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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, multi-unit 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., difference racial or ethnic groups) in the population.

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 routinely 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 comprise of cord blood units that meet consistent standards for regulatory compliance and that 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 as such, 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 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 policymakers can determine how many units are needed, they must first ascertain how many units are actually available and useful.

[1]Most banks set thresholds for what they consider to be a bankable unit. Based on 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.

[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.

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 HLAs 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 living donors 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 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 requirements for what constitutes an acceptable cord blood unit. (For more information on HLA typing, see Appendix F.)

Racial and Ethnic Representation

Given the diversity of the U.S. population, the likelihood of finding a 4/6 or a 5/6 HLA match greatly exceeds the likelihood of finding a 6/6 HLA match. These matching

difficulties are even more pronounced 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). Additionally, 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 is generally easiest to find, 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 ($>5 \times 10^7$ 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 which 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 likely decrease. At the same time, it is conceivable that given the pain and time all 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 (for the purposes of the study which is assumed to be 20 years). The benefits of storing additional units—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 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, below, 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.

[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 (C0)	$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

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 HPCs.**

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 those 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 multi-unit 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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