Allogeneic stem cell transplantation methods

Philip Jacobs, David Hailey, Nadine MacLean

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the report are welcome and should be sent to:

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Summary

- Bone marrow transplantation (BMT), peripheral blood cell transplantation (PBCT) and cord blood transplantation (CBT) are technologies for providing stem cells to individuals requiring treatment for various hemopoietic disorders, including leukemias.

- In Canada, BMT is well established while the other two methods have been introduced on a more limited scale. In 1997 there were 181 requests for BMT in Canada, and 110 transplantations.

- BMT, PBCT and CBT are technologies which include complex collection and testing procedures.

- Comparative data on the three techniques are limited. On the basis of available literature:
  - There appears to be no clear difference in the safety of BMT and PBCT. CBT has an advantage as rates of infection in donors and recipients are lower.
  - The comparative efficacy/ effectiveness of the three methods is not established. There appears to be little difference in outcomes between BMT and PBCT. On the basis of weak evidence, there is some indication that engraftment following CBT is slower than that following BMT; CBT may have advantages in terms of graft versus host disease, which for this procedure is reported to be mild and with a relatively low incidence.
  - There is insufficient information to indicate any differences in survival following the three methods.

- Using data from Canadian sources and making realistic assumptions about the size of the donor pool, the costs per transplantation for BMT and PBCT are similar ($270,681 and $273,0440 respectively). Cost per transplantation for CBT is substantially higher ($410,130) because of the additional laboratory testing that is required.

- A sensitivity analysis indicated that these cost estimates are reasonably robust.

- Ethical issues related to privacy, ownership and resource allocation require consideration for each of the technologies.
Introduction

This report has been prepared following interest by the Alberta Cord Blood Bank in obtaining advice on the comparative effectiveness and costs of different types of stem cell transplantation. Earlier assessments by the Foundation have considered peripheral blood stem cell transplantation (1) and cord blood transplantation (8).

Stem cells are immature blood cells which give rise to red cells, white cells and platelets. They are found in bone marrow (where they generate into red and white cells and platelets), in umbilical cord-blood and in peripheral (circulating) blood. Certain diseases, such as breast cancer, are treated with high dosage chemotherapy, which damages existing stem cells. In cases such as these stem cells can be collected from the patient before the therapy, and transplanted afterwards; this process is called autologous transplantation.

In some abnormal circumstances, stem cells produce immature (blastic) cells or differentiated cells, whose immune properties are not well developed. This situation is associated with leukemia and related diseases. These illnesses are often treated with chemotherapy, which may be followed by a transplantation of stem cells. Because in these cases the patient's stem cells are affected by the disease, they must be replaced with those of other persons (called allogeneic transplantation).

In order for the transplanted cells to engraft, the antigens in the patient's cell system must closely match those in the donor's system. Ideally, the cells of a sibling or relative can be found. If this is not the case, then the clinician must try to obtain matching stem cells from unrelated donors. Registries of potential donors exist worldwide, attempting to match the antigens of stem cell donors with those of transplant recipients.

There are three ways of obtaining stem cells from unrelated donors. The first is through a bone marrow donation and transplantation (BMT). This procedure is invasive, and the time from search to transplantation depends on the speed with which the donor registry can identify and obtain the bone marrow. The second way is through a peripheral blood stem cell transplantation (PBCT); this is similar in many ways to the BMT process, except the harvesting of the cells is not as invasive. The third way of obtaining a stem cell transplant is through use of umbilical cord blood (CBT). Cord blood can be collected and stored in a donor bank for a long period of time; its characteristics can be catalogued for future matching with an unrelated transplant patient.

The entire stem cell transplantation process has economic and social, as well as clinical, aspects. Persons with leukemia, and related diseases, have poor survival rates in the absence of stem cell transplantation. Stem cell transplantation
technology offers hope in an area once considered desperate. The process is both
costly and time consuming; it includes the selection of patients; the recruitment
of donors; the testing of samples; the harvesting, shipping, and storage of stem
cells; the search for matched antigens; and the performing of transplants.
The time from search to transplant is an essential element in the success of the
procedure. In addition, there are numerous uncertainties; these include the
uncertainty of obtaining a match, and of a transplantation occurring even when
there is a match. In addition, there are ethical issues surrounding confidentiality
and commercialization.

This assessment is in three sections. First, we present information on the
illnesses which can be treated with allogeneic stem cell transplantation; from
these data, inferences can be drawn about the need for the technology. In the
second section, we describe the technology in its institutional context, as well as
the factors which influence its use. We then consider attributes of the three stem
cell transplantation methods, addressing safety, effectiveness, cost, cost
effectiveness, availability and ethical issues. Although stem cell transplantation
can be used to treat a number of conditions, the focus here is on leukemia, and
especially childhood leukemia. Details of the literature search are given in
Appendix A.
Disease treatment using allogeneic stem cell transplantation

Certain diseases, which are accompanied by damaged stem cells, are commonly treated with large doses of chemotherapy and radiation therapy. Immunological damage associated with these approaches necessitates the use of allogeneic transplants. In Table 1 we provide a list of the diseases with damaged cells for which stem cell transplants are used as part of their treatment, and numbers of Canadian patients. Leukemia is the most prominent of these conditions.

Table 1: Diagnosis and numbers of Canadian patients receiving unrelated bone marrow donor transplants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cumulative # of cases</th>
<th>Condition</th>
<th>Annual (1994) # of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>181</td>
<td>Acute lymphoblastic leukemia</td>
<td>31</td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>138</td>
<td>Acute myelogenous leukemia</td>
<td>17</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>225</td>
<td>Chronic myelogenous leukemia</td>
<td>31</td>
</tr>
<tr>
<td>Myelodysplastic Disorder Syndromes</td>
<td>78</td>
<td>Myelodysplastic Disorder Syndromes</td>
<td>10</td>
</tr>
<tr>
<td>Non-Hodgkins Lymphoma</td>
<td>25</td>
<td>Non-Hodgkins Lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency</td>
<td>19</td>
<td>Severe Combined Immunodeficiency</td>
<td>4</td>
</tr>
<tr>
<td>Severe Aplastic Anemia</td>
<td>43</td>
<td>Severe Aplastic Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>86</td>
<td>Other</td>
<td>12</td>
</tr>
<tr>
<td>TOTAL</td>
<td>795</td>
<td>TOTAL</td>
<td>110</td>
</tr>
</tbody>
</table>

Source: Unrelated Bone Marrow Donor Registry Program, March 1997.

In Table 2 we provide statistics on the rates and number of cases of different types of leukemia cases in Canada. Rates are higher for older persons, with the exception of those with acute lymphocytic leukemia (ALL), which is primarily a childhood disease. In Canada in 1994 there were 212 new cases of ALL for children under 15.

Table 2: Numbers of cases and rates for leukemia, by type and age category, Canada, 1994

<table>
<thead>
<tr>
<th>Type of leukemia</th>
<th>Rate per 100,000</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age 0-14</td>
<td>age 15+</td>
</tr>
<tr>
<td>Acute lymphocytic (AL)</td>
<td>3.52</td>
<td>0.65</td>
</tr>
<tr>
<td>Acute non-lymphocytic (ANL)</td>
<td>0.44</td>
<td>2.93</td>
</tr>
<tr>
<td>Chronic lymphoid (CL)</td>
<td>0</td>
<td>5.1</td>
</tr>
<tr>
<td>Chronic myeloid (CML)</td>
<td>0.02</td>
<td>1.74</td>
</tr>
<tr>
<td>Other</td>
<td>0.38</td>
<td>1.82</td>
</tr>
<tr>
<td>All leukemia</td>
<td>4.35</td>
<td>12.24</td>
</tr>
</tbody>
</table>

Source: Health Canada, Laboratory Centre for Disease Control
Stem cell transplantation technologies and their organization

Bone marrow stem cell transplantation

The donor is recruited by a local area office of the registry. Following contact and consent, the donor is sent to a laboratory to have his/her blood typed. The local laboratory collects two samples of donor blood. One sample is typed for A and B antigens, and the other is frozen and stored. (Protocols may differ, and at some centres a complete DNA test is done on the donor at this stage. Both practices are followed in Canada, although complete DNA testing seems to be preferred.) The laboratory sends the results of the serological test to the registry, where they are catalogued.

When a search begins, the transplant centre makes a request to the registry for a matched donor. A list of matched or partially matched donors is sent to the transplant centre, which chooses several. The laboratory centre is contacted. If only A and B antigens were typed initially, then the more complete DNA test is conducted on the frozen sample. Otherwise, the DNA results are available from initial testing.

The laboratory centre sends the results to the registry, which in turn sends them (preserving anonymity of the donors) to the transplant centre. If the transplant centre orders a specific unit, the service area office where the donor lives is contacted. The office arranges for an additional sample to be taken. The blood is tested for infectious diseases and a sample is also sent to the transplant centre. The transplant centre performs confirmatory testing.

If the sample is acceptable to the transplant physicians, the local centre is again contacted to arrange for a medical exam; if the results of this exam are satisfactory, the bone marrow is harvested. Harvesting bone marrow can be done on an inpatient or outpatient basis; the donor is placed under general anesthesia, and remains in the hospital for several hours after the procedure, or overnight. The bone marrow is refrigerated and shipped to the transplant centre. Transplantation then takes place, with the bone marrow being infused into the patient intravenously. Appropriate precautions are taken while the patient is immunosuppressed (for three weeks or more) until the infused stem cells begin to engraft.

Peripheral blood stem cell transplantation

The technology for the transplantation of peripheral blood stem cells is similar to that in bone marrow transplantation, except that, once the decision is made to use the donor's stem cells, harvesting is done in a different manner. The donor is "primed" with granulocyte-colony stimulating factor (GCSF) and the stem cells
are collected from peripheral blood using an apheresis process, usually in two separate sessions. The procedure is done in a clinic on an outpatient basis. The blood is drawn from the donor, fractionated, and returned to the patient minus the stem cells. The cells are frozen and shipped to the transplant centre.

**Cord blood stem cell transplantation**

The donor is recruited by the local area centre. Immediately following birth, the obstetrics team collects the cord blood and a sample of the mother's blood. These are placed in bags and shipped to the laboratory/processing centre. The laboratory staff extract the stem cells from the cord blood. A small sample of cord blood is retained and typed, using a DNA test for A, B, and DR antigens and for colony forming units (an indicator of the potential for engraftment). The mother's blood is tested for infectious diseases, and the results are coded and sent to the central registry. The cord blood is frozen and stored. Once the absence of transmissible diseases in the mother is assured, all personal identifiers are removed from the cord blood and it becomes available for use in a transplant. In some instances, the mother could be re-tested within six months as an added precaution that a transmissible disease was not present at birth.

The transplant centre sends a request to the registry for stem cells with specific antigens. The registry conducts a search in its data bank; if a specific unit of cord blood is matched, the registry sends the specifications to the transplant centre, which can then order a small sample of the stem cells for confirmatory testing. If the results of the confirmatory test are approved by the transplant centre, the CBT is ordered. The cord blood collection centre ships the cord blood unit to the transplant centre where the frozen unit is thawed and transplanted.

**Matching donor and patient antigens**

Each person has a total of six antigens in their blood cells, two each from the father and mother (called A and B antigens) and two additional DR antigens. There are two levels of testing to determine antigen types. Serological testing is a less detailed approach, and identifies the four A and B antigens. DNA testing is more detailed, and determines all six antigens.

The degree of success of a match will depend on the number of antigens which are matched. The best success (in terms of patient outcome) is achieved with a 6/6 match. However, successful outcomes with unrelated donors has been achieved with 5/6 matches. To a lesser extent, successful outcomes have been achieved in some individuals with even less complete (4/6) matches. Not everyone has the same probability of being matched. There are common and uncommon combinations of antigens, and for those with rare combinations, matching can prove to be very difficult.
The organization of stem cell transplantation

Currently, in Canada, only bone marrow transplantation is nationally organized. The organization of cord blood transplantation is in its infancy, and there is no organised allogeneic collection of peripheral blood stem cells. We will therefore begin our description of the organizational structure by describing the bone marrow transplantation system which now exists. We will then present our projections of what the organization of peripheral blood and cord blood transplantation might look like.

The descriptions are based on the entire search process occurring in Canada. In fact, a large percentage of marrows are harvested internationally, and a smaller proportion are sent to recipients outside Canada.

The organization of bone marrow transplantation

There are several different institutions which participate in the transplantation process, and there are a number of different ways that the process can be organized. The description given here resembles to some degree the current Canadian structure. In our simplified presentation, there are four different centres - the Registry, the Laboratory, the Collection Centre, and the Transplant Centre.

The Registry is responsible for donor recruitment, registration, searches, and contact between the transplant and the laboratory. The Laboratory is responsible for donor blood sampling, typing, infectious disease testing and storage. The Transplant Centre is responsible for patient testing, compatibility testing and treatment. The Collection Centre is responsible for the patient work-up, the bone marrow harvesting operation and the storing and shipping of the marrow.

In Figure 1 we outline the stem cell transplantation process within the organizational structure. Each organizational centre is represented by a patterned frame. Within each frame are the activities which occur within that organization.

There are two separate processes occurring. These are donor recruitment, registration and collection; and patient treatment, including the ordering of marrow. The process consumes time, and communications between the donor and the transplant centre are mediated by the Registry. Even after a match is made the donor must be examined and the marrow harvested.

There are many steps within each process, and the patient cannot be assured that a match will be made. This is because patients have many different serological types, and some will be quite rare. However, even if donors and patients are matched, there might be slippage after the match has been made.
One way that the probability of a match can be increased is to increase the size of the donor pool. This can be done through an increase in donor recruitment domestically, or through the use of international registries, which increases access to donors. Nowadays, searches can be conducted internationally, although the cost of obtaining marrow internationally can be quite high. For example, the fee for obtaining marrow from the United States, through the National Marrow Donor Program, was $29,835 as of March, 1999 (Bone Marrow Donors Worldwide: www.BMTdw.leidenuniv.nl). European prices, which vary by country, were in the range of $20,000 to $30,000.

The organization of peripheral blood stem cell transplantation

In Figure 2 we present an outline of the peripheral blood stem cell (PBCT) process. This process is very similar to that of the bone marrow organization, except that a granulocyte colony stimulating factor (GCSF) is administered by the collection centre medical staff for five consecutive days, and then the stem cells are collected in two apheresis procedures.

Cord blood transplantation organization

There are several differences in the organization of the cord blood transplantation process (see Figure 3). The cord blood is collected at the hospital where the baby is delivered. The cord blood is then shipped, processed and tested at the clinic/ laboratory. The role of the Registry is similar to that for PBCT and BMT. The role of the Transplant Centre is the same as in the other types of transplantation.
Figure 1: Bone marrow transplantation process (unrelated donors)

1. Diagnose and prescribe treatment
2. Initial family search
   - unsuccessful
   - Contact registry
     - yes
     - Continue search
     - no
     - Treatment outcome
   - Transport marrow/cells
3. Test for compatibility
   - no match
   - order work-up
   - match
   - Harvest marrow/stem cells
4. Recruit donor
5. Search registry for match (Central coordinating unit)
   - Prospective match
   - Contact service area office
   - Local org. contact donor
   - no
   - Receive donor acceptance
   - yes
   - Maintain registry
   - Type DR
   - Test for transmissible diseases, sample to Transfusion Center
6. Draw samples
7. LAB
   - donor data
   - Freeze and store sample (if AB)
   - Test for infectious diseases, sample to Transfusion Center
8. REGISTRY
   - Recruit donor
   - Donor registry
   - Prospective match
   - Contact service area office
   - Local org. contact donor
   - no
   - Receive donor acceptance
   - yes
   - Maintain registry
   - Type DR
   - Test for transmissible diseases, sample to Transfusion Center
9. COLLECT CENTRE
   - No sign-off
   - Physician sign-off
   - Medical exam for donor
Figure 2: Peripheral blood stem cell transplantation process (unrelated donors)

Diagnose and prescribe treatment

Initial family search

unsuccessful

Contact registry

yes

Search registry for match (Central coordinating unit)

Recruit donor

Donor registry

attrition

Maintain registry

no

Contact service area office

Local org. contact donor

Recipient

Sample not matched

Type DR

Transplant center orders sample

Take sample for Transfusion center

no sign off

no

Hospice

Compatible and non-infectious

Order work-up

Harvest and process PBSC

Medical exam for donor

Organ sign-off

no

Continued search

Transplant centre

Draw samples

Serological test (or DNA test)

Freeze and store sample (if AB)

Sample not matched

Sample not matched

donor data

not compatible

Test for compatibility (CT) and infectious disease test

not compatible

Transport marrow/cells

continued search

Transport marrow/cells

COLLECTION CENTRE

REGISTRY

LAB

Keep registry

TRANSPLANT CENTRE
Figure 3: Cord blood transplantation process

**TRANSPLANT CENTRE**
- Diagnose and prescribe transplant
- Initial family search
  - Unsuccessful
  - Contact cord blood registry
- Confirmatory testing
- Treatment

**REGISTRY**
- Recruit donor inform collection center
- Maintain registry
- Search registry for match (AB, DR)

**COLLECTION SITE**
- Collect cord blood and sample of mother's blood
- Transport to processing center

**CLINIC/LABORATORY**
- Retrieve sample for confirmatory testing
- Retrieve cord blood
  - Test for viability
  - Process for shipping
  - Transport
- Ship kit
- Volume reduction: Process for stem cells
- Tissue typing (DNA) Test CD34, CFU Mother's blood: infectious disease typed/non-infectious
- Cryopreserve and store
- Adjust for shelf life

Legend:
- Cost centre
Current transplantation activity in Canada

Bone marrow donor activity in Canada

As of September, 1998 there were 174,993 donors in Canada who were registered with the Canadian Blood Services Unrelated Bone Marrow Donor Registry, located in Vancouver (Canadian Blood Services, Donor Statistics: [http://www.bloodservices.ca/english/donor/don_stats.html](http://www.bloodservices.ca/english/donor/don_stats.html)). Table 3 shows donor rates for selected countries. In 1997 Canada had 553 donors per 100,000 population. The rate in early 1998 was 564 per 100,000 (Table 4). (It should be noted that only individuals between the ages of 17 and 59 donate bone marrow to unrelated registries.)

Table 3: Number of donors for selected countries, 1997

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Donors</th>
<th>Donors per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>877,572</td>
<td>1,069</td>
</tr>
<tr>
<td>USA</td>
<td>2,369,269</td>
<td>885</td>
</tr>
<tr>
<td>Australia</td>
<td>114,402</td>
<td>620</td>
</tr>
<tr>
<td>Canada</td>
<td>166,009</td>
<td>553</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>280,934</td>
<td>479</td>
</tr>
<tr>
<td>Sweden</td>
<td>40,720</td>
<td>460</td>
</tr>
<tr>
<td>Finland</td>
<td>15,000</td>
<td>291</td>
</tr>
<tr>
<td>France</td>
<td>91,619</td>
<td>156</td>
</tr>
<tr>
<td>Spain</td>
<td>23,099</td>
<td>58</td>
</tr>
</tbody>
</table>

a Using 1995 population  
b Using 1997 population

Sources:
Number of Donors: Registries Annual Report 1997
Populations:
Spain: Instituto Nacional de Estadistica; Spain in Figures 1997
There are considerable differences in donation rates among the Canadian provinces. In Table 4 we show the per capita donations in each province. Alberta and British Columbia have the highest proportion of donors (over 800 donors per 100,000 population). Quebec (299 per 100,000) and Newfoundland (128,000 per 100,000) have the lowest.

Further, Canada is a net "importer" of bone marrow. In 1997, of the 116 marrows which were transplanted in Canadian centres, 69 (60%) came from international donors. Canadian donors provided 90 marrows, of which 43 were sent abroad and 47 to Canadian transplant centres.

As well, in Canada, most donors are typed with the Type I serological method, which indicates four A and B antigens. The other two DR antigens are obtained using DNA typing, which is done at the matching stage. In some countries, there is a higher proportion of DNA matching of prospective donors.

Table 4: Number of donors by province, total and per 100,000 population, March, 1998

<table>
<thead>
<tr>
<th>Province</th>
<th>Total Number of Donors</th>
<th>Donors per 100,000 Population&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>30,928</td>
<td>821</td>
</tr>
<tr>
<td>Alberta</td>
<td>23,567</td>
<td>856</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>7,365</td>
<td>725</td>
</tr>
<tr>
<td>Manitoba</td>
<td>7,892</td>
<td>694</td>
</tr>
<tr>
<td>Ontario</td>
<td>71,277</td>
<td>642</td>
</tr>
<tr>
<td>Quebec</td>
<td>21,935</td>
<td>299</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>2,631</td>
<td>346</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>2,911</td>
<td>310</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>738</td>
<td>128</td>
</tr>
<tr>
<td>Total</td>
<td>169,224</td>
<td>564</td>
</tr>
</tbody>
</table>

<sup>a</sup> Using 1995 population.

Sources:
Number of Donors: Registries Annual Report 1997
Populations: Statistics Canada

Searches and their resolutions

Searches initiated
A search is a rather intensive process that involves further typing for antigens, testing for infectious diseases, drawing blood samples from donors and sending them for confirmatory testing to the transplant centre. There were 181 searches by Canadian transplant centres which were concluded (not all positively) by the Canadian Bone Marrow Registry in 1997.
Tests resulting from initiated searches

Searches are attempts to match donor stem cell characteristics with those of patients. They therefore result in tests for determining antigen types and the presence of transmissible diseases. Prior to the search, only a portion of donors are DNA tested; these donors can be matched immediately. However, of 262 searches for Canadian and foreign transplant centres which were completed in 1997 by the Unrelated Bone Marrow Donor Recruitment (UBMDR) Centre, only 35 percent were fully matched (6/6 DNA match) at initiation. Of the remainder, 42 percent had a serological match at search initiation, and 22 percent had no match (Canadian Blood Services, personal communication).

In 1997, eight Canadian transplant centres requested results from 7,905 DR tests from potentially matched donors; of these 3,895 were from Canadian donors and 4,010 were from international donors. A total of 1,009 confirmatory tests were made from these donors, 249 of which came from Canadian donor centres and 760 from international centres. In total, these tests led to 116 transplants. (CNBMTR, Briefing papers prepared by the National Advisory Committee, June 10, 1998, page 11).

Matches and Transplants

Not all tests result in a match, and not all matches result in a transplant. In Table 5 we present an estimate of the outcome of bone marrow searches for a sample of searches which were initiated by the Canadian Bone Marrow Donor Centre. Of the total searches initiated, 87 percent were matched, and 13 percent were unmatched. Of those which were matched, we estimate that 30.4 percent did not proceed to transplant. Table 6 lists reasons why the cases which were matched did not proceed to transplant. Reasons differ by disease type. For ALL, disease acceleration was a critical factor. For CML, the choice of other therapies was the biggest reason. And for AML, the choice of an autologous transplant was the major reason.

Time from search to transplantation

The median time to transplantation for bone marrow transplants is quite variable. The UBMDR reports that in 1994 the median time to transplant was 260 days for CML cases, 142 days for ALL cases, and 99 days for AML cases (UMBDR Program Business Plan, March 1997, Table 36).
Table 5: Disposition and bone marrow transplant searches, Canada, 1994

<table>
<thead>
<tr>
<th>Total searches conducted</th>
<th>181</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(100%)</td>
</tr>
<tr>
<td>Matched</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>(87.3%)</td>
</tr>
<tr>
<td>Proceeded to transplant</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>(60.7%)</td>
</tr>
<tr>
<td>Did not proceed to transplant</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>(26.5%)</td>
</tr>
<tr>
<td>Not matched</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(12.7%)</td>
</tr>
</tbody>
</table>

Source: Unrelated Bone Marrow Donor Registry Program Business Plan, March 1997.

Table 6: Reasons for not proceeding to transplant, by diagnosis, 1994

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reasons for not proceeding</th>
<th>Number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Patient died or disease accelerated</td>
<td>20 (63%)</td>
</tr>
<tr>
<td></td>
<td>Patient or family declined treatment</td>
<td>5 (16%)</td>
</tr>
<tr>
<td></td>
<td><strong>Physician declined</strong></td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>Other (alternative therapy, patient improved)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Acute myeloid (nonlymphoblastic) leukemia</td>
<td>Patient died or disease accelerated</td>
<td>18 (56%)</td>
</tr>
<tr>
<td></td>
<td>Patient or family declined treatment</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td><strong>Physician declined</strong></td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td><strong>Autologous transplantation</strong></td>
<td>7 (22%)</td>
</tr>
<tr>
<td></td>
<td>Other (alternative therapy, patient improved)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Patient died or disease accelerated</td>
<td>9 (26%)</td>
</tr>
<tr>
<td></td>
<td>Patient or family declined treatment</td>
<td>9 (26%)</td>
</tr>
<tr>
<td></td>
<td><strong>Autologous transplantation</strong></td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td><strong>Related Tx</strong></td>
<td>3 (9%)</td>
</tr>
<tr>
<td></td>
<td>Other (alternative therapy, patient improved)</td>
<td>13 (37%)</td>
</tr>
</tbody>
</table>

Source: Unrelated Bone Marrow Donor Registry Program Business Plan, March 1997
The probability of a successful match

There is an enormous range of possible characteristics of any one person's antigens. Some antigen combinations are more common than others, and the number of different HLA types is positively skewed. The probability of any patient being matched with a donor will therefore depend on the patient's HLA-type, and on the number of donors who have a matching HLA-type.

The ideal match is one in which all six antigens (A, B and DR from both parents) are identical. Transplants have been done with one or more mismatched antigens, although the greater the extent of the match, the better the outcome is likely to be. At the same time, there is a greater probability of having a 5/6 match than a 6/6 match, and an even greater one of having a 4/6 match.

Beatty et al. (2) and Schipper (personal communication) have determined the relationship between the probability of obtaining a match and the size of the donor pool. In Figure 4 we illustrate three relationships in double log form - a 4/6 match, a 5/6 match and a 6/6 match. With a 6/6 match, a donor pool of 1,000 is needed in order to achieve a ten percent probability of one match. For a 25 percent probability of a match, a donor pool of 6,000 is needed.

The target size of the number of donors who are needed to obtain one match would have to be multiplied by the total number of desired matches in order to obtain an estimate of the total donor pool.

Figure 4: Hypothesized relationships between size of donor pool and probability of a matched donor
The required donor pool size would be smaller if only a 5/6 match is desired. A donor pool of 8,000 per match will achieve a probability of match of roughly 80 percent. Even if the donor pool grows to 12,000 donors per match, the probability of a 6/6 match is only about 33 percent.

The above numbers are only illustrative, and there seems to be a fair amount of controversy over this issue. For example, according to Sirchia et al (14) a cell bank of 50,000 – 100,000 “will probably allow us to identify at least one compatible unit for all recipients”.

From another perspective, the Canadian UBM DR has 170,000 registered donors. Annually there are about 180 requests; of these, roughly 85 percent are matched; 40 percent of these are matched domestically and 60 percent from international donors. A donor registry of 425,000 (1.0/ 0.4 x 170,000) would be consistent with 85% of all cases being matched within Canada (although the rarer types may never find a match with such a small registry).

We thus have several very different estimates of the desirable size of a stem cell donor registry: 50,000 – 100,000 from the Milan Cord Bank; our rough estimate of 425,000 for Canada; and the estimates from Schipper and Beatty et al., which are much higher than these numbers.
Safety issues

Definition and method

Safety refers to freedom from harm. In the case of stem cell collection and transplantation, harm refers to the adverse events experienced by donors as well as by recipients. Adverse events which are related to donors would include the adverse reactions of using GCSF to stimulate the stem cells prior to the collection of peripheral blood stem cells and of infection from bone marrow and peripheral blood cell collections. Adverse events which are related to transplant recipients include infections from procedures and toxicities from drugs. We measured infections after transplant as a single category, i.e., including transplants for all types of disease.

Adverse events in donors by stem cell source

Adverse events were experienced by donors under both BMT and PBCT technologies. Schmitz et al. (13) provided the most complete documentation of adverse events in donors. Serious, but not life-threatening, events were experienced in both arms of their clinical trial. In addition, they found that PBC donors incurred on average one day of restricted activity, as opposed to six days for bone marrow donors.

Adverse events in recipients by stem cell source

Only two studies reported post-transplant infections. Schmitz et al. (13) did not find a difference between collection techniques, but Przepiorka et al. (9) found a much higher rate in bone marrow-transplants (compared to PBCT).

Post-transplant infection was reported as a serious problem in CBT by Rubinstein et al. (11) and Gluckman et al. (5) but comparability with BMT and PBCT cases was not possible because of non-standardized reporting.

Determinants of safety

No studies have explicitly analysed the determinants of safety. Donor infections should be lower in CBT than in BMT and PBCT. There is very little information available to compare recipient information.

Effectiveness

Definition and measures used

Effectiveness is defined as the difference in health-related outcomes between types of interventions, under actual practice conditions. It is sometimes difficult to distinguish between safety and effectiveness; safety almost always translates into health outcomes, and so it may be difficult to distinguish between the "effect" and the "side-effect" of an intervention. We use the following measures as outcome measures: time to engraftment for both platelets and neutrophils;
presence of graft versus host disease; days of survival following transplant; and
days in hospital.

Engraftment criteria were as follows: Failure to engraft was measured by the
failure to achieve either an identified neutrophil or platelet count by a specific
time following transplantation. The neutrophil count was given as 0.5 x
\(10^9\)/litre, to be achieved by 45 days. The target platelet count was 20 x \(10^9\)/litre,
to be achieved by 45 days.

Survival is most difficult to compare between studies. Different authors use
different time horizons and time markers in their studies; because of the lack of
standardization, we cannot attain comparable measures. Even with
standardization, it would be difficult to obtain a standarized summary measure.
Authors have noted a wide variance in survival times between patients: the
mean or median values, by themselves, do not provide enough of the picture.

Hospital days (used both as an outcome and resource-use measure) can be
measured as the length of stay for the transplant procedure alone, or for the
transplant procedure and any rehospitalizations which are related to the
transplant. We included both measures.

Data related to outcomes comparing PBCT and BMT were abstracted from the
same studies used to review safety. Data related to CBT outcomes were obtained
from the observational studies of Rubinstein et al. (11) and Gluckman et al. (5).

Effectiveness by stem cell source

Engraftment failure and time to engraftment

There was no clear difference in engraftment failure between PBCT and BMT.
Schmitz et al. (13) and Bensinger et al. (3) both recorded considerably higher
engraftment failures in BMT, but this was not reported in other studies.

Failure of engraftment for CBT transplants was reported in 160 out of 546
patients (29%) in the historical analysis by Rubinstein et al. (11). However, the
population that was studied included unrelated recipients with one, two or more
mismatches. These results are not comparable with those from the BMT versus
PBCT studies which included only 6/6 matches. If we include only the
completely matched recipients, the rate of failure to engraftment in CBT is 14
percent; this is comparable to that reported in BMT versus PBCT trials. Similar
results for CBT were obtained from the study by Gluckman et al. (5). As noted in
an earlier report (8) several studies on CBT suggested that engraftment is slow,
as compared to BMT.

Time to platelet recovery was significantly shorter for PBCT than BMT in both
randomized trials (15 versus 19 days in Schmitz et al. (13) and 12 versus 17 days
in Vigorito et al. (16). The historical studies also recorded consistent results,
although differences were significant only in the studies by Przepiorka et al. (9)
and Ringden et al. (10). The median time to engraftment for platelets for cord
blood recipients who reached engraftment was 71 days (11); however, the CBT population was not comparable with that of the BMT and PBCT populations.

Time to neutrophil engraftment was generally shorter for PBCT than for BMT recipients, in both the clinical trial and historical studies (14 versus 15 days in Schmitz et al. (13); 16 versus 18 days in Vigorito et al. (16); and shorter in all historical studies except that of Przepiorka et al. (9). The median time for CBT patients was 28 days (11) but again, the populations were not comparable.

**Graft versus host disease**

There was no clear trend in acute or chronic GVHD. Investigators in the two randomized clinical trials (13, 16) reported higher rates of acute GVHD in PBCT; this was not reported in the historical control studies. Only Bensinger et al. (3) and Couban et al. (4) reported instances of BMT and PBCT chronic GVHD; rates were the same for both types of transplantation.

Acute GVHD for CBT was reported in 399 evaluable cases by Rubinstein et al. (11). In total, GVHD was recorded in 46 percent of all evaluable cases; this figure is comparable with the rates found both for PBCT and BMT in Schmitz et al. (13) but the patient and matching characteristics are very different. Opinion from studies on CBT is that GVHD following the procedure is mild and the incidence relatively low (8).

**Survival**

Mean survival was not significantly different between PBCT and BMT for all studies. Sixty percent of the CBT recipients survived more than 100 days after transplant.

**Length of hospitalization**

Hospital stays for persons receiving a transplant were reported to be lower for PBCT than for BMT (4, 9, 10, 12, 13). However in the one study which reported follow-up hospitalizations, PBCT hospital stay was longer than that for BMT, for the entire episode, including follow-up (13).

**Determinants of effectiveness**

The primary outcomes that have been identified in the literature are time to neutrophil engraftment, time to platelet engraftment, survival following transplant, and disease-free survival following transplant. There are variants of survival measures (e.g., the percent of recipients who survive up to a given time horizon).

Rubinstein et al. (11) studied the determinants of neutrophil survival in cord-blood stem-cell recipients. The variables which had a significant effect on engraftment were diagnosis (i.e. type of disease), cytomegalovirus (CMV) status and the extent of match.
Gluckman et al. (5) developed a model to predict one-year survival following CBT; only diagnosis and CMV status of recipients were statistically significant. Kernan et al. (6) developed a model to predict leukemia-free survival in BMT; recipient age and CMV status were significant variables. In their statistical analysis, the authors reported that the following variables had a significant influence on survival: recipient age, recipient CMV status, extent of HLA match, diagnosis, and time from diagnosis to transplant.

Using data from CBT patients, the following variables were determined to have an influence on acute GVHD: recipient CMV status (5), patient age, extent of match, and the presence of an infection after transplant (11). Storek et al. (15) examined a number of variables using bone marrow recipients, and found none to be statistically significant. Very little can be concluded about the differences between transplant sources in factors which influence safety.

We cannot infer from these variables that there is a differential effect between stem-cells which come from different sources. However, we can make an inference that there may be a differential effect associated with the variable, time from search to transplant. The time from diagnosis to transplant may differ between sources of stem cells.

Cord blood is stored in freezer-units and can be readily shipped following confirmatory testing; the time from match to transplant would be the lowest for this source of stem cells. The time from search to match would be higher for PBCT because of the need to contact the donor, mobilize the donor's white cell count and collect the stem-cells using the pheresis method. Finally, collection of stem cells from the bone marrow source would be longest, because of the time taken to examine the donor and arrange for the harvesting of the bone marrow. There should not be a great deal of difference in time between the methods of collection for peripheral blood stem cells and bone marrow.

**Summary of safety and effectiveness**

In Table 7 we provide a summary of the various components of safety and effectiveness for the three stem cell transplantation methods. The most complete comparisons can be made between BMT and PBCT, because there were a number of studies comparing the two methods. Fewer data are available to compare CBT with the other two methods.

Based on the available data, there is no single method that is clearly superior. PBCT is superior to BMT in some categories (time to platelet engraftment, time to neutrophil engraftment, post-transplant infections, and post-transplant hospitalizations) and BMT is superior in other categories (probability of chronic GVHD). CBT has fewer donor infections than the others, and a longer survival period. However, all of these conclusions have been based on lower levels of evidence. As a result, we conclude that no method has emerged as being categorically superior.
Table 7: Summary of outcomes for three stem cell collection methods

<table>
<thead>
<tr>
<th>Transplantation method</th>
<th>Bone marrow (BMT)</th>
<th>Peripheral blood (PBCT)</th>
<th>Cord blood (CBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety aspects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Donor infections</td>
<td>Same as PBCT</td>
<td>Same as BMT</td>
<td>No infections</td>
</tr>
<tr>
<td>• Recipient post – transplant infections</td>
<td>Highest amount of infections</td>
<td>Lowest amount of infections</td>
<td>No comparable infections</td>
</tr>
<tr>
<td><strong>Probability of successful engraftment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Platelets</td>
<td>All methods have same results</td>
<td>All methods have same results</td>
<td>All methods have same results</td>
</tr>
<tr>
<td>• Neutrophils</td>
<td>All methods have same results</td>
<td>All methods have same results</td>
<td>All methods have same results</td>
</tr>
<tr>
<td><strong>Time to engraftment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Platelets</td>
<td>Longer than PBCT</td>
<td>Shorter than BMT</td>
<td>Possibly longer than BMT</td>
</tr>
<tr>
<td>• Neutrophils</td>
<td>Longer than PBCT</td>
<td>Shorter than BMT</td>
<td></td>
</tr>
<tr>
<td><strong>GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute GVHD</td>
<td>Data inconclusive</td>
<td>Data inconclusive</td>
<td>No comparable data, possibly milder/fewer cases than BMT</td>
</tr>
<tr>
<td>• Chronic GVHD</td>
<td>Less than PBCT</td>
<td>More than BMT</td>
<td>No comparable data</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>Same as PBCT</td>
<td>Same as BMT</td>
<td>No evidence</td>
</tr>
<tr>
<td><strong>Hospital length of stay</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Post transplant</td>
<td>Longer than PBCT</td>
<td>Shorter than BMT</td>
<td>No comparable data</td>
</tr>
<tr>
<td>• Post transplant with follow-up</td>
<td>Shorter than PBCT</td>
<td>Longer than BMT</td>
<td>No comparable data</td>
</tr>
</tbody>
</table>
Cost

Cost by function

Following the organizational description which is shown in Figures 1 - 3, we developed a classification of functions for each of the three methods of collecting stem cells. We also developed a categorization of cost centres and matrices for each method of stem cell collection. These are shown in Appendices 2-4. For example, the bone marrow transplantation process was divided up into the following functions:

- donor recruitment,
- registry maintenance,
- initial (AB) typing,
- additional typing (DR),
- testing for infectious diseases,
- confirmatory testing,
- donor examination,
- bone marrow harvesting,
- marrow transportation, and
- transplantation.

These functions occur in the following cost centres: central registry, regional recruitment centre, laboratory, clinical centre for donors, and the transplant centre. Similar matrices were developed for the PBCT and CBT processes.

We developed measures of cost for each of the functions. These costs were broken down into fixed and variable components. The fixed components are one-time costs such as equipment and overhead. The variable costs are costs which increase whenever the number of donors (or other relevant units) changes. The methods used to measure the cost of each function, and the data sources for these methods, are presented in Appendix 5.

Cost by stem cell technique

In order to assess the cost of each of the three techniques for collecting stem cells, we have developed scenarios which are based on Canadian data, where available. We have adopted this approach in order to place the three methods on a common ground, so that they can be comparable. The cost statistic which we use to compare the three techniques is the total annual cost of providing stem cells to a population of 200 potential recipients.

The background assumptions for our costing analysis are as follows:

- There are 200 new cases requiring stem cell transplants each year.
- Cells from related donors are not available.
• Cells from CBT, BMT and PBCT all contain sufficient volumes for a successful transplant.

• Stem cells from unrelated donors can be obtained through a donor bank. The size of the donor bank will depend on the desired probability of a match and on the degree of the match. We assume that a donor bank of 425,000 units is sufficient to meet domestic needs.

• All donors are DNA typed at the time of recruitment.

• Five potential donors per prospective recipient will be selected for confirmatory testing by the transplant centre.

• In total, 85 percent (170) of the patients will be matched to donors.

• Of the 170 matches, 70 percent (120 recipients) will proceed to transplant.

• A transplantation uses 50 hospital (ICU) days. The cost of treatment and post treatment complications is $140,000 (Calgary Regional Health Authority).

• The time horizon is ten years. All BMT and PBCT donors will be recruited in the first year and will remain active for ten years. In the case of cord blood, all stem cells are collected in the first year and have a ten year shelf-life.

• All one-time costs (e.g., the collection of cord blood) are annualized over 10 years at a discount rate of five percent.

Based on these assumptions, and on the costs of each activity, we compute the annual costs for each technique. These are summarized in Table 8.

BMT is the least costly method ($32.4 million annually for the 200 potential recipients or 120 transplants), followed by PBCT ($32.7 million), and then CBT ($49.2 million).

Cost per recipient is $270,000 for BMT, $273,000 for PBCT, and $410,000 for CBT. These unit costs include hospitalization. The difference between CBT and the other two techniques is due to the fact that more processing costs are embodied in the cord blood inventories.
<table>
<thead>
<tr>
<th>Technology</th>
<th>Function</th>
<th>Calculations</th>
<th>Annual Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBT</strong></td>
<td>Donor maintenance</td>
<td>3,266,310 p.a. (fixed cost)</td>
<td>$3,266,310</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Donor recruitment, collection, and processing of cord blood</td>
<td>$28,950,748</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cost of 425,000 units x $526 unit cost ($9 donor recruitment + $35 collection + $60 transport to processing centre + $70 processing for storage + $295 typing and testing + $50 sterility test + $7 cryopreservation) = 223,550,000, annualized over 10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confirmatory testing</td>
<td>850 tests x $210 each</td>
<td>$178,500</td>
</tr>
<tr>
<td></td>
<td>Units ordered</td>
<td>120 units x $167 shipping</td>
<td>$20,040</td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
<td>$140,000 per case x 120 patients</td>
<td>$16,800,000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>$49,215,598</td>
</tr>
<tr>
<td></td>
<td>Cost per recipient</td>
<td></td>
<td>$410,130</td>
</tr>
<tr>
<td><strong>BMT</strong></td>
<td>Donor maintenance</td>
<td>3,266,310 p.a. (fixed cost)</td>
<td>$3,266,310</td>
</tr>
<tr>
<td></td>
<td>Donor recruitment and screening</td>
<td>425,000 donors x $219 ($9 recruitment + $150 tissue typing + $60 shipping) = 93,075,000, annualized over 10 years</td>
<td>$12,053,638</td>
</tr>
<tr>
<td></td>
<td>Confirmatory testing</td>
<td>850 units x $210 ($150 test + $60 shipping)</td>
<td>$178,500</td>
</tr>
<tr>
<td></td>
<td>Harvesting</td>
<td>120 units x $1,527 ($1,150 harvest + $167 shipping + $120 infectious disease testing + $90 medical exam)</td>
<td>$183,240</td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
<td>$140,000 per case x 120 patients</td>
<td>$16,800,000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>$32,481,688</td>
</tr>
<tr>
<td></td>
<td>Cost per recipient</td>
<td></td>
<td>$270,681</td>
</tr>
<tr>
<td><strong>PBCT</strong></td>
<td>Donor maintenance</td>
<td>3,266,310 p.a. (fixed cost)</td>
<td>$3,266,310</td>
</tr>
<tr>
<td></td>
<td>Donor recruitment and screening</td>
<td>425,000 donors x $219 ($9 recruitment + $150 tissue typing + $60 shipping) = 93,075,000, annualized over 10 years</td>
<td>$12,053,638</td>
</tr>
<tr>
<td></td>
<td>Confirmatory testing</td>
<td>850 units x $210 ($150 test + $60 shipping)</td>
<td>$178,500</td>
</tr>
<tr>
<td></td>
<td>Harvesting</td>
<td>120 units x $3,890 ($1,700 pheresis + $1,813 drugs + $167 shipping + $90 medical exam + $120 infectious disease testing)</td>
<td>$466,800</td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
<td>$140,000 per case x 120 patients</td>
<td>$16,800,000</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>$32,765,248</td>
</tr>
<tr>
<td></td>
<td>Cost per recipient</td>
<td></td>
<td>$273,044</td>
</tr>
</tbody>
</table>
Sensitivity analysis of costs

Our analysis of costs was based on a number of assumptions. In this section we conduct an analysis to determine how sensitive these costs are to changes in critical assumptions.

- Degrees of typing. We assumed that all units were DR (DNA) typed. Worldwide, the ratio is about 40 percent. We examine the effect if 40 percent of all bone marrow and peripheral blood donors are DR typed while the rest are A and B typed only.

  The cost of DR typing is $150 whereas the cost of AB typing is only $45. When 40% of bone marrow and peripheral blood donors are DR typed and the remaining 60% AB typed, the total cost of donor recruitment and screening (annualized over ten years) is $8,586,153. Therefore, the costs per bone marrow recipient and peripheral blood recipient become $241,785 and $244,148 respectively.

- Patient hospitalization. It has been claimed that PBCT uses less hospitalization. We examined the effect on costs if PBCT patients were hospitalized for 25 days.

  The cost of hospitalization for transplant and post transplant treatment is estimated as $140,000 based on 50 days of hospitalization. If the length of stay was varied to be only 25 days, the total cost of the peripheral blood stem cell transplantation process per recipient would be $203,044.

- Donor attrition and cord blood shelf-life. A ten year life might be too high for cord blood specimens and there would be donor attrition for the BMT and PBCST approaches over this time. We have conducted the cost analysis with a five year time horizon for donors and cord blood.

  Costs which were annualized would now be done over a five year period rather than ten years. The cost of a cord blood transplant, a bone marrow transplant, and a peripheral blood stem cell transplant increases to $599,161, $349,384, and $351,747 respectively, per recipient.

- Cost of different size donor pools. As discussed above, we assumed that 425,000 was the size of donor pool which would allow 100 percent of all Canadian requests to be met. However, there is considerable uncertainty with this figure. We therefore have conducted our analysis with 100,000 donors and 600,000 donors, to see the difference.

  When the donor pool is changed from 425,000 to 100,000 donors, the cost per recipient of each type of transplant decreases. Specifically, these costs are: $225,640 (cord blood), $193,868 (bone marrow), and $196,231 (peripheral blood) per recipient.
On the other hand, when the size of the donor pool is increased from 425,000 to 600,000 donors, the cost for each type of transplant increases. The costs per recipient for each type are: $509,471 (cord blood), $312,041 (bone marrow), and $314,404 (peripheral blood) per recipient.

- Fewer donors needed for cord blood. It has been stated that cord blood recipients might do as well with a higher degree of mis-match. We take this factor into account by assuming that a smaller donor pool would be needed. The calculations are the same for the analysis immediately preceding this one.

- Lower recruitment costs for cord blood collection. In order to allow for the possibility that donor recruitment costs are lower for cord blood than for other sources of stem cells, we conducted a cost analysis under the assumption that there are no donor recruitment costs for cord blood (assumed to be $9 per donor for other types).

  With this assumption, the cost per cord blood transplant recipient is still higher than the cost per bone marrow or peripheral blood recipient. However it does fall slightly, from $410,130 to $406,002 per recipient.

- All 200 cord blood units are assumed to be matched to a donor. The ratio of transplantations to matches remains the same as in the base case.

  Under this assumption, the cost per cord blood recipient decreases from $424,186 (as in the base case) to $383,762 per recipient.

  Overall, on the basis of this sensitivity analysis, it appears that the cost analysis is reasonably robust.
Availability of stem cells for transplantation

The availability of stem cell units refers to the number of units supplied in relation to the number requested. The components of the two aspects, supply and demand, are presented in Figure 5. Here we see the demand aspects being dependent on the number of persons whose treatments require stem cell transfusions, and on the number of searches that are initiated for such treatments.

Figure 5: A flowchart indicating availability of stem cells

The supply of stem cell units will depend initially on the number of donors who are recruited. In addition, these donors will have different HLA characteristics. Therefore the number of potential matches which go to confirmatory testing will depend on the number of potential donors as well as on their HLA make-up. The number of donors and patients who are actually matched will also depend on these factors.

Not all matched donors are harvested. Donors may refuse to be harvested even though they have been matched. Further, even if a donor agrees, or is deemed to be a candidate for harvesting, the transplant may not take place because the patient’s condition changes, or because the patient changes his/her mind.

The number of unmet requests is one measure of the availability of stem cells. As shown in Table 5, of the 181 requests for stem cells by Canadian centres in 1994, 158 (87 percent) were matched. However, this statistic does not indicate the degree of the matches, nor does it take into account the number which did not proceed to transplant. In the case of ALL, time may be an aspect of availability.
Determinants of availability

There are several factors which might impact on the relative availability of the three techniques of stem cell transplantation. One factor which might have an influence on CBT availability is the degree of HLA disparity which is required in a transplant. Gluckman (5) has suggested that a greater degree of disparity is acceptable for CBT than for PBCT or BMT. The evidence for this is mixed (11). If cord blood stem cell transplants with a lower degree of matching are equally effective as transplants using peripheral cells or bone marrow, but with a higher degree of matching, then the number of required units will be less for a CBT program.

A second factor which might influence the relative availabilities of the three stem cell sources is the time from search to transplant. With CBT, the units, once collected, are already available, and once identified, can be readily tested for confirmation. With peripheral blood and bone marrow units, there is both a time delay and uncertainty involved after a potential donor has been identified. Therefore the use of cord blood units should increase availability.

Cord blood availability is reduced by the high cost of creating a CBT inventory and the small volume of each unit. The high cost of cord blood units is created by the requirement that DNA typing, infectious disease testing, and processing be done on every unit. Such testing need only be done on matched units for the other stem cell methods, not on every donor. This amounts to a large saving for the use of PBCT and BMT, but this may be offset to some degree if a lower volume of CBT units is required.

The small volume of stem cells that can be collected from umbilical cord blood reduces the number of recipients who can be transplanted with any one unit. Younger persons would be the prime recipients of cord blood transplants.

Peripheral blood has a greater availability than cord blood due to the larger volume of each unit. A unit of peripheral blood stem cells can be used for a wider range of potential recipients than can a cord blood unit as the larger volume (and numbers of stem cells) makes this approach more realistic for adults. It is contended that a higher degree of matching is needed for PBCT stem cells. This reduces the availability of PBCT relative to CBT. The above two factors will be the same for BMT as for PBCT.

When comparing BMT to PBCT, we should note that the harvesting of BMT is a more invasive procedure than for PBCT, a factor which might reduce the relative availability of BMT. However, with the use of expensive growth factors, the PBCT procedure, though less invasive, may be more costly than the BMT procedures.
Ethical issues

Ethical issues associated with CBT were considered in a previous report (8). There are three primary ethical aspects of stem cell collection and transfusion (7) – privacy, ownership, and resource allocation issues (equity).

Privacy refers to the anonymity of the donor following donation. If the recipient knows the donor’s identity, then they can request additional units, though the donor may not want to be approached. It is possible to maintain total anonymity with all three stem cell technologies.

There is a particular problem with cord blood, which has a long shelf life. If, subsequent to the donation, the donor discovers that he/she has a transmissible disease, then if the stem cell unit becomes anonymous, the cord blood bank will not be able to remove the unit from its inventory. Under current practice, cord blood banks maintain the unit’s identity for six months. During this period additional tests can be run on the mother to identify infectious diseases.

A second ethical issue deals with ownership of the unit. This is particularly relevant to cord blood units, which can (potentially) be claimed back by the donor. Ensuring the anonymity of the cord blood source would seem to preclude such an action.

The third set of issues deals with resource allocation. There are numerous market arrangements which can be developed for cord blood units, ranging from purely commercial markets to purely non-profit markets.

Stem cells are a product whose availability has life or death consequences. In a purely commercial market, the donating family, the cord blood bank, or both, are free to set the price of the unit at any level. In contrast to many (but not all) health care services, the recipient’s family would be bound to pay this price if the recipient were to receive the transplant.

Under a non-market system these incentives could be reduced substantially, though they may not be totally eliminated. Cord blood banks are aware of the nature of their products, and can set the price of cord blood quite high. They can thus obtain revenues from these sales, though these revenues cannot be turned into (take-home) profits. In theory, the non-profit agency will only charge what the stem cell unit “costs”, but agencies can engage in a large variety of activities which increase these costs.

This characteristic is the same for all sources of stem cells. In a commercial world, peripheral blood and bone marrow donors can still demand a high price for their cells, as could the donors of the cord blood cells (if they retained ownership of the cells). Similarly, if donors gave their blood or cells to commercial banks, then the stem cell banks could profit, but not the donors.
The commercialization aspect is a very important aspect of all stem cell banking. Potentially, these arrangements might have an effect on whether someone who was in need of a transplant could obtain one, even if a match was found. Currently in Canada the arrangements are not commercialized, and so the financial status of recipients and their families does not influence availability.
Discussion

While BMT has been established for many years, current technologies for stem cell transplantation represents a relatively new area of treatment, offering promise in an area which was once considered hopeless. In this assessment we have compared three separate technologies - BMT, PBCT and CBT. In Table 9 we present the categories which we assessed, and the major elements in each category. Within each cell in the table is an assessment of the relative performance of each technology within that element.

With regard to safety, cord blood rates the best, in terms of lower donor and recipient infections.

There are a number of separate elements in the efficacy category. Because of a lack of comparable information between CBT and the other two methods, we cannot present a complete picture of their relative efficacies. PBCT performs better than BMT with regard to the time to engraftment. Time to engraftment may be slower for CBT. In regard to acute GVHD, CBT may have some advantage over the other two methods; data for BMT and PBCT are inconclusive. Quite possibly, survival has been shown to be better for CBT than for BMT or PBCT, but these results are far from conclusive.

For most of the scenarios that we developed, CBT costs more than PBCT and BMT; these latter two cost about the same.

Several factors, such as the degree of invasiveness of the procedure, the degree of match needed and the time from search to transplant, all result in a greater degree of availability for CBT than for the other two sources. However, units of CBT have a lower volume, which reduces the degree of availability. Finally, we did not determine any significant ethical issues which would favor one of the stem cell methods over others.

No single method is dominant over the others on all counts. There is simply not enough information to make a final recommendation. Considerable progress has been made in all three technologies in recent years and innovation is continuing. It is difficult to predict where each technology is headed, and so we believe that on economic grounds one cannot categorically recommend one technique over another. In particular, our report may draw attention to the higher cost of CBT; however, that method is the newest and there appear to be other significant factors which work in its favor. We therefore caution against too much emphasis on the “bottom line” that may stem from our results.

From the recent registry data, the demand for BMT in Canada has been around 180 cases per year, of which about 60% proceeded to transplantation. The
demand will increase because of population growth and widening of indications for such treatment.

Developments with the three stem cell transplantation methods should help to meet the demand from this relatively small caseload of critically ill individuals, and to narrow the gap between numbers of requests and numbers of transplants.

Table 9: Summary of factors which contribute to differences in the performance of bone marrow, peripheral blood, and cord blood technologies

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific element</th>
<th>Bone marrow (BMT)</th>
<th>Peripheral blood (PBCT)</th>
<th>Cord blood (CBT)</th>
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</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Donor infections</td>
<td>Similar to PBCT</td>
<td>Similar to BMT</td>
<td>Negligible</td>
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<td></td>
<td>Recipient infections</td>
<td>Highest</td>
<td>Lower than BMT</td>
<td>Lowest rate</td>
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<td>Efficacy</td>
<td>Probability of engraftment</td>
<td>Same for all</td>
<td>Same for all</td>
<td>Same for all</td>
</tr>
<tr>
<td></td>
<td>Time to engraftment – platelets</td>
<td>Longer than PBCT</td>
<td>Shorter than BMT</td>
<td>Longer than BMT? (limited evidence)</td>
</tr>
<tr>
<td></td>
<td>Time to engraftment – neutrophils</td>
<td>Longer than PBCT</td>
<td>Shorter than BMT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute GVHD</td>
<td>Data inconclusive</td>
<td>Data inconclusive</td>
<td>Not established, possibly less than BMT</td>
</tr>
<tr>
<td></td>
<td>Chronic GVHD</td>
<td>Less than PBCT</td>
<td>More than BMT</td>
<td>Not established</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
<td>Similar to PBCT</td>
<td>Similar to BMT</td>
<td>Possibly longer than PBCT and BMT</td>
</tr>
<tr>
<td></td>
<td>Days of hospitalization</td>
<td>Longer post-transplant, shorter in total, than PBCT</td>
<td>Shorter post-transplant, longer in total, than BMT</td>
<td>No comparable data</td>
</tr>
<tr>
<td>Cost</td>
<td></td>
<td>Slightly lower than PBCT</td>
<td>Slightly higher than BMT</td>
<td>Highest</td>
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<tr>
<td>Availability</td>
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<td>Adequate volume</td>
<td>Volume low for some users</td>
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<td>Moderately invasive</td>
<td>Not invasive</td>
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<tr>
<td></td>
<td>Degree of match needed</td>
<td>Higher degree needed</td>
<td>Higher degree needed</td>
<td>Possibly lower degree is adequate</td>
</tr>
<tr>
<td></td>
<td>Time from search to transplant</td>
<td>Longest</td>
<td>Slightly shorter than BMT</td>
<td>Shortest</td>
</tr>
<tr>
<td>Ethical issues</td>
<td></td>
<td>No major differences, except as noted in CBT</td>
<td>No major differences, except as noted in CBT</td>
<td>Anonymity may have an adverse impact if donor is subsequently found to have a disease</td>
</tr>
</tbody>
</table>
Appendix A: Methodology

This assessment was based on literature relating to current stem cell transplantation practices. As a first step, we compared PBCT and BMT techniques. We sought published articles which directly compared PBCT and BMT collections and transplants. We searched the Cancer Lit database from 1996 to 1998 for human studies with "bone marrow transplant" and "stem cell transplant" in the titles. We also searched the HealthSTAR database from 1990 to end 1998 with 'bone marrow transplantation' and 'hematopoietic stem cell transplantation' as subject words. We searched manually for additional articles using the bibliographies of any articles that were identified.

From the articles which we identified in the literature search, we abstracted information on transplants associated with infections. We also noted adverse events which were associated with donors. We conducted a separate search for information on cord blood transplants, and also drew on literature identified in an earlier report. Relevant categories of adverse events were separately abstracted.

In total we identified seven studies which compared PBCT and BMT technologies. Two of the studies (13, 16) were randomized control trials. The remaining five studies were retrospective studies (3, 4, 9, 10, 12).

In this report:
Efficacy refers to the performance of a technology under ‘ideal’ conditions or conditions of best practice; and

Effectiveness refers to the performance of a technology under ‘routine’ conditions, for example when it has become widely distributed in a health care system.
Appendix B: Costs associated with the bone marrow process.

NOTE: Annualized costs of machines and corresponding inventory systems are based on a depreciation rate of 5% per year over a ten year period.

Transplant Centre

Confirmatory Testing: Confirmatory testing costs $150 per donor.
Source: Unrelated Bone Marrow Donor Registry Business Plan, March 1997.

Transplant: The cost of transplantation $140,000 per case.
Source: Calgary Regional Health Authority.

Recruitment Centre

Recruitment: The cost of donor recruitment is $9 per recruit. This consists of the following components.

Pamphlets: Based on the assumption of printing 100,000 five-panel color pamphlets, at twenty cents each, total cost of providing pamphlets is $20,000.00.

Information sessions: Each session takes approximately four hours to coordinate by staff who receive $15 per hour. The cost of coordinating each session is therefore $60. Based on 30 recruits attending each session, the cost is $2 per recruit/donor.

Review of health assessment forms: Everyone willing to join the registry completes a consent form and a health assessment form. The staff then reviews the health assessment form; this takes approximately five minutes per form. Based on 30 people per session, the cost of reviewing these forms is $37.50, or $1.25 per recruit/donor.

Interview: An interview, lasting about fifteen minutes, may also be done with each potential participant by the staff. This involves the cost of laboratory, which is $15 per hour or $3.75 per recruit/donor.

Source: Kim Brundrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

Registry

Donor Maintenance: The overhead costs of operating a registry is calculated as $3,266,310. Included in this figure are the following business units:

- Donor Centres (includes Western Region $648,885; Ontario Region $649,885; Quebec Region $551,075; Atlantic Region $161,280).
- CNCC (Search Office $364,000)
- Program Management (includes Program Office $612,020; Ethnic Recruitment Strategy $35,100; Corporate Sponsorship & Partners $10,100; Ethnic Racial Recruitment Promotion $25,145; Computer Services $91,200; Amortization of Hardware & Software $117,620)

Collection Centre

Medical Exam for Donor: The cost is $50.00 for a medical exam for the donor. There is an additional charge of $40 when forms are completed.
Source: Kim Brudrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

Harvest Bone Marrow: The cost of harvesting the bone marrow is $1,150 per donor.
Source: Cross Cancer Institute

Ship to Laboratory for Testing: The average shipment cost is $50. Additionally, the transport container costs $10.
Source: Dr. H. Yang, Canadian Blood Services.

Laboratory

Tissue Typing:
The following testing is done:
• Type DR: DR Typing costs $150 per unit. It is assumed that all recruits are DR screened.
  Source: Dr. H. Yang, Canadian Blood Services
• Infectious Disease Test: Testing for infectious diseases costs $120.00 per donor.
  Source: Dr. H. Yang, Canadian

Transport marrow for confirmatory testing: The bone marrow is transported from the laboratory for confirmatory testing, in a way similar to cord blood. The cost of the container and the transport payment are approximately $10 and $50 each for a total cost of $60.
Source: Dr. H. Yang, Canadian Blood Services.

Transport marrow for transplant: Once a unit is ordered, it is transported to the transplant centre via airplane, at an average cost of $167 per unit. This cost was calculated by the following: the bone marrow is shipped in a similar fashion to the way which cord blood is shipped. The container dimensions are roughly 30" x 30" x 14" and weighs approximately 50 pounds. The approximate cost to ship this from Edmonton to Toronto by express was obtained from both Air Canada and Canadian Airlines. The average of the two is $166.82 or approximately $167.00.
Sources: Air Canada, Air Freight Sales and Services and Canadian Airlines, Air Cargo Services.
Appendix C:  Costs associated with the peripheral blood process.

NOTE: Annualized costs of machines and corresponding inventory systems are based on a depreciation rate of 5% per year over a ten year period.

Transplant Centre

Confirmatory Testing:  Confirmatory testing costs $150 per donor.
Source: Unrelated Bone Marrow Donor Registry Business Plan, March 1997.

Transplant:  The cost of transplantation $140,000 per case.
Source: Calgary Regional Health Authority.

Recruitment Centre

Recruitment:  The cost of donor recruitment is $9 per recruit.  This consists of the following components.

Pamphlets: Based on the assumption of printing 100,000 five-panel color pamphlets, at twenty cents each, total cost of providing pamphlets is $20,000.00.

Information sessions:  Each session takes approximately four hours to coordinate by staff who receive $15 per hour.  The cost of coordinating each session is therefore $60.  Based on 30 recruits attending each session, the cost is $2 per recruit/donor.

Review of health assessment forms:  Everyone willing to join the registry completes a consent form and a health assessment form.  The staff then reviews the health assessment form; this takes approximately five minutes per form.  Based on 30 people per session, the cost of reviewing these forms is $37.50, or $1.25 per recruit/donor.

Interview:  An interview, lasting about fifteen minutes, may also be done with each potential participant by the staff.  This involves the cost of labor, which is $15 per hour or $3.75 per recruit/donor.

Source: Kim Brundrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

Registry

Donor Maintenance:  The overhead costs of operating a registry is calculated as $3,266,310.  Included in this figure are the following business units:

- Donor Centres (includes Western Region $648,885; Ontario Region $649,885; Quebec Region $551,075; Atlantic Region $161,280).
- CNCC (Search Office $364,000)
• Program Management (includes Program Office $612,020; Ethnic Recruitment Strategy $35,100; Corporate Sponsorship & Partners $10,100; Ethnic Racial Recruitment Promotion $25,145; Computer Services $91,200; Amortization of Hardware & Software $117,620)
  Source: Unrelated Bone Marrow Donor Registry Business Plan, March 1997.

Collection Centre

**Medical Exam for Donor:** The cost is $50.00 for a medical exam for the donor. There is an additional charge of $40 when forms are completed.
Source: Kim Brudrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

**Harvest Peripheral Blood Stem Cells:** The peripheral blood stem cells are collected using pheresis procedures. Three procedures are done; for each collection the Canadian Blood Services charges $1700. There is also a drug used called granulocyte colony-stimulating factor. It is given in a dosage of 480 micrograms for eight days. Each dosage costs $226.73, for a total cost of $1813.84.
Source: Kim Brudrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

**Ship to Laboratory for Testing:** The average shipment cost is $50. Additionally, the transport container costs $10.
Source: Dr. H. Yang, Canadian Blood Services.

Laboratory

**Tissue Typing:**
The following testing is done:
• **Type DR:** DR Typing costs $150 per unit. It is assumed that all recruits are DR screened.
  Source: Dr. H. Yang, Canadian Blood Services
• **Infectious Disease Test:** Testing for infectious diseases costs $120.00 per donor.
  Source: Dr. H. Yang, Canadian Blood Services

Transport peripheral blood stem cells for confirmatory testing: peripheral blood stem cells are transported in a way similar to cord blood. The cost of the container and the transport payment are approximately $10 and $50 each for a total cost of $60.
Source: Dr. H. Yang, Canadian Blood Services.
Transport for transplantation: Once a unit is ordered, it is transported to the transplant centre via airplane, at an average cost of $167 per unit. This cost was calculated by the following: the peripheral blood stem cells are shipped in a similar fashion to the way which cord blood is shipped. The container dimensions are roughly 30" x 30" x 14" and weighs approximately 50 pounds. The approximate cost to ship this from Edmonton to Toronto by express was obtained from both Air Canada and Canadian Airlines. The average of the two is $166.82 or approximately $167.00.

Sources: Air Canada, Air Freight Sales and Services and Canadian Airlines, Air Cargo Services.
Appendix D: Data appendix of costs associated with the cord blood process.

NOTE: Annualized costs of machines and corresponding inventory systems are based on a depreciation rate of 5% per year over a ten year period.

Transplant Centre

Confirmatory Testing: Confirmatory HLA typing (class I and class II) is done using a very small sample of the cord blood. The cost is $150 per unit.
Source: Dr. H. Yang, Canadian Blood Services

Thaw Frozen Cells: To thaw the frozen cells, a warm water bath is used. The machine, itself, costs $2000 to purchase; annualized cost is $159.01. The machine requires maintenance at a cost of $500 over a five year period, therefore averaging $100 per year.
Source: Dr. H. Yang, Canadian Blood Services.

Transplant: The cost of transplantation is based on 30 days of hospitalization / treatment at $1000 per day, for a total of $30,000.
Source: Kim Brundrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.

Cord Blood Recruitment:

Recruitment: The cost of donor recruitment is $9 per recruit. This consists of the following components.

Pamphlets: Based on the assumption of printing 100,000 five-panel color pamphlets, at twenty cents each, total cost of providing pamphlets is $20,000.00.

Information sessions: Each session takes approximately four hours to coordinate by staff who receive $15 per hour. The cost of coordinating each session is therefore $60. Based on 30 recruits attending each session, the cost is $2 per recruit/donor.

Review of health assessment forms: Everyone willing to join the registry completes a consent form and a health assessment form. The staff then reviews the health assessment form; this takes approximately five minutes per form. Based on 30 people per session, the cost of reviewing these forms is $37.50, or $1.25 per recruit/donor.

Interview: An interview, lasting about fifteen minutes, may also be done with each potential participant by the staff. This involves the cost of labor, which is $15 per hour or $3.75 per recruit/donor.

Source: Kim Brundrit, Canadian Blood Services, Unrelated Bone Marrow Donor Registry.
Cord Blood Registry

**Donor Maintenance:** The overhead costs of operating a registry is calculated as $3,266,310. Included in this figure are the following business units:
- Donor Centres (includes Western Region $648,885; Ontario Region $649,885; Quebec Region $551,075; Atlantic Region $161,280).
- CNCC (Search Office $364,000)
- Program Management (includes Program Office $612,020; Ethnic Recruitment Strategy $35,100; Corporate Sponsorship & Partners $10,100; Ethnic Racial Recruitment Promotion $25,145; Computer Services $91,200; Amortization of Hardware & Software $117,620)

Source: Unrelated Bone Marrow Donor Registry Business Plan, March 1997.

Collection Site

**Collection of Cord Blood:** Total cost of collecting the cord blood is $35. This cost is broken down as follows. The cord blood is collected using a collection kit which includes the blood bag and other supplies necessary. The cost of the kit is $20 per unit. Once collected, the cord blood is transported to the collection centre, at a cost of $10 per cord. A sample of the mother’s blood is also drawn at a cost of approximately $5.

Source: Dr. H. Yang, Canadian Blood Services.

**Transportation to the Processing Centre:** Total cost of shipping the cord blood is $60. The cord blood is transported to the processing centre in a styrofoam transport container, which costs $10. The transport fee is an average of $50 per cord.

Source: Dr. H. Yang, Canadian Blood Services.

Laboratory

**Process for Storage:** In processing the cord blood, a volume reduction machine is used, which costs approximately $15,000; annualized to $1,192.58. Supplies (plasma transfer bags, syringes, swabs, and tubes) cost $70. This $70 covers the cost of supplies and the processing fee, but not labor.

Source: Dr. H. Yang, Canadian Blood Services.

**Tissue Typing:** Tissue typing involves the following tests:
- Class I and Class II HLA typing at a cost of $150 per sample. Everything is included in this cost: supplies, labor, and results.
- Colony Forming Units: $25, which includes the cost of supplies only.
- Tests for infectious diseases: These tests include screening for the following: HbsAg, Anti-HBs, Anti-HIV-1 and 2, Anti-HCV, Anti-HTLV 1 and 2, HIV-p24 Ag, Syphilis, ABO/Rh, and Anti-CMV. This series of tests costs $120 per sample, which includes both supplies and labor. A brief description of each
of the screening tests follows. Indicated in parentheses is the source of blood on which each test is done.

- HBsAg: is a serologic marker for HBV, a hepatitis B surface antigen. (mother’s blood)
- Anti-HBs: is an antibody to HBsAg. (mother’s blood)
- Anti-HIV-1/2: antibodies to HIV-1/2. (mother’s blood)
- Anti-HCV: an antibody to the hepatitis C virus. (mother’s blood)
- Anti-HTLV-1/2: screening tests are done for HTLV (Human T-Cell Lymphotropic Viruses) – type 1 and 2 antibodies. (mother’s blood)
- HIV-p24Ag: antigenic viral material. (mother’s blood)
- Syphilis: Serologic testing for syphilis is required as an indicator of potentially high-risk behavior that makes transmission of more organisms more likely. (mother’s blood)
- ABO/Rh: This test is done for the blood type. (mother’s blood, recipient)
- Anti-CMV: antibodies to cytomegalovirus. (mother’s blood)

Sources: Dr. H. Yang, Canadian Blood Services.
Linda Podlosky

**Sterility test:** This is a bacterial culture test done using a sample of the cord blood. It costs $50, including both supplies and labor.
Source: Dr. H. Yang, Canadian Blood Services.

**Cyropreservation and Storage:** Total cost is approximated as $7 and consists of the following:
- The Control rate machine costs $20,000; annualized cost is $1,590.10.
- The quarantine tank costs $4,000; annualized cost is $318.02.
- The inventory system for the quarantine tank is $2400; annualized cost is $190.81.
- Cost of the freezer and its inventory system are $13,000 and $17,000 respectively. The annualized costs are $1,033.57 and $1,351.59. Each freezer holds 852 units.
- Liquid nitrogen is used and costs $2500 per freezer.
Source: Dr. H. Yang, Canadian Blood Services.

**Process for shipping:** The cord blood is shipped in a dry shipper container, which is $3,000 to purchase; annualized cost is $238.52.
Source: Dr. H. Yang, Canadian Blood Services.
Transport for transplant: Once a unit is ordered, it is transported to the transplant centre via airplane, at an average cost of $167 per unit. This cost was calculated by the following: the cord blood is shipped in the dry shipper for which the dimensions are roughly 30" x 30" x 14" and weighs approximately 50 pounds. The approximate cost to ship this from Edmonton to Toronto by express was obtained from both Air Canada and Canadian Airlines. The average of the two is $166.82 or approximately $167.00.
Sources: Air Canada, Air Freight Sales and Services and Canadian Airlines, Air Cargo Services.

Sensitivity Analysis of Costs
(Refer to text for precise details on each scenario)

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<tr>
<th>Scenario Description</th>
<th>Bone Marrow</th>
<th>Peripheral Blood</th>
<th>Cord Blood</th>
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<td>Base case</td>
<td>$270,681</td>
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<td>Fewer donors needed for cord blood / lower recruitment costs for cord blood</td>
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References


