Stem Cells and Ethics

A case study of a specific stem cell therapy: bone marrow transplantation, where the donor is a child.

Followed by issues concerning the ethics of human genome editing.

Ethics: Rules of behavior based on what is morally good and bad\(^1\).

A conundrum: What is the basis for the definition of “good” and “bad”?  

\(^1\) Merriam-Webster Dictionary
X-linked lymphproliferative disease causes exaggerated response to E-B virus and destruction of bone marrow.
The First Stem Cell Therapy: Bone Marrow Transplantation

First bone marrow transplant: 1968

Other sources of blood stem cells for transplantation: Peripheral blood or umbilical cord blood

Success of a transplant requires a good HLA haplotype match between donor and recipient.
The Human Leukocyte Antigen (HLA) haplotype defines cells as “self” or “non-self” to the Immune system.

- **Class I**
  - HLA-A
  - HLA-B
  - HLA-C
  - DR
  - DQB
  - DPA
  - DPB

- **Class II**
  - DP
  - DQ
  - DR

**Number of known alleles**

- **Class I**
  - HLA-A: 214
  - HLA-B: 425
  - HLA-C: 108
  - DRA: 2
  - DRB1: 289
  - DQA1: 21
  - DQB1: 46
  - DPA1: 19
  - DPB1: 94

- **Class II**
  - DP: 747
  - DQ: 479

**Total alleles**

- **Class I**: 747
- **Class II**: 479

Additional resources:

- [HLA Complex Diagram](http://jmd.amjpathol.org/cms/attachment/935790/6815854/si1.gif)
- [HLA Nomenclature](http://hla.alleles.org/ nomenclature/index.html)
Bone Marrow Transplantation and Matching Human Leukocyte Antigens (HLA) Antigens.

The closer the numbers of matches of HLA antigens for the patient and the donor, the higher the probability that a transplant will be therapeutically successful.
Patient Survival after Bone Marrow Transplantation vs. Numbers of HLA Mismatches


All bone marrow transplants in U.S. from 1988-1996. 91% of patients transplanted as part of therapy for a malignant disease.
Graft vs. Host Disease (GvHD) after Bone Marrow Transplantation vs. Numbers of HLA Mismatches

Percent of Patients that Develop GvHD

Days After Transplant

0 7 14 21 28 35 42 49 56 63 70 77 84 91 98

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

P = .001

2+ mismatches (n=114)
1 mismatch (n=318)
0 mismatches (n=825)


GvHD-Graft vs. Host Disease

©2004 by American Society of Hematology
Diseases where bone marrow transplantation is used as therapy

- Acute lymphoblastic leukemia (Childhood leukemia)
- Acute myeloid Leukemia
- Chronic myeloid leukemia
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma
- Neuroblastoma
- Myelodysplastic syndrome
- Multiple myeloma
- Severe aplastic anemia
- Chronic lymphocytic leukemia
The HLA haplotypes of two siblings are likely to be significantly closer than between two unrelated Individuals. Thus, siblings may be the best possible donors of bone marrow or of other cells, tissue or organs.

What are the ethical issues inherent to bone marrow transplantation, especially when the donor is a sibling?
What is the probability that a bone marrow transplant will be therapeutically effective?

*The therapeutic efficacy of bone marrow transplantation differs with the disease that it is being used to cure.*
Bone Marrow Transplantation as Treatment for Severe Aplastic Anemia is Often Successful

But the probability that the transplant will succeed depends on the relatedness of the donor and the transplant recipient as well as the age of the donor.
Bone Marrow Transplantation as Treatment for Hodgkin Lymphoma

Less than 50% of patients survive for 5 years. However, survival rates are statistically higher if the donor is a sibling.
Should you weigh the probable therapeutic efficacy of a bone marrow transplant in making a decision to offer a patient a transplant?

How does this probability affect a decision to use a sibling as the donor?
Informed consent is the process by which the treating health care provider discloses appropriate information to a competent potential donor so that he/she may make a voluntary choice to donate. (Appelbaum, 2007). It originates from the legal and ethical right the patient has to direct what happens to her body and from the ethical duty of the physician to involve the patient in her health care.

In the consent process, the care giver should answer the following questions for the patient:

What is involved in donating bone marrow?
What are the alternatives?
What are the risks and benefits?
Does the patient understand what he/she is being told?
Does the patient agree to the procedure?

Consent must be voluntary. Coercive measures can not be used to obtain consent.

Is asking a sibling to be a donor inherently coercive?

Adapted from: https://depts.washington.edu/bioethx/topics/consent.html
Ethical Considerations in Bone Marrow Transplantation
Especially when Both the Recipient and Donor Are Children.

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
Ethical Considerations in Bone Marrow Transplantation

*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
   What is the probability that the transplant will significantly benefit the recipient?
   If the recipient is a child, how do they give informed consent?
   If the child is the recipient, how do you weigh the risks verses the benefits?
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
Risks to the recipient of a bone marrow transplant.

### Table 3

Bone marrow transplant (BMT) recipient health complications. The long-term health complications children face post-BMT

<table>
<thead>
<tr>
<th>Health complication</th>
<th>Percent of survivors afflicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Cataracts</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Chronic graft versus host disease</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Infertility</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Delayed sexual development</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Oral and dental problems</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Secondary malignant neoplasms</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
Ethical Considerations in Bone Marrow Transplantation

Both the recipient and donor are children.

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
   How do they give informed consent?
   What do you do if a child is the only possible donor and appears to be at risk for significant psychological trauma from the procedure?
   Are slight medical risks to the donor acceptable?
   How do you measure benefits to the donor?
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
Ethical Considerations in Bone Marrow Transplantation

*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
   *Savior siblings.*
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
Born to save her sister's life: Anissa was conceived simply to save her cancer stricken sister...and said she has never looked back

By RACHEL QUISELEY
UPDATED: 18:17 EST, 5 June 2011

Some people are born to do certain things.
Marissa Ayala was born simply to save her sister’s life.
The Ayala family, from California, shocked the world 20 years ago when it was revealed that they were conceiving a child just so they could provide a suitable bone marrow match for their leukemia-stricken daughter Anissa.

The Saved Sibling, child with leukemia saved by bone marrow transplant from her savior sibling

The Savior Sibling conceived to provide bone marrow
Ethical Considerations in Bone Marrow Transplantation

*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
   - **Savior Siblings**: Some parents of a child needing a bone marrow donation decide to have a second child so that there is a bone marrow donor for a sibling.
   - **Savior Siblings**: HLA typing of preimplantation embryos to determine if the child that is born can be a donor.
   - **Savior Siblings**: Conception of a child so that placental cord blood can be used as a source of blood stem cells.
   - **Future**: Human embryos produced solely for the generation of stem cells.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
Ethical Considerations in Bone Marrow Transplantation

*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
   - If the donor and the recipient are related, how can the donor be put through the process of giving consent without the donor experiencing psychological pressure?
5. The socio-economic context surrounding bone marrow transplantation.
Ethical Considerations in Bone Marrow Transplantation

*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.
   
   Do patients who need a bone marrow transplant have a right to treatment even if they can not pay for the treatment?
   
   **If they do, who pays?**
Bone Marrow Transplantation in the United States: 
*Cases and Costs*

<table>
<thead>
<tr>
<th>Transplant type</th>
<th>No. of Transplants</th>
<th>Cost/transplant</th>
<th>Total dollars spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>10,542</td>
<td>$360,000</td>
<td>$3,795,120,000</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>7,742</td>
<td>$800,000</td>
<td>6,193,600,000</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>18,284</strong></td>
<td></td>
<td><strong>$9,988,720,000</strong></td>
</tr>
</tbody>
</table>

Autologous: Bone marrow comes from the patient
Allogeneic: From a patient's family or a volunteer donor.

*A prerequisite for obtaining allogeneic bone marrow is that the donor gives informed consent.*
Ethical Considerations in Bone Marrow Transplantation
*Both the recipient and donor are children.*

1. The risks and benefits to the recipient
2. The risks and benefits to the child that donates the bone marrow.
3. New approaches to obtaining a donor.
4. The Context and structure of the decision-making process
5. The socio-economic context surrounding bone marrow transplantation.

Do patients who need a bone marrow transplant have a right to treatment even if they can not pay for the treatment?
**If they do, who pays?**

If a potential donor is *impoverished*, can financial *inducements* be used to secure informed consent from that donor?

Since health care dollars are *finite*, how do we *balance* paying for this procedure with not paying for others? Who decides if transplantation is funded by private health insurance, or by medicaid and other governmental insurance programs?

Some *ethnic* groups are more likely to donate bone marrow than others. Should *funds be expended* to secure donors from those specific groups?
Policy Statement—Children as Hematopoietic Stem Cell Donors

CONDITIONS UNDER WHICH A MINOR MAY PARTICIPATE AS A HEMATOPOIETIC STEM CELL DONOR

Currently, there are no guidelines regarding participation of minors as hematopoietic stem cell donors. The AAP believes it is ethically permissible for minors to participate as donors if 5 criteria are fulfilled. The criteria are: (1) there is no medically equivalent histocompatible adult relative who is willing and able to donate; (2) there is a strong personal and emotionally positive relationship between the donor and recipient; (3) there is some likelihood that the recipient will benefit from transplantation; (4) the clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient; and (5) parental permission and, where appropriate, child assent have been obtained.

Donor is a histocompatible sibling.
Policy Statement—Children as Hematopoietic Stem Cell Donors

1. A donor advocate with expertise in pediatric development be assigned to the potential donor.
2. Include the child who is a potential donor in the decision making process. The advocate should assist the child in making the decision. Hospital ethics committees should be empowered to prevent donation if they determine there will be long-term psychological damage to the potential donor.
3. Ablative therapy of the recipient should not begin until there is a clear decision to go forward with the transplant. Once therapy has started, the child donor can not renege.
4. Pediatricians should be aware that they may be asked about IVF with preimplantation genetic diagnosis to insure that the child that cord blood stem cells can be used for transplantation.

Do these recommendations exclude savior siblings?
Stem Cells and Ethics

A case study of a specific stem cell therapy: bone marrow transplantation, where the donor is a child.

Ethics: Rules of behavior based on what is morally good and bad\(^1\).

A conundrum: What is the basis for the definition of “good” and “bad”?

\(^1\) Merriam-Webster Dictionary
HUMAN GENOME EDITING
Science, Ethics, and Governance

Committee on Human Gene Editing:
Scientific, Medical, and Ethical Considerations

A Report of
NATIONAL ACADEMY OF SCIENCES AND
NATIONAL ACADEMY OF MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu
Sequence-Specific DNA Cleavage by Crispr/Cas9

Crispr/Cas9 and guide RNA.

Guide RNA, a synthetic fusion of the endogenous bacterial crRNA (Crispr RNA) and tracrRNA (transactivating Crispr RNA); Provides both targeting specificity and scaffolding/binding ability for Cas9 nuclease; Does not exist in nature; Also referred to as "single guide RNA" or “sgRNA”.

PAM = Protocospacer Adjacent Motif In bacteria, the PAM sequence is essential for distinguishing between “self” and ‘Non-self” (viral) DNA. For Cas 9, the PAM sequence is NGG

Cas9 is from Streptococcus pyogenes. (Addgene: CRISPR/Cas9 Guide)

https://www.neb.com/products/m0386-cas9-nuclease-s-pyogenes

Sequence design: http://crispr.mit.edu/
DNA Repair When Eukaryote DNA is Cut by Crispr/Cas9 Crispr-Cas9 and DNA Repair is Achieved by Homologous Repair, Not NHEJ.
**Gene Editing Clinical Trials**

**Ex vivo editing** of a patients cells and infusion of edited cells back into the patient:

Trial 1: Editing/inactivation in hematopoietic stem cells of *BCL11A gene*, a repressor of the fetal hemoglobin expression.
  Disease: β Thalassemia (life threatening anemia).
Trial 2: Editing/inactivation in CD4^+^ T cells of the AIDS virus co-receptor, *CCR5*.
  Disease: AIDS
Trial 3: Editing T cells to enhance their ability to kill cancer cells in relapsed patients.
  Disease: Cancer

**In vivo editing** using virus to deliver vectors to cells.

Trial 1: Injection into the eye to correct a point mutation in the *CEP290* gene, which is important to proper cilia formation.
  Disease: Childhood blindness.
Trial 2: Insertion of the iduronate 2-sulfatase gene into the albumin locus of liver.
  Disease: Lysosomal storage (Hunter) disease- short stature, multiple skeletal abnormalities, macrocephaly, hydrocephaly, enlarged liver.
What are the prerequisites for beginning human genome editing?

CONCLUSIONS AND RECOMMENDATIONS

Significant scientific progress will be necessary before any genome-editing intervention for indications other than the treatment or prevention of disease or disability can satisfy the risk/benefit standards for initiating a clinical trial. This conclusion holds for both somatic and heritable germline interventions. There is significant public discomfort with the use of genome editing for so-called “enhancement” of human traits and capacities beyond those typical of adequate health. Therefore, a robust public discussion is needed concerning the values to be placed upon the individual and societal benefits and risks of genome editing for purposes other than treatment or prevention of disease or disability. These discussions would include consideration of the potential for introducing or exacerbating societal inequities, so that these values can be incorporated as appropriate into the risk/benefit assessments that will precede any decision about whether to authorize clinical trials.

RECOMMENDATION 6-1. Regulatory agencies should not at this time authorize clinical trials of somatic or germline genome editing for purposes other than treatment or prevention of disease or disability.

RECOMMENDATION 6-2. Government bodies should encourage public discussion and policy debate regarding governance of somatic human genome editing for purposes other than treatment or prevention of disease or disability.
RECOMMENDATION 2-1. The following principles should undergird the oversight systems, the research on, and the clinical uses of human genome editing:

• 1. Promoting well-being
• 2. Transparency
• 3. Due care
• 4. Responsible science
• 5. Respect for persons
• 6. Fairness
• 7. Transnational cooperation

What is the definition of “well-being?”

What is the definition of “fairness?”
There are Finite Funds for Health Care and for Biomedical Research. 
*How should we prioritize use of these funds?*

### Infant Mortality in U.S.A.

<table>
<thead>
<tr>
<th>Country</th>
<th>Deaths per 1,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monaco</td>
<td>1.8</td>
</tr>
<tr>
<td>Japan</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>3.3</td>
</tr>
<tr>
<td>Israel</td>
<td>3.4</td>
</tr>
<tr>
<td>Germany</td>
<td>3.4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>4.3</td>
</tr>
<tr>
<td>Cuba</td>
<td>4.4</td>
</tr>
<tr>
<td>Canada</td>
<td>4.5</td>
</tr>
<tr>
<td>USA</td>
<td>5.8</td>
</tr>
</tbody>
</table>

In 2017 there were approximately 22,000 infant deaths in the United States.

Sources: CIA World Factbook
CDC National Center for Health Statistics