1*03 alleles not found are present at <1 percent of the population (77).

is found primarily in the African American population. Most of the 28 DRB1*03 alleles (22 out of 28, 79 percent) were not observed in the testing, suggesting that they will be found in less than 1 percent of the population.

The frequencies of HLA haplotypes found in individuals differ among ethnic/racial groups. Some haplotypes are common to several populations; others may be predominantly confined to one particular population group. Most of the theoretical haplotypes are rarely observed. The most common haplotype in whites (A1,B8,DR3) is the second most frequent haplotype in African Americans and the third most frequent haplotype in Latinos, but it is the 54th most frequent haplotype in Asian Americans (52). It is likely that not all potential haplotypes will be found. When large databases of HLA typed individuals are analyzed, only a small percent of potential HLA phenotypes are found. Using serologic assignments from the National Marrow Donor Program, of the predicted 19,536,660 HLA-A, -B, -DR phenotypes, only 1.6 percent were observed (52).

Information of the frequencies of specific alleles and haplotypes (defined at allele level) in specific populations is limited (72). Populations have been studied through the International Histocompatibility Workshops, but the typing methods and resolution of testing have been inadequate to detect the full extent of HLA diversity (38, 42). Lack of allele level data seriously impacts our ability to predict the probability of finding an allele matched donor for patients and our ability to determine the most effective size for a registry or bank (44, 45).

Understanding common haplotypes or allele associations is useful for predicting which alleles are most likely to be present in donors who have only low resolution typing information and no family data to define haplotypes. For this reason, information on the ethnic background of the volunteer donors is often provided in registries and umbilical cord blood banks.

TISSUE TYPING

Clinical Testing and Quality Control

Testing to identify HLA allelic differences among individuals is classified as a high complexity assay by Clinical Laboratory Improvement Amendments (CLIA) guidelines (http://www.fda.gov/cdrh/CLIA/categorization.html). The complexity arises from the need to detect multiple loci, the similarity among loci and alleles, the complex nature of the polymorphism (multiple polymorphic motifs shared among alleles define an allele), and the continuing discovery of new alleles. HLA testing is routinely carried out by laboratories using either commercial and/or "home-made" reagents.

The American Society for Histocompatibility and Immunogenetics (ASHI), the European Federation for Immunogenetics (EFI) and other orga-

nizations have standards for DNA-based HLA typing and an accreditation process (75). For example, extensive guidelines for quality control and quality assurance related to all stages of DNA-based HLA testing are described in the ASHI Standards for HLA Testing (ASHI, http://www.ashi-hla.org) (1). Additional ASHI guidelines apply for laboratories performing high-volume (>50,000 tests per year) HLA testing (i.e., large-scale registry typing). The ASHI program has accredited over 200 histocompatibility laboratories. The Health Care Financing Administration (HCFA), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), National Marrow Donor Program (NMDP), SouthEastern Organ Procurement Foundation (SEOPF), United Network for Organ Sharing (UNOS); and the states of California, Florida, Oregon, and Washington grant deemed status to ASHI accredited labs.

HLA Assignments—Nomenclature

HLA assignments, testing methods, and reagents were developed through a series of International Histocompatibility Workshops, which began in 1964 and continue today (the 14th workshop is scheduled for December 2005; http://www.microbiol.unimelb.edu.au/micro/14ihiws/). The World Health Organization HLA Nomenclature Committee is responsible for the naming of HLA "types," and their assignments are included on a web site (http://www.anthonynolan.org.uk/HIG) (50, 69). The names are based on the method of testing used to define HLA "types." The naming system arose historically so that the nomenclature is difficult to understand.

Testing Methodology—Serology

The first method used for HLA typing was serology, and its use continues today (47). Serology detects different forms of the HLA proteins on the surface of peripheral blood lymphocytes. The assay uses antibodies, predominantly human alloantisera, in a microcytotoxicity assay. The alloantisera are obtained from humans who have been sensitized to HLA antigens by pregnancy or previous transplant. These antibodies are used as reagents to identify serologic specificities (or HLA types). The antibodies react with the HLA molecules present on the cell surface. The serologic specificities of the HLA antigens, HLA-A, -B, -C, -DR, and -DQ can be found on a Web site (http://www.anthonynolan.org.uk/HIG). Antibodies defining HLA-DP antigens are rare, so DP is not identified by serologic typing. Alloantisera are complex reagents containing multiple antibodies; they can react with more than one serologic epitope making interpretation of the results more of an "art." Most serologic epitopes are thought to lie in the antigen binding region of the HLA molecule.

Each serologic specificity (or HLA type) is designated by a letter indi-

cating the HLA antigen group and a number (e.g., A2, A34, B7, DR4). The number indicates the order in which the type was discovered. For example, B7 is a serologic specificity localized on an HLA-B molecule, while DR4 is a serologic specificity localized on an HLA-DR molecule. Some serologic specificities have been subdivided, defining broad and split classifications (e.g., B5 was subdivided into B51 and B52; DR6 into DR13 and DR14). Some antisera recognize amino acid sequences shared among allelic products. For example, B5-specific sera recognize a shared serologic epitope on molecules carrying either B51 or B52 serologic specificities. Because these serologic types were named as they were discovered, the naming system is confusing.

The limited availability of alloantisera and the implementation of more powerful techniques to detect HLA differences among individuals (DNA-based typing) have resulted in the decision by the HLA community to discontinue the definition of new HLA serologic specificities. This means that a cell expressing a new HLA allele with unique serologic epitopes must be defined using pre-existing serologic types (e.g., B*8201 is defined as a combination of B45 and B22 serologic specificities).

Testing Methodology—DNA-Based Methods

Most of the DNA-based assays rely on the polymerase chain reaction to amplify the HLA genes and the detection of nucleotide sequence differences among HLA alleles to predict "HLA types" (51). Techniques for testing include use of sequence specific oligonucleotide probes (SSOP), sequence specific primer (SSP) typing, and DNA sequencing (SBT, sequence based typing). Where SSOP and SSP typing methods only assess polymorphic regions of the amplified gene, SBT methods assess both the polymorphic and the invariant regions of the gene. SSOP and SSP are techniques used for testing of volunteer donors in a registry at the time of recruitment, while SBT is more often used for patient and potential donor typing. Most typing systems focus on polymorphisms in the gene encoding the antigen binding region of the MHC molecules.

Depending on the two alleles carried by an individual and on the reagents, methods, and strategies used for the testing, a single individual tested in different laboratories may receive a variety of typing results. Even the same individual tested in the same laboratory at different times may receive differing assignments depending on how the reagents in the typing kit have changed over time and on the set of HLA alleles known to exist at the time that the test result was interpreted.

Each HLA allele is designated by the name of the gene, followed by an asterisk and a four- to eight-digit number indicating the allele (http://www.anthonynolan.org.uk/HIG). For example, B*2701 is an allele of the HLA-B

gene. The first two numbers in the numerical designation of each allele are based on the similarity to other alleles and sometimes on the serologic type of the resultant protein molecule. For example, the HLA-A molecule expressed by the A*02010101 allele bears the A2 serological specificity defining the HLA-A2 molecule (or antigen). The A*0226 allele has a similar DNA sequence to other A*02 alleles; however, the HLA-A molecule specified by A*0226 has not been characterized using serology so no information is available on its serologic specificity. The second example illustrates an allele whose name is based on its similarity to other alleles, in this case, similarity to A*02010101, A*0202, A*0203 and so forth. New alleles which appear significantly different in nucleotide sequence from previously described alleles may receive a unique WHO assignment for the first two digits of their name. Thus, B*8101, which was frequently serologically typed as B7, received a unique designation setting it apart from the B*07, allele family. The third and fourth digits in an allele designation refer to the order in which the allele was discovered. For example, DRB1*030101 was the first DRB1*03 allele to be discovered and DRB1*030201 was the second.

Some combinations of alleles share the first four digits of a six-digit designation (e.g., DRB1*110101 and DRB1*110102). The digits indicate that the two alleles differ in DNA sequence, but that the amino acid sequence of the HLA proteins specified by the two alleles do not differ (i.e., differing by silent or synonymous substitutions). Some combinations of alleles are identified by eight-digit designations (e.g., DRB4*01030101 and DRB4*01030102). These alleles differ in DNA sequence only outside of their protein coding sequences (e.g., intron or 3'UTR differences). In some cases, these differences may affect the expression of the alleles. In the case of DRB4*0103102, the allele is not expressed due to a defect in a mRNA splice site. The addition of an AN@ indicates the presence of an allele which is not expressed as a normal HLA protein at the cell surface. The N may not always be included but is implied (ie., DRB4*01030102N = DRB4* 01030102). Other letters indicate HLA products that might be secreted (B*44020102S) or expressed at a low level (A*24020102L).

Most DNA-based typing results narrow down but do not define the precise alleles carried by an individual. The results are various alternative genotypes (combinations of two alleles at a locus). Unfortunately, computer matching programs cannot accommodate listings of different possibilities for the allele present on a single chromosome, so registries such as the NMDP have adopted a "shorthand" nomenclature to indicate this typing result. Thus, in the NMDP database, the intermediate type DRB1*1101 or DRB1*1104 is labeled DRB1*11AD where AD is a code specifying 01 or 04. A Web site (http://www.nmdpresearch.org) lists this shorthand code.

Comparison of Typing Methods

Serology was initially used for HLA typing. DNA-based typing was implemented in the late 1980s with the advent of the polymerase chain reaction and the availability of the nucleotide sequences of many HLA alleles. The advantages of DNA-based testing over the long-established serology assay are summarized in many publications (6, 57, 59). DNA-based assays are favored because they utilize synthetic reagents, use reagents of well defined specificity, do not require viable cells, and can detect all HLA diversity. For example, different HLA alleles defined by DNA typing can specify HLA proteins which are indistinguishable using serology. For example, an individual carrying the B*070201 allele would have the same serologic type (B7) as an individual carrying the B*0705 allele (B7). Because serologic reagents that are specific enough to define this subdivision (or Asplit@) are not available, serology can not distinguish between the two proteins specified by the two alleles, B*070201 and B*0705 (Figure F-1). There are many, many other examples of alleles defined using DNA typing which can not be individually identified using protein-based typing methods.

Because serologic HLA typing had limitations in the consistency of test results, searches for potential HLA matched donors might have to include alternative phenotype searches to identify donors who may have been serologically mistyped. This will become less common as more and more DNA-typed donors are listed in the registry files.

Because the transition in typing methodology has taken place over a number of years, databases of HLA types (such as bone marrow registries) contain a mixture of serologic and DNA assignments. Some volunteer donor HLA types are a mixture of both serology and DNA assignments.

Testing Resolution

The ability to identify which HLA alleles are carried by an individual depends on the testing method and reagents used. Examples of the relationships among assignments are shown in Table F-3.

Low Resolution at Serologic Broad

The level of testing is achieved by serologic testing. A broad specificity is one that can be split further into two or more subtypes (or splits). For example, DR3 is a broad assignment that has been split into DR17 and DR18.

TABLE F-3 Examples of Relationships Between Serologically Defined Antigens and DNA-Defined Types

Serology			DNA-Based Testing	
Broad	Split	Low Resolution	Intermediate Resolution	High Resolution
A2	—	A*02 (A*02XX)[a]	A*0202 or A*0206 or A*0211 or A*0220	A*0202
B15	B62	B*15 (B*15AAA)	B*1501 or B*1504 or B*1505, etc.	B*1501
Cw7	—	Cw*07 (Cw*07XX)	Cw*0702 or Cw*0704 or Cw*0708	Cw*0702
DR3	DR17	DRB1*03 (DRB1*03XX)	DRB1*0301 or DRB1*0304 or DRB1*0305 or etc.	DRB1*0301

[a]The National Marrow Donor Program has a 2–4 letter code that includes specific alleles. XX means all alleles in an allele group (e.g., A*02XX includes about 67 alleles, A*0201, A*0202, A*0203, through and including A*0267).

Low Resolution at Serologic Split

The level of testing is achieved by serologic testing. A split is a subdivision of a broad specificity. For example, DR17 and DR18 are splits of the broad specificity DR3. Many volunteer donors on registries are typed at this level of resolution.

Low Resolution (Generic or Serologic or Antigen) Level

This is DNA-based typing that produces results that are similar in appearance and detail to serologic types. For example, the DRB1*11 (or DRB1*11XX) DNA type is the equivalent to the DR11 serologic type. The "XX" indicates that the allele was not further defined. At this level of resolution, it is not possible to determine which of the over 50 DRB1*11 alleles is carried by the individual being tested. Many volunteer donors on registries are typed at this level of resolution.

Intermediate Resolution Level

DNA-based typing can reduce the number of possible alleles but lists several different alleles as being candidates for the type of an individual. For example, an individual who was typed as DRB1*11XX at low resolution, might be typed as DRB1*1101 or DRB1*1104 at intermediate resolution. Registries such as the NMDP have adopted a "shorthand" nomenclature to indicate this typing result (http://www.nmdpresearch.org). Thus, in the

NMDP database, DRB1*11AD is used. AD is a code specifying 01 or 04. Many volunteer donors on registries are typed at this level of resolution.

High Resolution Level

DNA-based typing identifies the specific allele carried by an individual (e.g., DRB1*1104) or may narrow down the possibilities to one highly likely allele and one to several rare alleles (e.g., A*0201 or A*0209 or A*0243N). This level of typing is not routinely carried out during the typing of new volunteers because of the cost and manpower involved. High-resolution testing is frequently carried out by the transplant center to determine the degree of the HLA match between a patient and a specific potential donor.

Allele Level

DNA-based typing identifies the specific allele carried by an individual (e.g., DRB1*1104). This level of typing is not routinely carried out during the typing of new volunteers because of the cost and manpower involved. High resolution testing is frequently carried out by the transplant center to determine the degree of the HLA match between a patient and a specific potential donor.

Cost of Typing

The cost of typing varies depending, in part, on the method, reagents, resolution, and volume of testing. For clinical HLA typing laboratories performing high numbers of new volunteer donor typing for a registry, the approximate cost is $55 to assign intermediate assignments at three loci (A, B, DRB1). (Price does not include phlebotomy.) For testing of 5 loci (A, B, C, DRB1, DQB1) at allele resolution in a laboratory performing large-volume testing, the assay may cost approximately $800–$1000. The cost will be higher in laboratories that perform testing on a smaller scale, for example, only for their own hospital.

Impact of Allele Discovery and Genotype Summarization on Test Interpretation

Approximately two new HLA alleles are reported each week (50). With the continued increase in the number of known HLA alleles, primary HLA testing data (nucleotide polymorphisms detected as present or absent) should be obtained and stored in addition to interpreted assignments (26, 27, 28, 49). This is particularly important for typing data which is used

over a long period of time (e.g., bone marrow registry, cord blood bank). Inclusion of these data are key to prevent the data from being outdated, to provide a list of genotypes for future matching strategies, and to facilitate the search for rare/newer alleles. This is often key for patients with uncommon alleles who do not have many potential donors. In these situations, tools to facilitate the selection of donors with the greatest potential to carry the rare allele are essential to save time and conserve resources.

Correlation of DNA-Based and Serologic Types

Although a single serologic specificity was once thought to define the product of a single HLA allele, we now know that a single serologic specificity is associated with multiple allelic products (Table F-4) (73). For example, the serologic type HLA-A2 is found on over 60 different allelic products. Today, many cells carrying newly described alleles have not been rigorously serologically tested and a neural network approach has been used to predict the serologic assignments (48). Also, because the typing method is predominantly by DNA based methods, allelic products encoding apparently unique serologic specificities are not assigned new serologic specificities.

The nomenclature used to assign DNA-based HLA types is based on that used in serology; however, there are many examples where the assignments applied to an allele and to its product appear to differ from one another (for example, a protein with a B62 serologic determinant is encoded by the allele B*1501). These differences are often the result of the complex nature of serologic testing and the nomenclature system used to assign allele names. In addition, some allelic products carry new combina-

TABLE F-4 Examples of Alleles Which Encode Specific HLA Proteins (or Antigens)

Serologic Assignment	Allelic Products Which Carry Serologic Type[a]
A2	A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, etc.
B7	B*0702, B*0703, B*0704, B*0705, B*0706, B*0707, etc.
B62	B*1501, B*1504, B*1505, B*1506, B*1507, B*1520, etc.
None assigned	B*8301
DR3	DRB1*0301, DRB1*0302, DRB1*0303, DRB1*0304, etc.

[a]Not all alleles in the group encode the antigen. For example, some of the A*02 alleles, e.g., A*0215N and A*0232N, do not encode a protein product. For example, not all alleles with names beginning B*15 encode proteins with the B62 serologic type. Other alleles in this group encode B63, B71, B72, B75, B76, B77 antigens.

TABLE F-5 Examples of the Types of Volunteers Carrying the Same Allele, A*0201

Assignment	Typing Method, Resolution
A2	Serology, low or antigen
A*0201	DNA-based, allele
A*02AJCH = A*0201, A*0207, A*0215N, A*0218, A*0220, A*0224, A*0225, A*0229, A*0230, A*0231, A*0232N, A*0233, A*0239, A*0242, A*0243N, A*0252, A*0253N, A*0259, A*0260	DNA-based, intermediate
A*02ACVV = A*0201, A*0204, A*0207, A*0209, A*0215N, A*0217, A*0218, A*0220, A*0224, A*0225, A*0226, A*0229, A*0230, A*0231, A*0232N, A*0233, A*0239, A*0242, A*0243N, A*0249, A*0252, A*0253N, A*0259, A*0260	DNA-based, intermediate
A*02AD = A*0201, A*0204	DNA-based, intermediate
A*02XX	DNA-based, low

tions of serologic determinants which do not fit within previously defined serologic specificities. These allelic products would be serologically typed as "blanks" or might be identified as carrying one of two or more specificities. For example, the allele B*8301 does not have a serologic assignment.

Even the same individual typed in different laboratories or typed by the same laboratory over time will likely receive a variety of HLA assignments. For example, the assignment A*0201, a very common allele, can be found within 844 different assignments within the NMDP registry (Table F-5).

HLA IN DISEASE AND TRANSPLANTATION

Disease

Specific HLA alleles have been associated with disease susceptibility (8, 17, 21, 23, 67). For example, when patients with the autoimmune disease multiple sclerosis are typed for HLA, the majority of patients carry a specific DRB1 allele, DRB1*1501. A study of many autoimmune diseases shows a similar association. The disease association will also discriminate among closely related alleles, for example, alleles of DRB1*04 differ in predisposition to type 1 diabetes. Although more difficult to detect, differences in disease susceptibility have also been shown with infectious diseases. Individuals who carry particular B*35 subtypes, e.g., B*3502,

B*3503, are more likely to progress to AIDS compared to individuals carrying other B*35 subtypes, B*3501 and B*3508 (20).

Allorecognition

Nobel prize winning studies by Drs. Snell, Dausset, and Benacerraf identified molecules that play a predominant role in the rejection of transplanted tissue (4, 13, 24, 76). Tissues from one individual transplanted into a patient are detected as foreign by the immune system. This recognition process is controlled in part by the major histocompatibility molecules, HLA. In hematopoietic stem cell transplantation, the immune response may be directed against the graft (patient's immune system rejecting the graft) or against the recipient (donor's immune cells rejecting the patient's cells, termed graft versus host disease).

T lymphocytes can respond to foreign HLA molecules either by direct recognition of the foreign HLA molecule or by indirect recognition of a self HLA molecule presenting a peptide from a foreign HLA molecule (19,78). Polymorphic molecules other than HLA may stimulate the immune system when presented by HLA molecules and are termed minor histocompatibility antigens (14). The impact of these "minor" responses on transplant is not yet clear. Natural killer (NK) cells have also been implicated in allorecognition responses, activated by missing HLA molecules (64). HLA alloantibodies synthesized by B lymphocytes have been associated with graft rejection (62). Although each of these immune cell types may affect transplant outcomes, current evidence suggests that T lymphocytes play the dominant role.

Since most HLA alleles encode proteins which differ from one another in the amino acid sequence of the antigen binding domains, most are theoretically capable of stimulating alloreactive T cells.

SOURCES OF HEMATOPOIETIC STEM CELL DONORS

Related Donors

In order to avoid allorecognition, physicians attempt to identify hematopoietic stem cell donors who are "HLA compatible" with their donors. Any two children in a family have a one in four chance of receiving the same two HLA gene-bearing chromosomes from their parents. Thus, within the United States, about 30 percent of patients identify an HLA compatible family donor. The remaining individuals must seek a histocompatible unrelated donor through registries of adult volunteer donors or through cord blood banks.

International Registries and Cord Blood Banks

About 90 registries and cord blood banks of HLA typed potential donors have been established in 41 countries and include over 9 million individuals/units (25, 79, 80). These registries/banks range in size from 42 units in a small cord blood bank to over 5 million adult volunteer donors in one registry. The HLA phenotypes available worldwide are summarized within the database of Bone Marrow Donors Worldwide (BMDW; http://www.bmdw.leidenuniv.nl). In 2002, worldwide registries received over 77,000 preliminary search requests and processed over 29,000 activated searches. There is, for example, an average of 7,000 patients searching the world's largest registry, the NMDP, at any given time.

While an unrelated donor search usually begins within the country of origin of the patient, searches failing to identify a donor can extend to foreign registries/banks. Of the almost 5,900 unrelated transplants worldwide, about one-third involved stem cells from a donor in another country. For the NMDP, approximately equal numbers of hematopoietic stem cells were provided from overseas donors to U.S. patients (1,700) as were provided by U.S. donors for patients abroad (1,946). An international voluntary organization of registries worldwide, the World Marrow Donor Association (WMDA; http://www.worldmarrow.org), has published policies and procedures for these international exchanges and WMDA working groups such as the Information Technology Working Group, are focused on standardizing data elements, forms and processes for international exchanges (18, 22, 30, 63).

DONOR SELECTION

Defining a "Match"

There is no single accepted definition of a "match" in regards to a specific transplant donor. The match can be at allele level or at antigen level. For example, a patient and donor sharing the alleles at the DRB1 locus, DRB1*0101, DRB1*0302, are said to be allele matched. Sharing DRB1*01, DRB1*03 (low resolution DNA typing) or DR1,DR3 (serologic assignment) would be defined as an antigen match. At the lower level of resolution, the donor and recipient are actually *potentially* matched at the allele level since they each carry one of 11 alleles of DRB1*01 and one of 25 alleles of DRB1*03. The probability of the two individuals carrying the same alleles depends on the frequency of the alleles in the racial/ethnic group of each individual. For example, if the patient carries DRB1*0302, the probability of a DRB1*03 positive African American volunteer carrying the same allele is about 46 percent, while the probability of a DRB1*03 positive white individual carrying the allele is 0 percent (see Table F-2).

TABLE F-6 Matches for a Patient Typed as A*0201, A*3201, B*0702, B*1501, Cw*0401, Cw*0702, DRB1*0101, DRB1*0302

Match	Example of HLA Types
6 of 6 antigen	A2, A32, B7, B62, DR1, DR3
6 of 6 allele	A*0201, A*3201, B*0702, B*1501, DRB1*0101, DRB1*0302
8 of 8 antigen	A*02, A*32, B*07, B*15, Cw*04, Cw*07, DRB1*01, DRB1*03
8 of 8 allele	A*0201, A*3201, B*0702, B*1501, Cw*0401, Cw*0702, DRB1*0101, DRB1*0302
5 of 6 antigen	A*02, A*01, B*07, B*15, DRB1*01, DRB1*03

The number of loci considered in the definition of a match also varies. A 6 of 6 antigen match is usually referring to matches at HLA-A, -B, and DRB1 (Table F-6). An 8 of 8 antigen match might refer to HLA-A, -B, -C, and -DRB1 loci or HLA-A, -B, -DRB1, -DQB1 loci. Six of 6 refers to matching for 2 assignments at each of 3 loci; 5 of 6 is matching for 5 of the potential 6 assignments. The extent of allele matching within a 6/6 antigen match can vary (Table F-7).

TABLE F-7 Possible Allele Assignment of Individual Typed as a 6 of 6 Antigen Match, A2, A32, B7, B62, DR1, DR3, for a Patient Typed as A*0201, A*3201, B*0702, B*1501, Cw*0401, Cw*0702, DRB1*0101, DRB1*0302

Allele Typing of Possible Donor	Allele Match for Patient
A*0201, A*3201, B*0702, B*1501, DRB1*0101, DRB1*0302	6 of 6 allele match, 6 of 6 antigen match
A*0205, A*3201, B*0702, B*1501, DRB1*0101, DRB1*0302	5 of 6 allele match, 6 of 6 antigen match
A*0205, A*3202, B*0702, B*1501, DRB1*0101, DRB1*0302	4 of 6 allele match, 6 of 6 antigen match
A*0205, A*3202, B*0705, B*1501, DRB1*0101, DRB1*0302	3 of 6 allele match, 6 of 6 antigen match
A*0205, A*3202, B*0705, B*1506, DRB1*0102, DRB1*0301	0 of 6 allele match, 6 of 6 antigen match

Defining a Mismatch

The word "mismatch" may be used differently, depending on the level of resolution of matching considered. For example, a 6 of 6 antigen match might contain allele mismatches (Table F-7). The term "low resolution mismatch" might be used for two individuals who differ for broad antigen groups such as DR1 vs DR3 (or DRB1*01 vs DRB1*03). This type of mismatch might also be called a "major" mismatch. A high resolution mismatch might refer to individuals who carry the same low resolution assignment but differ at the allele level, for example, DRB1*0102 versus DRB1*0103. This type of mismatch might be called a "minor" mismatch. The evidence supporting the difference between a major and minor mismatch in terms of importance to outcome is limited (16) and so-called "minor" mismatches may actually provoke strong allorecognition.

HLA Matching to Optimize Outcome in Marrow Transplantation

There are 12 HLA loci that could potentially impact outcome: A, B, C, DRA, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1. Various studies on marrow transplants using allele level typing for a subset of these loci to evaluate their impact on transplant outcome have somewhat different results (16, 54, 65, 66, 70, 74, 82). Differences among studies could arise because of differences in the resolution of HLA testing, the number of HLA loci considered, differences in the types of mismatches observed, study size, and other complex variables (disease, stage, age, treatment, etc.) (33).

Based on a study of transplants through their network and review of the literature, NMDP guidelines for marrow donations recommend matching at the allele level for HLA-A, -B, -C, and -DRB1 (33). For patients who have multiple, highly matched, suitable donors, there might be additional benefit from matching alleles of HLA-DQB1, -DPB1, and -DRB3/4/5. (The association between HLA-DQ and -DP mismatching and survival is controversial; the association of HLA-DRB3/4/5 mismatching and survival has not been studied.) There are no convincing data to show that deliberate HLA mismatching may be beneficial to achieve graft-versus-leukemia effects. Other groups have also proposed matching guidelines (61).

The availability of only HLA partially matched donors is not a contraindication to transplant. Many patients with mismatches can do well; however, there are no clear guidelines for selecting "permissive" mismatches. Limiting the number of mismatches is recommended (33). The latter requires more complex search strategies to identify the best donor.

HLA Testing at Recruitment and at the Time of Donor Selection

Strategies for HLA testing at the time of recruitment/banking are designed to obtain the best resolution for volunteer/unit selection and the greatest accuracy with the lowest possible cost (34, 35, 58). Usually HLA-A, -B and -DRB1 are typed. In general, low to intermediate resolution testing is used (Table F-8). However, with limited access to material for testing in cord units, the level of testing may be higher, since the ability to perform repeat testing may be limited. DNA testing is favored over serologic testing due to its consistency, accuracy, and increased resolution (32, 60). The higher the resolution of the patient typing at the time of search, the more specific the search (15, 33). However, patient searches carrying lower resolution assignments are often performed at the preliminary search stage, when the physician is evaluating alternatives for treatment.

During a search for a specific patient, a list of HLA types from potentially matched volunteers/units is provided by the registry to the patient's physician. From this list of potential matches, the transplant center selects individual volunteers for additional testing (Table F-9). Since some potential donors are typed only for HLA-A and -B but not for HLA-DR, HLA-DR typing may be required of HLA-A, -B matched potential donors for those patients who do not find an HLA-A, -B, -DR match in their initial search. Additional histocompatibility testing may be performed to include a higher level of resolution for the three primary HLA loci or to test additional histocompatibility loci such as HLA-C and -DQB1. Donors who appear to be potential HLA matches based on transplant center matching

TABLE F-8 Examples of HLA Typing Assignments Carried by Volunteer Donors on Registries

Recruitment Typing[a]	Typing Method, Resolution
A1,2, B7,8	Serology A and B, DR testing not done
A1,2, B7,8, DRB1*03XX, *15XX	Serology A & B, low resolution DNA-based DRB1
A*01XX, *02XX, B*07XX, *08XX, DRB1*03XX, *15XX	Low resolution DNA-based HLA-A, -B, -DRB1
A*01AB, *02MNK, B*07XX, *08AB, DRB1*03AD, *15MN	Low (XX) to intermediate resolution (AB, MNK, AD, MN) DNA-based HLA-A, -B, -DRB1

[a]National Marrow Donor Program defined allele codes, where AB, A*0101 or *0102; MNK, A*0202 or *0215N or *0221 or *0222 or *0223; XX, all alleles in that allele group; AD, DRB1*0301 or *0304; MN, DRB1*1501 or *1502 or *1503.

TABLE F-9 Steps in Donor Selection

Steps in Donor Selection	HLA Assignments
1—Recruitment of new volunteer	Low to intermediate HLA-A, B, DRB1
2—Selection of volunteer as potential match	Typing at time of selection is usually recruitment typing. A transplant center will select several (3–10) potentially matched donors if available and if resources are not limited for additional testing in step 3.
3—Additional HLA testing to evaluate match with patient. This step has various names (high-resolution testing, confirmatory typing, DR typing)	High- or intermediate-resolution DNA-based testing of HLA loci to determine match. Loci might include HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPA1, DPB1; the NMDP recommends high-resolution testing of A, B, C, DRB1 for matching and DRB3/4/5 and DQB1 if possible. The testing might be carried out on a sample from the NMDP DNA repository or on a fresh donor sample. If the sample comes from the repository, a fresh donor sample must be tested to insure identity of the repository sample (see below). The testing may be carried out in stages. Serologic testing of HLA class I as a screen to select the best matched donor and/or to monitor expression of antigens. Some centers use serologic testing as an initial screen to select donors for higher resolution DNA-based testing of HLA loci. In addition, this assay might also be used to monitor the expression of some HLA antigens if null or nonexpressed HLA alleles are expected. Only HLA class I is tested; class II null alleles are usually not evaluated due to the poorer quality of the serology.
4—Workup (time at which a selected donor undergoes medical testing to evaluate if medically fit to donate)	A fresh donor sample is required to confirm that the donor is indeed the person identified as a potential match and to confirm the HLA assignment. The DNA-based testing may be various levels of resolution for various HLA loci. It may, for example, confirm the identity using low resolution A, B, DRB1 testing or may retest alleles at these and other loci. The status of the patient might be considered in deciding on the resolution; high-risk patients might require a less stringent check of donor allele identity than low-risk patients because their urgent status indicates a rapid decision regarding transplant. The transplant center will check blood type at the time of transplant to confirm identity.

criteria are requested for confirmatory typing (CT). At this stage, a fresh blood sample from the donor and the patient are tested to confirm HLA identity.

Quality control of the donor HLA database is critical to speed the search for donors and to identify all suitable matches. This quality control may include requiring HLA typing laboratory accreditation, establishing a registry program for proficiency testing at the time of recruitment typing (32, 60), comparison of recruitment typing to repeat CT (31), use of automated systems for HLA data entry and submission, and reanalysis of primary typing data in the registry (49).

Selection of Potential HLA Matches by Registry Search Algorithms

Two sets of criteria are used to determine the minimal HLA match between patient and a specific donor. The first set contains the criteria a registry or bank might have regarding how closely the donor must be matched to the patient to allow the donor to be used for transplant. In general, these guidelines are meant to protect the adult volunteer donor from undergoing the risks of donation for a transplant that is likely to fail. This also prevents cord blood units from being used for a transplant that is likely to fail. A second set of match criteria are dictated by the transplant center protocols and are usually more stringent than those used by the registry or bank.

Since a volunteer donor or unit might be HLA typed several times (Table F-9), the registry must have an approach to incorporate and prioritize the updated information while maintaining older information in a history file. Since the newer HLA typing is usually, but not always, at a higher resolution, a computer algorithm (supplemented by staff review) should prioritize which HLA assignment to use in the match algorithm. For example, data for additional HLA loci may be added or the resolution of existing HLA types may be altered during confirmatory typing.

Since an HLA typing may be obtained by serology or DNA and at various levels of resolution, comparison of patient and donor assignments is a complex process (45, 53, 55). As an example, the allele A*0201 can be found within 844 different assignments submitted to the NMDP registry (Table F-10). Often the HLA typing result is converted into an assignment called a search determinant to provide a rapid comparison for finding a potentially matched donor (36). The goal is to identify all potentially matched donors yet to keep the list short and exclude suboptimal donors. The report listing potential donors is often sorted so that the best matched donors might be easily identified. Strategies to identify and prioritize mismatched donors on search reports are also complex.

PROBABILITY OF FINDING AN ALLELE MATCH FOR HLA LOCI

The probability of finding an allele match for specific patients varies dramatically (2, 53). Patients with common alleles and common haplotypes will find many allele matched donors. The probability of a low resolution typed volunteer selected as a potential match carrying the same alleles as one of these patients is very high. In contrast, some patients have fairly common HLA alleles but they have uncommon haplotypes (the collection of alleles carried on a chromosome). In these cases it can be extremely difficult to find matched donors. Some patients have rare alleles and these are also difficult to find matches for unless the allele is found in a conserved haplotype.

Within the NMDP registry, it is calculated that 85 percent of individuals find 6 of 6 antigen matches (31). In an evaluation of 1422 NMDP transplants matched at the 6/6 antigen level, 28 percent carried allele mismatches at HLA-A, -B and/or -DRB1 and most carried mismatches at other HLA loci, predominantly DP (29) (Table F-10). Selection of six antigen matched donors did not result in allele matching throughout the HLA complex in 92 percent of the cases, in 50 percent if DP was ignored (29). Of the 6 of 6 antigen matches undergoing transplant, the probability of finding a 6 of 6 allele match is about 72 percent, a 10 of 10 allele match is about 50 percent, and a 12 of 12 match is 11 percent. The chance of finding a 6 of 6

TABLE F-10 Summary of HLA Matches at Each Locus in 6/6 Antigen Matched Donor-Recipient Pairs (n = 1422) from NMDP (29)

		Mismatched at Allele Level (%)[b]		
Locus	Matched at Allele Level (%)[a]	Total Mismatches[b]	1 Allele Mismatched	2 Alleles Mismatched
A	1355 (92)	107 (8)	105 (7)	2 (0)
B	1217 (86)	205 (14)	192 (14)	13 (1)
C	986 (69)	436 (31)	382 (27)	54 (4)
DRB1	1225 (86)	197 (14)	184 (13)	13 (1)
DQA1[d]	1258 (88)	164 (12)	154 (11)	10 (1)
DQB1[d]	1183 (83)	239 (17)	224 (16)	15 (1)
DPA1[d]	791 (56)	631 (44)	563 (40)	68 (5)
DPB1[d]	192 (14)	1230 (86)	794 (56)	436 (31)

[a]Both alleles at the locus are identical in donor and recipient.
[b]One or both alleles are mismatched.
NOTE: These are patients with common types who may have undergone further testing to select the best donor.

TABLE F-11 Summary of HLA Matches at Each Locus in 5/6 Antigen Matched Donor-Recipient Pairs (n = 429) (29)

	Matched at Allele Level (%)[a]			
		Antigen Mismatched Locus[b]		
Locus	Total	HLA-A (n = 203)	HLA-B (n = 186)	HLA-DRB1 (n = 40)
A	180 (42)	0 (0)	146 (78)	34 (85)
B	178 (41)	151 (74)	0 (0)	27 (68)
C	136 (32)	106 (52)	14 (8)	16 (40)
DRB1	328 (76)	183 (90)	145 (78)	0 (0)
DQA1	338 (79)	184 (91)	150 (81)	4 (10)
DQB1	299 (70)	165 (81)	130 (70)	4 (10)
DPA1	224 (52)	107 (53)	96 (52)	21 (53)
DPB1	45 (10)	23 (11)	17 (9)	5 (13)

[a]Both alleles at the locus are identical in donor and recipient.
[b]The mismatched antigen giving rise to the 5/6 match status. When the pairs were intentionally mismatched at a locus, there were no allele matches at that locus (e.g., the 203 pairs with HLA-A antigen mismatches had no pairs matched for HLA-A alleles).

antigen match for minorities is lower, 65 percent for an African American patient, and probability of allele matching has not yet been evaluated.

The level of allele matching in the 5/6 matched pairs is lower than 6/6 antigen matched pairs; however, the lower percentage of matching did not derive solely from the known mismatch. For example, in the 5/6 matched pairs in which the known mismatch was at the HLA-A locus (n = 203), only 74 percent of the HLA-B and 52 percent of the C loci were matched for both alleles (Table F-11). Likewise, in the 5/6 matched pairs with a known HLA-B antigen mismatch (n = 186), only 78 percent of the pairs were matched at the HLA-A locus and 8 percent at the HLA-C locus (29).

Optimizing Registry Size to Find a Match

Defining the optimal size of a registry is a public policy decision (44). Competing goals have to be balanced: (1) maximizing the number of patients who find a suitably matched donor, (2) providing comparable access to transplantation for patients regardless of race, and (3) containing costs. Definition of a "suitable match" must be defined based on the clinical outcome literature. The resolution of the registry typing will determine how accurately the probability of a match for searching patients can be predicted.

The extensive diversity of HLA alleles and haplotypes makes it very

unlikely that a patient will match any given unrelated individual. This diversity requires a large donor registry to provide suitably HLA-matched donors for patients. If cord blood allows more mismatching, the required size of such a bank will likely be smaller (3). Even with over 9 million volunteer donors worldwide, there are still significant numbers of patients who fail to identify a donor (31). Racial/ethnic minority patients have a lower likelihood of finding an unrelated donor, resulting in part from a small number of minority volunteer donors available in registries and the greater HLA polymorphism for some of these groups (2). In the United States, there are more white patients than minorities failing to find a matched donor.

Unfortunately, each additional volunteer added to a registry is less likely to carry a new set of HLA assignments and is more likely to carry a type already found in the registry (56). As a result, continued recruitment does improve the likelihood of finding an HLA-matched donor but still leaves many patients without a match. The number of patients without a donor will depend on the level of match required for a successful outcome. Published studies on the probability of finding a match are based on matching at a low resolution level, since most volunteers are typed at this level. These studies likely overestimate the likelihood of finding matches because, in practice, many transplant centers define an acceptable match at an allele level of resolution.

RESEARCH

Registries/Cord Blood Banks as Repositories of Extensive HLA Data

As large repositories of HLA and often clinical data, registries/banks should have the resources to analyze this information to direct registry recruitment (e.g., evaluate HLA diversity to serve searching patients), to refine search and matching algorithms, to create search tools, and to define matching requirements for optimal outcome (52, 71, 72). Access to expertise in informatics, population genetics, and histocompatibility is essential to capitalize on this wealth of information.

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Statistical Report

ANALYSIS OF THE NYBC, NMDP, AND NHLBI CORD BLOOD DATA

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OVERVIEW

This brief report outlines the results of an analysis of the combined New York Blood Center (NYBC), National Marrow Donor Program (NMDP), and the National Heart, Lung, and Blood Institute (NHLBI) Cord Blood Banking and Transplantation (COBLT) study cord blood datasets. The objective of the analysis was to examine the determinants of long-term survival of patients who received cord blood transplants during the period from 1993 to 2004. In doing so, we simultaneously examined the time to transplant failure (i.e., failure to engraft with donor cells) and mortality using a competing risk survival model. As such, we can estimate cumulative time-to-event curves for transplant failure, mortality, and survival. These curves can in turn be compared between subpopulations characterized by cell dose and human leukocyte antigen (HLA) mismatch, the two primary variables that are the focus of our analysis. These comparisons can be further adjusted for case-mix variability in terms of age, weight, sex, race, cytomegalovirus (CMV) infection, disease type, and disease severity. Based on the statistical model, we can draw inferences regarding the effects of cell dose and HLA mismatch on long-term survival, transplant failure, and death. These statistical inferences can then be used to derive policy statements regarding which combinations of cell dose and HLA mismatch are acceptable in order to optimize long-term survival.

METHODS

The median length of follow-up of these patients was 4 months, with a range of 1 to 129 months (time to death or length of living at follow-

up). The data were analyzed using a person-time competing risk survival model (see Gibbons et al., 2003), in which the competing risks were death or transplant failure. Transplant failure included failure to engraft or autologous reconstitution (i.e., engraftment with the recipients own cells). In those cases in which engraftment time was not recorded, it was set to time of autologous reconstitution, or time of backup transplant, or time of death. If none of these events occurred (n = 43 cases), engraftment time was set to 31 days, which is the value recommended by NYBC. The primary variables of interest were the degree of HLA match (low/intermediate at HLA-A and HLA-B and high resolution for HLA-DRB1), and the total nucleated cells per kilogram (TNC/kg), expressed as low ($<2.5 \times 10^7$ cells/kg), medium (2.5 to 5.0×10^7 cells/kg), and high ($>5.0 \times 10^7$ cells/kg). The primary hypotheses were that (1) an imperfect match decreases survival time by increasing transplant failure and mortality, and (2) an increase in cell dose increases survival time by decreasing transplant failure and decreasing the rate of mortality. To adjust for case mix, the covariates of time (in months), age, weight (kg), disease type (leukemia versus genetic or other), risk (0 to 3 on the International Bone Marrow Transplant Registry [IBMTR] scale), race, sex, and CMV infection were also included in the analysis. Site was added to the model to adjust for overall differences among the three sites in both transplant failure and mortality rates. The NYBC Blood Bank provided all transplants from 1993 through 1998 (n = 562). NMDP provided all transplants for their blood banks for which consent for outcomes research was obtained, in which presumed consent was assumed for patients who died before they could provide consent (n = 192). This occurred because for many cases consent was obtained retrospectively. NHLBI provided all on-study (COBLT study) protocol cases that received a COBLT study cord blood unit (n = 210). The final data set comprised 755 cases (NYBC, n = 384; NMDP, n = 165; NHLBI, n = 206) after exclusion of patients with prior transplants, HLA matches of less than 4/6, cases with missing data, and transplants that were not conducted in the United States.

Two model parameterizations were used. The first was a main-effects model, and the second included the interaction between cell dose and HLA mismatch. The second, more flexible model allows the effect of cell dose to vary depending on the degree of HLA mismatch. Both models included case-mix adjustment for the previously mentioned covariates. The main-effects model provides a more easily interpretable test of the two primary null hypotheses, whereas the model with cell dose-by-HLA interaction better reproduces the observed proportions of patients who survived, had transplant failures, and died.

One-tailed statistical tests were used to test HLA and TNC/kg effects; otherwise, two-sided tests were used to test the case-mix covariates.

RESULTS

Table G-1 displays the summary statistics for all variables used in the analysis by outcome (alive, dead, and failure to engraft with donor cells). Table G-1 reveals that of the three blood banks, NHLBI had the highest survival rates ($p < .021$). This finding is consistent with the fact that the NHLBI COBLT study was a controlled trial with entrance criteria that may have excluded some patients with potentially poorer outcomes. Furthermore, the data from NYBC were for an earlier period in time (1993 to 1998), and may reflect higher mortality rates because of the use of the older technology available at that time. By contrast, the NMDP had the highest transplant failure rate. One must be careful about interpreting these results, given that the different sites sampled different populations during different time periods, and these different populations may not have been fully represented by the case-mix adjustment in the model. Nevertheless, the use of three different sites provides a result that is more generalizable to the entire U.S. population.

TABLE G-1 Summary Statistics Predictors by Outcome (n = 755 Transplants)

		Outcome			
Predictor		Alive	Dead	Engraftment Failure	Probability
N		323	214	218	
Site	NYBC	0.41	0.32	0.28	
	NMDP	0.39	0.24	0.36	
	NHLBI	0.50	0.25	0.25	.021
Leukemia	Yes	0.64	0.67	0.73	.071
Sex	Female	0.41	0.42	0.44	.802
Race	African American	0.06	0.17	0.13	.001
CMV	Positive	0.40	0.48	0.45	.182
HLA	6/6	0.61	0.23	0.15	
	5/6	0.48	0.25	0.28	
	4/6	0.35	0.33	0.32	.001
Age (yr)		3.76	5.49	6.51	.006
Weight (kg)		13.03	15.46	17.62	.065
Risk IBMTR		1.18	1.41	1.60	.001
TNC/kg (10^7)		7.01	6.33	5.43	.015

Table G-1 also reveals that for the surviving patients, blacks represented only 6 percent of all patients but represented 17 percent of the patients who engrafted and then died and 13 percent of the patients who failed to engraft ($p < .001$). HLA mismatch shows that patients with a perfect match had increased survival rates, decreased death rates, and higher engraftment rates than mismatched patients in general and patients matched at 4/6 antigent in particular ($p < .001$). Age was related to outcome, where surviving patients were younger (3.76 years) than patients who died (5.49 years) and patients who failed to engraft (6.51 years) ($p < .006$). Differences in weight paralleled those found for age ($p < .065$). Surviving patients had lower IBMTR risk scores (1.18) than patients who died (1.41) or patients who failed to engraft (1.60) ($p < .001$). Finally, higher TNC/kg ratios were found for surviving patients (7.01×10^7 TNC/kg) relative to those ratios for those who died (6.33×10^7 TNC/kg), and those in whom engraftment failed (5.43×10^7 TNC/kg) ($p < .015$).

Table G-2 contains the maximum-likelihood estimates, standard errors, and probability values for the main-effects model. In terms of death versus survival, mortality rates decreased over time (the month variable in Table G-2, which indicates the time to the event in months; $p < .001$); older age significantly increased the likelihood of death ($p < .027$), as did race other than Caucasian ($p < .004$). As previously noted, the NHLBI COBLT study had lower mortality rates than the NYBC site ($p < .045$). In terms of cell dose, both the medium ($p < .003$) and high ($p < .046$) cell doses significantly decreased the rate of mortality from that achieved with the low cell dose. The same was true for high versus low TNC/kg on engraftment ($p < .002$). Similarly, a 4/6 HLA match increased the rate of mortality relative to that of a 6/6 HLA match ($p < .008$), and both 4/6 and 5/6 HLA matches increased the engraftment failure rate relative to that achieved with a 6/6 match ($p < .002$ and $p < .007$ respectively).

The model with cell dose-by-HLA mismatch interactions improved the fit of the model to the data to a degree that approached significance ($p < .096$). For mortality, significant interactions for high cell dose versus low cell dose by 4/6 HLA match ($p < .035$) and 5/6 HLA match ($p < .011$) were found, which indicated that the differences between a perfect match (6/6) and imperfect matches (4/6 and 5/6) significantly decreased with increasing cell dose. No significant interactions were found for treatment failure. To illustrate these effects, the parameter estimates for the model with interactions were used to obtain case-mix-adjusted estimated proportions (see Table G-3). Table G-3 reveals that the model does an excellent job of tracking the observed data, despite the relatively small sample sizes, particularly for 6/6 of HLA matches (i.e., the predicted proportions are close to the observed proportions). In terms of survival, dramatic differences are observed between imperfect matches (4/6 and 5/6) and a perfect match (6/

TABLE G-2 Maximum Likelihood Estimates, Standard Errors, and Probabilities Main Effects Model

Variable	Estimate	Standard Error	Z	p value
Dead vs. Alive				
Intercept	–2.73475	0.37533	–7.28628	.00000
Month	–0.13208	0.00906	–14.57568	.00000
Age	0.02265	0.01021	2.21911	.02648
Weight (kg)	–0.00519	0.00620	–0.83705	.40257
Leukemia	–0.35251	0.26778	–1.31640	.18804
Risk	0.18298	0.10609	1.72487	.08455
Sex (female)	–0.00246	0.15148	–0.01622	.98706
Race (black)	0.57549	0.19849	2.89933	.00374
CMV	0.18812	0.15245	1.23396	.21722
TNC/kg medium vs. low	0.62626	0.22513	–2.78181	.00271
TNC/kg high vs. low	0.44457	0.26332	–1.68832	.04568
HLA 5/6 vs. 6/6	0.36007	0.28361	1.26957	.10212
HLA 4/6 vs. 6/6	0.67548	0.28213	2.39424	.00833
NMDP vs. NYBC	0.00482	0.20431	–0.02358	.98119
NHLBI vs. NYBC	0.36697	0.18294	–2.00598	.04486
Engraftment Failure vs. Alive				
Intercept	–1.39919	0.45306	–3.08834	.00201
Month	–0.79460	0.12055	–6.59149	.00000
Age	0.01562	0.00954	1.63613	.10181
Weight (kg)	–0.00834	0.00571	–1.46062	.14412
Leukemia	–0.27092	0.26109	–1.03764	.29944
Risk	0.25370	0.10328	2.45647	.01403
Sex (female)	0.14352	0.15087	0.95132	.34144
Race (black)	0.15866	0.21846	0.72629	.46766
CMV	–0.03539	0.15221	–0.23253	.81613
TNC/kg, medium vs. low	–0.23414	0.21963	–1.06607	.14320
TNC/kg, high vs. low	0.80524	0.27153	–2.96561	.00151
HLA 5/6 vs. 6/6	0.81424	0.32836	2.47969	.00658
HLA 4/6 vs. 6/6	0.99567	0.33598	2.96350	.00152
NMDP vs. NYBC	0.48969	0.19458	2.51661	.01185
NHLBI vs. NYBC	–0.02394	0.19630	–0.12194	.90294

6) for low cell doses. The difference is approximately 40 percent in 2-year survival (see Table G-3 and Figure G-1). As cell dose increases, the HLA effect decreases. Although this finding is biologically questionable, the highest cell dose for a 6/6 match yielded a lower survival rate than the low and medium cell doses. This effect may simply be due to the small number of 6/6 HLA matches in the combined database (n = 34, see Table G-3). In terms of mortality, large differences between imperfect and imperfect matches

TABLE G-3 Estimated (Observed) Cumulative Competing Risk Survival Functions Proportion Experiencing the Event

	HLA Match		
Outcome and TNC/KG $\times 10^7$	4/6	5/6	6/6
2-Year Survival Rates			
<2.5	0.27 (0.18)	0.27 (0.22)	0.64 (0.60)
2.5–5.0	0.39 (0.36)	0.49 (0.48)	0.73 (0.71)
>5.0	0.44 (0.46)	0.57 (0.57)	0.54 (0.56)
2-Year Mortality Rates (Engrafted)			
<2.5	0.38 (0.43)	0.36 (0.36)	0.19 (0.20)
2.5–5.0	0.27 (0.28)	0.21 (0.20)	0.11 (0.10)
>5.0	0.34 (0.30)	0.26 (0.23)	0.37 (0.32)
3-Month Engraftment Failure Rates			
<2.5	0.33 (0.39)	0.35 (0.42)	0.16 (0.20)
2.5–5.0	0.31 (0.36)	0.27 (.032)	0.15 (0.19)
>5.0	0.21 (0.24)	0.16 (0.20)	0.09 (0.12)
Sample Sizes			
<2.5	95	59	20
2.5–5.0	132	94	21
>5.0	144	156	34

NOTE: Estimated proportions are adjusted for case mix. Observed rates do not consider time.

were seen for the lowest cell dose, but these differences decreased with the medium cell dose, and then increased with the highest cell dose (relative to the medium cell dose). The effect of the highest cell dose on mortality should be the subject of further investigation, since there is no apparent biological explanation. In terms of treatment failure, patients with 6/6 matches exhibited dramatically decreased rates of engraftment failure relative to those for patients with 4/6 and 5/6 HLA matches for all cell doses; however, the HLA effect decreased with increasing cell dose.

To further illustrate the magnitudes of these effects, the cumulative survival distributions for each HLA group and TNC/kg group are displayed in Figures G-1 to G-3. The figures provide estimated cumulative survival distributions out to 5 years. The most striking effect is displayed in Figure G-1 for the low cell dose, in which patients treated with units with 4/6 and 5/6 matches have virtually identical survival distributions that are approximately one-third of that seen for a perfect 6/6 match. This finding makes us question whether anything less than a perfect match should be considered for use in transplantation with a cell dose of 2.5×10^7 TNC/kg or less.

Finally, we tested the assumption underlying the use of the ratio TNC/kg. By taking the ratio, we must assume that the effects of TNC and weight

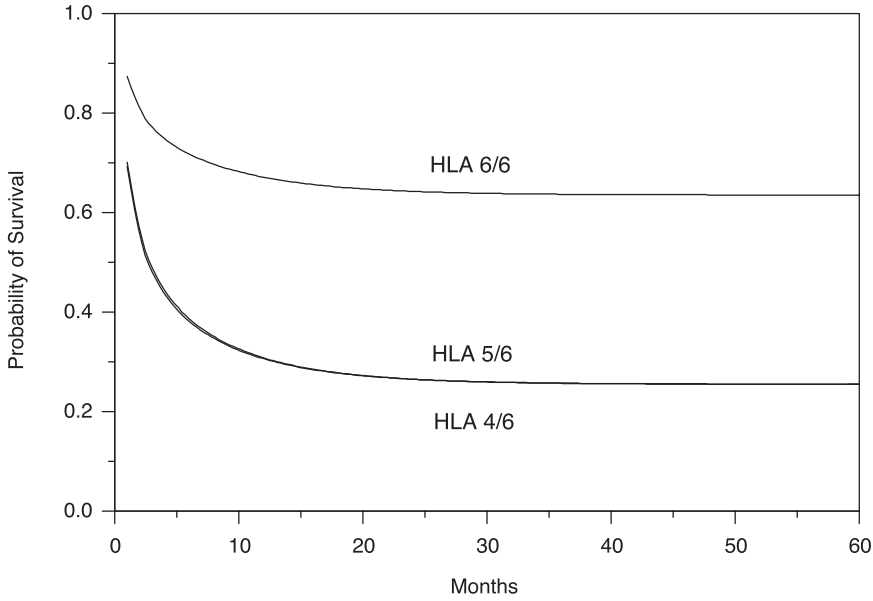

FIGURE G-1 Cumulative proportion alive (engrafted) (TNC/kg < 2.5×10^7).

are equally weighted in the ability to predict death and engraftment failure. Mathematically, the regression model is $y = [a \times \log(TNC)] + [b \times \log(kg)]$ and the basic ratio assumption is that a is equal to –b (since increased TNC/kg is associated with a decreased risk of death and/or a decreased rate of failure to engraft). Adjusting for HLA mismatch, we found that for mortality, *a* was equal to –0.19 and *b* was equal to 0.36, whereas for engraftment failure *a* was equal to –0.32 and *b* was equal to 0.44. These findings support the use of the ratio TNC/kg for the modeling of cord blood transplant outcomes.

DISCUSSION

The results of this analysis reveal that if we take the competing risks of mortality and engraftment failure into consideration and adjust for disease type, risk, age, weight, CMV infection, sex, race, and time, the cumulative survival benefits for 4/6 and 5/6 HLA matches are grossly inferior to a perfect 6/6 HLA match for small cell doses (<2.5×10^7 TNC/kg). As cell

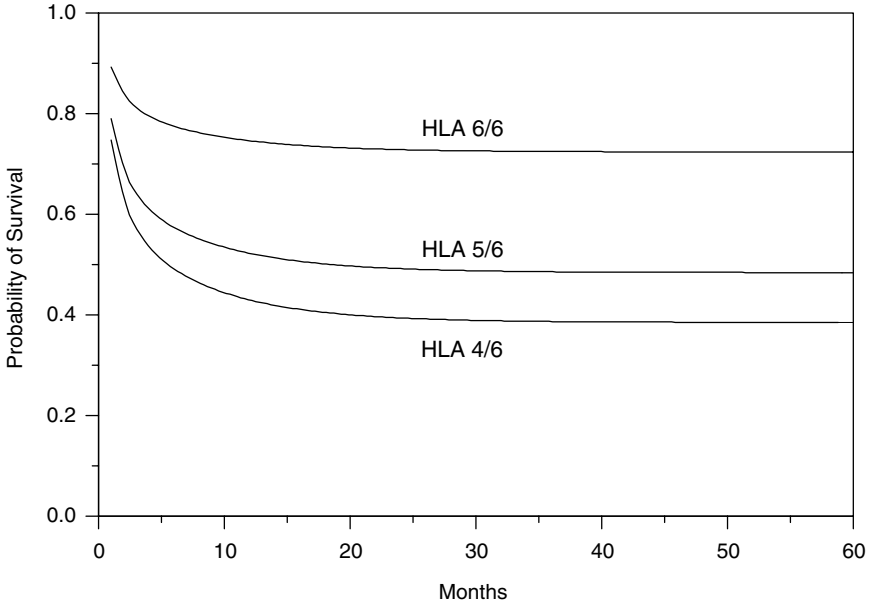

FIGURE G-2 Cumulative proportion alive (engrafted) (TNC/kg = $2.5 - 5.0 \times 10^7$).

dose increases, the HLA effects diminish. The residual differences are largely due to the significantly reduced engraftment rates for 4/6 and 5/6 HLA matches relative to that for a perfect 6/6 HLA match. These results suggest that units with lower cell dose can be given to recipients with a perfect match, whereas the highest cell doses should be given to recipients with 4/6 or 5/6 HLA matches, assuming that two potential recipients are in competition for the same unit. Table G-4 presents a breakdown of cell dose by HLA matches. Table G-4 reveals that 20 percent of all transplants were conducted with low cell doses in patients with 4/6 and 5/6 HLA matches. This amounts to 154 patients for whom the survival rate could have been doubled by use of a medium cell dose, or almost tripled by use of a high cell dose. In addition, 7 percent of all transplants were done using medium or high cell doses in perfectly matched (6/6) patient-donor pairs. These larger cell doses could have potentially been used to increase survival for 4/6 or 5/6 mismatched patients, without compromise to the 6/6 patient had a similar unit with smaller cell dose been available. These two results indicate that over 25 percent of the actual transplants were inefficiently allocated, leading to either unnecessarily poor survival or the use of an unnecessarily high cell dose for a patient-donor pair with a 6/6 HLA match. Both cell dose and HLA match should be considered in the final allocation system.

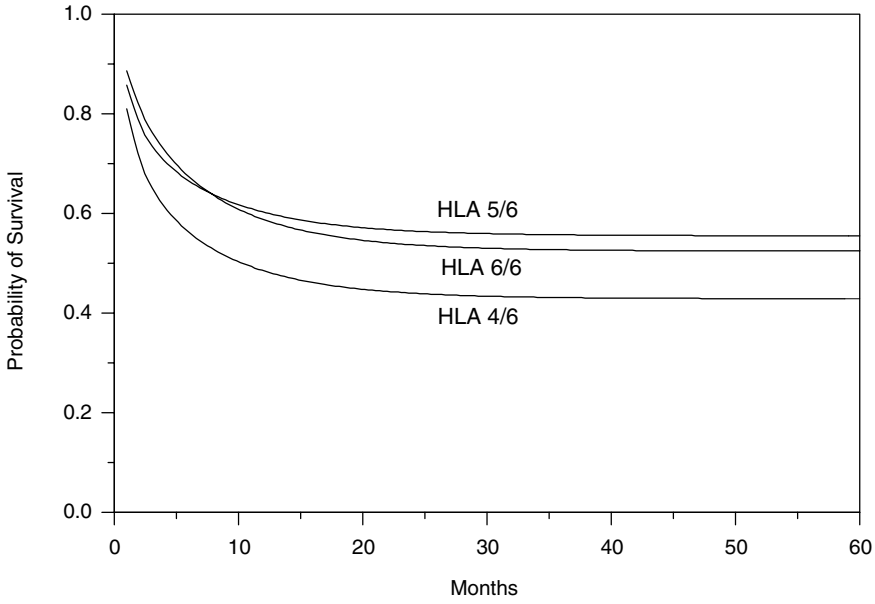

FIGURE G-3 Cumulative proportion alive (engrafted) (TNC/kg > 5.0×10^7).

TABLE G-4 Summary Statistics Cell Dose, Age, and HLA Mismatch, Number (Percent) of Patients (n = 755 Transplants)

	Age (yr)			HLA		
TNC/kg (10^7)	<5	5–16	>16	4/6	5/6	6/6
<2.5	118 (68)	21 (13)	35 (20)	95 (54)	59 (34)	20 (12)
2.5–5.0	157 (64)	70 (28)	20 (8)	132 (54)	94 (38)	21 (9)
>5.0	265 (79)	63 (19)	6 (2)	144 (43)	156 (47)	34 (10)

There are several limitations of this analysis. First, despite the pooling of data from all three major cord blood banks, the sample size is still small, given the large number of effects estimated from these data and the separate set of coefficients for the two competing risks. Second, there are only a small proportion of patients with a perfect 6/6 HLA match. Third, age and

cell dose are confounded in that only young children are capable of receiving high cell doses. For example, Table G-4 reveals that only 2 percent of the high cell doses were transplanted into patients over 16 years of age. Since cell dose is expressed as TNC/kg, presumably there are few units that have sufficient numbers of cells to yield ratios above 5×10^7 TNC/kg for adults. Research into the viability of combining multiple units for a single transplant should be investigated. Finally, analysis of larger datasets with larger cell volumes and greater numbers of perfectly matched recipients is needed to confirm these preliminary results.

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Biographical Sketches of Committee Members and Staff

KRISTINE M. GEBBIE (*Chair*) is the Elizabeth Standish Gill Associate Professor of Nursing, director for the Center for Health Policy, and the director of the Doctor of Nursing Science Program at Columbia University School of Nursing. Her teaching and research focus is on health policy and health services, with particular attention to population-based health services. Prior to Columbia, she was the first White House National AIDS Policy Coordinator (1993–1994) and served 4 years as a senior consultant on health initiatives to the Office of Public Health and Science for the U.S. Department of Health and Human Services. Dr. Gebbie is active in many professional organizations and has served as a member on the executive board of the American Public Health Association. Most recently, her completed research includes the first enumeration of the public health workforce in 20 years, and the development of core competencies in emergency preparedness for public health workers. Among her previous Institute of Medicine (IOM) committee experience, Dr. Gebbie served as the vice chair of the Committee on Smallpox Vaccination Program Implementation, and co-chair on the Committee on Educating Public Health Professionals for the 21st Century. Dr. Gebbie received her master's of nursing from the University of California, Los Angeles, and her doctorate in public health from the University of Michigan School of Public Health. She is a member of the Institute of Medicine.

WADE M. AUBRY is a senior advisor with the Health Technology Center. In this capacity he produces forecast reports on such subjects as the future of stem cells, genetic testing, cancer pharmaceuticals, and remote patient

management. He also serves as associate physician diplomate at the UCSF Institute for Health Policy Studies, a health care consultant, and has a practice in internal medicine and endocrinology. Dr. Aubry also served as a medical consultant for Blue Cross Blue Shield Association until 2002. In that capacity he represented their system in a number of national roles related to health and disease management, technology assessment and coverage decision making, research initiatives, performance measurement, CPT coding, and quality of care. Dr. Aubry is a member of the Medicare Coverage Advisory Committee and also served on the IOM Committee on Technologies for Early Detection of Breast Cancer and as a member of the IOM Clinical Research Roundtable. He is a member of the American College of Physicians, the American Medical Association, the California Medical Association, and the Academy for Health Services Research and Health Policy, among others. Dr. Aubry has published in a wide variety of periodicals on subjects ranging from managed care to balancing science, economics, and policy. He earned his B.S. in biological sciences from Stanford University and his M.D. degree from the University of California Los Angeles.

RICHARD CHAMPLIN is chairman, professor of medicine, Department of Blood and Marrow Transplantation Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, and associate head, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center. Dr. Champlin is the 2004 winner of the Thomas Lecture Award of the American Society for Blood and Marrow Transplantation. He is president of the Autologous Bone Marrow Transplant Registry and a member of the American Society for Blood and Marrow Transplantation, the American Society of Hematology, and the International Society for Cell Therapy. Dr. Champlin has published more than 300 articles in peer-reviewed journals and edited or written 9 books. He serves as an editor of *Biology of Blood and Marrow Transplantation,* a regional editor of *Cytotherapy,* and an associate editor of *Experimental Hematology*. Dr. Champlin earned his B.S. in engineering sciences from Purdue University and his M.D. from the University of Chicago Pritzker School of Medicine.

JAMES F. CHILDRESS is the John Allen Hollingsworth Professor of Ethics and professor of medical education at the University of Virginia, where he teaches in the Department of Religious Studies and directs the Institute for Practical Ethics and Public Life. He served as chair of the Department of Religious Studies, 1972–1975 and 1986–1994, as principal of UVA's Monroe Hill College from 1988 to 1991, and as codirector of the Virginia Health Policy Center 1991–1999. In 1990 he was named Professor of the Year in the state of Virginia by the Council for the Advancement and

Support of Education, and in 2002 he received the University of Virginia's highest honor—the Thomas Jefferson Award.

Childress is the author of numerous articles and several books in biomedical ethics, including *Principles of Biomedical Ethics* (with Tom L. Beauchamp), now in its fifth edition and translated into several other languages; *Priorities in Biomedical Ethics*; *Who Should Decide? Paternalism in Health Care*; and *Practical Reasoning in Bioethics*, along with a number of articles and books in other areas of ethics.

Childress was vice chair of the national Task Force on Organ Transplantation, and he has also served on the board of directors of the United Network for Organ Sharing (UNOS), the UNOS Ethics Committee, the Recombinant DNA Advisory Committee, the Human Gene Therapy Subcommittee, the Biomedical Ethics Advisory Committee, and several Data and Safety Monitoring Boards for National Institutes of Health clinical trials. He was a member of the presidentially appointed National Bioethics Advisory Commission 1996–2001.

Childress is an elected member of the Institute of Medicine and a fellow of the American Academy of Arts and Sciences. He is also a fellow of the Hastings Center.

He has been the Joseph P. Kennedy, Sr., Professor of Christian Ethics at the Kennedy Institute of Ethics at Georgetown University (1975–79) and a visiting professor at the University of Chicago Divinity School and Princeton University. He received his B.A. from Guilford College, his B.D. from Yale Divinity School, and his M.A. and Ph.D. from Yale University.

CHARLES FISKE founded and spent 10 years as the director of the National Organ Transplant Action Committee, an organ transplant patient advocacy organization. Since 1986, he has also served as the director of the Family Inn Foundation. This foundation established and operates temporary housing for families of medical patients. Mr. Fisk is also a senior executive of Brockton Area Multi-Services, Inc. This agency runs over 120 human services programs in Massachusetts which specialize in mental health, developmental disabilities, education, public health, informational, elderly, and children's services. Mr. Fiske coordinates all aspects of the agency's communication, government relations, and developmental needs. He served as a reviewer of the IOM's "Organ Procurement and Transplantation" report. Mr. Fiske holds a B.A. and an M.Div. from St. John's College and an M.Ed. from Boston State University. He is a licensed clinical social worker.

ROBERT D. GIBBONS is a professor of biostatistics, psychiatry, and director of the Center for Health Statistics at the University of Illinois at Chicago. He received his doctorate in statistics and psychometrics from the

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N. REBECCA HALEY is currently serving as vice president of StemCo Biomedical, Inc., directing regulatory policy, quality assurance programs, and medical and clinical studies. Prior to that position, Dr. Haley served as the senior medical officer for cell therapy at the American Red Cross. There she was responsible for overseeing National Marrow Donor Program-American Red Cross donor recruitment and collection activities at 23 centers, and managed the applications for the programs associated with the National Marrow Donor Program on a national level. Dr. Haley is a member of the American Society of Hematology, the American Association of Blood Banks, the International Society of Cell Therapy, the International Society, and a diplomate on the National Board of Medical Examiners. She is widely published on the subject of blood and banking operations. Dr. Haley holds a B.S. in medical technology from the University of North Carolina Chapel Hill and an M.D. from Eastern Virginia Medical School.

MARY M. HOROWITZ is the scientific director of the International Bone Marrow Transplant Registry. In addition to that role, she also serves as a professor in the Health Policy Institute at the Medical College of Wisconsin, as interim director of the Bone Marrow Transplant Program at the Medical College of Wisconsin, and as chair of hematologic research in the division of neoplastic diseases and related disorders at the Medical College of Wisconsin. She is on the board of directors at the National Marrow Donor Program. Among other professional activities, Dr. Horowitz served on the ad hoc Cord Blood Advisory Committee at the National Heart, Lung, and Blood Institute, was an invited participant in the National Cancer Institute/National Heart, Lung, and Blood Institute's workshop on clinical trials in transplantation, and served on the American Society for Clinical

Oncology's expert panel on stem cell transplantation. She is a member several professional organizations, including: the American Society for Clinical Oncology, the American Society for Hematology, the International Society for Experimental Hematology, and the World Marrow Donor Association. Dr. Horowitz has written well over 150 articles in reviewed journals, and more than 30 book chapters. She sits on the editorial boards of several journals, including: *Blood, Bone Marrow Transplantation*, and *Biology of Blood and Marrow Transplantation*. She earned her B.S. in zoology from the University of Wisconsin-Milwaukee, her M.D. from the Medical College of Wisconsin, and her M.S. in biostatistics/clinical epidemiology from the Medical College of Wisconsin.

SUZANNE T. ILDSTAD is director of the Institute for Cellular Therapeutics (ICT), the Jewish Hospital Distinguished Professor of Transplantation, and professor of surgery at the University of Louisville. ICT is a multidisciplinary translational research program designed to develop cellular therapies and rapidly transfer them from the laboratory to the clinic.

Dr. Ildstad's research focuses on developing methods to make bone marrow transplantation safe enough for widespread application to treat autoimmune diseases, to induce tolerance to organ and islet cell transplants, and to treat hemoglobinopathies like sickle-cell disease and thalassemia. She is credited with the first discovery of "facilitator cells," bone marrow cells that enhance engraftment of bone marrow stem cells while avoiding graft-versus-host reactivity. She also pioneered the use of mixed chimerism to induce tolerance to allografts and xenografts. More recently her work has focused on stem cell plasticity for regeneration of damaged organs, including cardiac and retinal tissue. She holds numerous patents related to her research and is the founding scientist of Regenerex, L.L.C., and a biotechnology company whose vision is to provide an engineered bone marrow graft to improve the safety of bone marrow transplantation.

She was elected to the Institute of Medicine (IOM) in 1997 and has served on the committee for human rights (1999 to present) as well as on IOM committees studying organ transplantation policies (1999), multiple sclerosis research strategies (2001), the challenges of small clinical trials (2001), a fast-track committee which she chaired, and spinal cord injury: strategies in a search for a cure (2003–2005).

LINDA L. KELLEY is the director of the Hematopoietic Stem Cell Laboratory, Department of Medicine at the University of Utah School of Medicine. She also serves as the director of Pediatric and Adult Aphaeresis at the Primary Children's Medical Center, University of Utah Hospital, director of Cellular Therapies at the US Tissue & Cell Western Division, and a member of the Huntsman Cancer Institute. Dr. Kelley is an inspector on the

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LARRY I. PALMER holds the Endowed Chair in Urban Health Policy at the University of Louisville, with appointments in the Department of Family and Community Medicine, the Institute for Bioethics, Health Policy and Law, and the School of Public Health and Information Sciences. Prior to joining the University of Louisville, he was a professor of law at Cornell University Law School in Ithaca, New York. Professor Palmer is the author of *Law, Medicine, and Social Justice* (1989), *Endings and Beginnings: Law, Medicine and Society in Assisted Life and Death* (2000), and numerous articles dealing with law, medicine, and health policy. Professor Palmer is also the executive producer and author of the study guide of the prize-winning educational video *Susceptible to Kindness: Miss Evers' Boys and the Tuskegee Syphilis Study*. He is a director of the Hastings Center in Garrison, New York, and a member of the American Bar Association's Bioethics and the Law Coordinating Committee. Previously, Professor Palmer served as a director of the National Patient Safety Foundation (1997–2002) and a trustee of the Phillips Exeter Academy (1990–2000).

Professor Palmer was a vice provost at Cornell from 1979–1984 and a vice president from 1987–1994. In addition to his positions at Cornell and the University of Louisville, he has held appointments at the University of Texas School of Law at Austin, the University of Virginia School of Law, Rutgers University Law School-Camden, Villanova School of Law, Emory Law School, The Friedrich-Alexander University, Erlangen-Nürnberg, and Clare Hall, Cambridge University. Professor Palmer received his B.A. from Harvard College and his LL.B. from Yale Law School.

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ANDREW M. YEAGER is director of the Stem Cell Transplantation Program, University of Pittsburgh Medical Center; director of the Stem Cell Transplantation Biology Program, University of Pittsburgh Cancer Institute; and professor of medicine (pediatrics) at the University of Pittsburgh School of Medicine. Dr. Yeager previously served in several capacities at Emory University, among them as director of the school's Interdisciplinary Stem Cell Biology and Transplantation Program at the school's departments of medicine and pediatrics and the Winship Cancer Institute. Dr. Yeager is a member of several professional societies, including: the American Society of Pediatric Hematology-Oncology, the International Society for Experimental Hematology, the American Society for Blood and Bone Marrow Transplantation, the International Bone Marrow Transplant Registry, and the International Pediatric Transplant Association. He is an editor of *Bone Marrow Transplantation*, *Stem Cells*, and the *American Journal of Clinical Oncology*. Dr. Yeager holds a B.A. in human biology and an M.D. from the Johns Hopkins University.

IOM PROJECT STAFF

EMILY ANN MEYER, J.D., is project director for the study *Establishing a National Cord Blood Stem Cell Bank Program*. Emily Ann earned her law degree at Hamline University, where she also served as a research fellow. Prior to coming to IOM, she worked in the Division of Engineering and Physical Sciences' National Materials Advisory Board. There she led a study on the globalization of materials research and development and spearheaded the development of a multi unit study on evaluating the feasibility of a national ballistics database.

SHIRA HANNAH FISCHER, B.A., is a research associate for the study *Establishing a National Cord Blood Stem Cell Bank Program*. She has worked at the IOM for 2 years on projects ranging from the strategic planning effort with the executive office to the report *New Frontiers in Contraceptive Research*. Shira received her degree in biochemical sciences from Harvard College.

BENJAMIN N. HAMLIN, B.A., is a research associate at the Institute of Medicine. He received his bachelor's degree in biology from the College of Wooster in 1993 and a degree in clinical health sciences from the University

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JUDITH L. ESTEP is the senior program assistant for the study *Establishing a National Cord Blood Stem Cell Bank Program*. She has worked at The National Academies/IOM since 1986 and has provided administrative support for more than 32 published reports. Her interests outside the IOM include family (11 grandchildren), four-wheeling, and working her draft horses for competition.

Acronyms

AABB	American Association of Blood Banks
ABMDR	Australian Bone Marrow Donor Registry
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ASBMT	American Society for Blood and Marrow Transplantation
ASHI	American Society for Histocompatibility and Immunogenetics
BFU-E	burst forming units-erythroid
BMDW	Bone Marrow Donors Worldwide
BMT	bone marrow transplantation
CAM	cell adhesion molecule
CAP	College of American Pathologists
CBU	cord blood unit(s)
CDC	Centers for Disease Control
CFU-GM	colony-forming units–granulocyte-macrophage
CFU-M	colony-forming units–megakaryocyte
CFU-MIX	colony forming units–mixed
cGMP	current good manufacturing processes
CIBMTR	Center for International Blood and Marrow Transplant Research
CLIA	Clinical Laboratory Improvement Amendments
CML	chronic myeloid leukemia
CMV	cytomegalovirus

COBLT	National Heart, Lung, and Blood Institute's Cord Blood Banking and Transplantation Study
CPD	citrate-phosphate-dextrose (an anticoagulant)
CRIR	Caitlin Raymond International Registry
DHHS	U.S. Department of Health and Human Services
DMSO	dimethylsulfoxide (a cryoprotectant)
EBMT	European Group for Bone Marrow Transplantation
EFS	event-free survival
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U.S. Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GLP	good laboratory practice
GMP	good manufacturing practice
GPA	genetic privacy act
GTP	good tissue practice
GVHD	graft versus host disease
GVL	graft-versus-leukemia
HIPAA	Health Insurance Portability and Accountability Act
HCT/Ps	human cellular and tissue-based products
HLA	human leukocyte antigen (human major histocompatibility complex)
HPC	hematopoietic progenitor cell
HR	high resolution
HRSA	Health Resources and Services Administration
HSC	hematopoietic stem cells
IBMTR	International Bone Marrow Transplant Registry
ICBTR	International Cord Blood Transplant Registry
IL-2	interleukin-2
IND	investigational new drug
IOM	Institute of Medicine
IRB	Institutional Review Board
ISBT	International Society of Blood Transfusion
ISCT	International Society for Cellular Therapy (formerly ISHAGE)
ISHAGE	International Society of Hematotherapy and Graft Engineering
ISO	International Standards Organization

JACIE	Joint Accreditation Committee (of EBMT)
JCAHO	Joint Commission for Accreditation of Healthcare Organizations
JCBBN	Japanese Cord Blood Bank Network
LN	liquid nitrogen
LR	low resolution
LTC-IC	long term culture-initiating cells
MHC	major histocompatibility complex
MSC	mesenchymal stem cells
NATF	North American Task Force
NIH	National Institutes of Health
NK	natural killer
NMDP	National Marrow Donor Program (USA)
NYBC	New York Blood Center (USA)
OHRP	Office of Human Research Protection (NIH)
PBSC	peripheral blood stem cells
PMN	polymorphonuclear leukocytes
SCID	severe combined immunodeficiency
TBI/Cy	total body irradiation/cytokine
TNC	total nucleated cell
TRM	transplant-related mortality
Tx	transplant
UCB	umbilical cord blood
UCLA	University of California, Los Angeles
URD	unrelated donor
WBC	white blood cell
WMDA	World Marrow Donor Association

GLOSSARY

Allele A form of a particular gene.

Allogeneic Transplantation The transfer of cells from one individual to another genetically different individual. That is, the individual receiving the transplant may or may not be related to the donor.

Autologous Transplantation Transplanation in which the person's own cells are collected and stored and then reinfused, generally after high-dose anticancer therapy

Chimerism The presence of more than one genetically distinct set of cells in an individual.

Collection Center The facility at which the hematopoietic stem cell collection takes place—the function of this facility will vary depending on the type of hematopoietic stem cell to be collected.

Cord Blood Bank A center that maintains umbilical cord blood units. A cord blood bank may combine some or all of the activities of a donor center, a collection center, and a registry.

Cord Blood Transplant The process by which a thawed hematopoietic progenitor cell unit from cord blood is infused into a patient for treatment.

Cord Blood Unit Umbilical cord blood that has been processed, frozen, and stored for future use.

Double Cord Blood Transplantation A transplant performed using two separate units of cord blood, rather than a single unit as used in a standard transplant.

Embryonic Stem Cell Stem cells capable of differentiating into virtually any adult cell line. These cells are derived from human embryos that are less than 1 week old, usually surplus frozen embryos.

Graft-Versus-Host Disease (GVHD) A common and serious complication of bone marrow or cord blood transplantation where there is a reaction of the donated cells to a patient's own tissue. GVHD can lead to organ damage.

Haplotype A set of genes that are linked closely enough to be inherited as a single set.

Hematopoiesis The formation of blood or blood cells.

Hematopoietic Progenitor Cell (HPC) A stem cell that has the ability to differentiate into cells capable of restoring myelopoiesis, erythropoiesis, throbopoiesis, and immune cells that make up the functional compartments of the human hematopoietic system. These cells are typically derived from the bone marrow, peripheral blood, or cord blood of humans.

Human Leukocyte Antigen (HLA) Part of the major histocompatibility complex (MHA), a group of closely linked loci, or gene locations, present in all humans, which plays an imperfectly understood but important role in immune phenomena.

Hemoglobinopathy A disorder due to abnormalities in the hemoglobin molecule. The best known hemogoblinopathy is sickle-cell anemia.

Immunosuppression Suppression of natural immune responses. Can be achieved with certain drugs.

Mixed Bank A bank principally collecting unrelated cord blood units donated for transplantation but also operating private facilities for low-risk autologous and family use. Money received from private banking activities helps to offset costs of the unrelated donor facility.

Private Cord Blood Bank Bank storing cord blood units for autologous or family use. Most private banks charge for this service, although some may offer their services at no cost to families with a medical need.

Public Cord Blood Bank Bank storing cord blood units donated for unrelated transplantation or research. Cord blood units may also be stored for autologous or family use where there is a known risk. The costs of processing and storing the cord blood unit are charged to the end user (transplant center or recipient). Public banks can be operated under either a nonprofit or for-profit cost model.

Registry A list of records—such as units available in a bank, or volunteer bone marrow donors.

Stem Cells Multipotent cells can differentiate into a variety of more specialized cells into the human body. Stem cells can be derived from bone marrow, stimulated peripheral blood, umbilical cord blood, a variety of other sources, including embryos. However, in this report

the term will *not* refer to stem cells derived from embryonic sources. (See also: Embryonic Stem Cell; Hematopoietic Progenitor Cell.)

Transplant Center A center that treats patients using transplantation of HPC to reconstitute bone marrow after high-dose chemotherapy. This treatment may be used for treatment of malignancy, bone marrow failure syndromes, inborn errors of metabolism, or some autoimmune conditions. In preparation for transplantation, a graft type and donor are selected. If the donor is unrelated, the transplant coordinator usually interacts with a registry or registries to secure the best HPC graft available to the patient.

Umbilical Cord Blood Blood collected from the umbilical cord and placenta post delivery of the infant. The blood can be collected either prior to or after the delivery of the placenta.

REFERENCE

The CancerWEB Project. 2004. *On-Line Medical Dictionary*. [Online] Available: http://cancerweb.ncl.ac.uk/cgi-bin/omd [accessed March 2005].

INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y