Bone Marrow Transplants
Conditioning
Chemotherapy or chemotherapy plus radiation
- destroys bone marrow so there is room for new
- destroys recipients immune system so it doesn’t destroy transplanted cells
- destroys diseased cells (leukemic or pre-leukemic)
These treatments lead to an increased risk for infections during treatment
- also nausea, vomiting, hair loss, skin rash, mouth sores
Long term these treatments lead to an increased risk for:
- sterility
- endocrinopathies
- cancer
- rarely - vessels in liver swell shut, jaundice, liver damage
- rarely - lung damage or cardiomyopathy
FA patients have impaired DNA repair, and thus these treatments are less well tolerated and more risky for them

Affected child in this case was treated with
- cyclophosphamamide
- total body irradiation also needed due to MDS (preleukemia)
Introduction of new cells
Bone marrow or cord blood is put into the blood of the transplant recipient. The bone marrow cells will travel to their proper locations in the recipient’s bones and establish themselves there.

Treatments to prevent infection during immunosuppression
Granulocyte colony stimulating factor
to increase white cell production
Anti-fungal (prevent candida and aspergillus)
Cefazolin (prevent Streptococcal infection)
Acyclovir (prevent herpes infection)
Cotrimoxazole (prevent pneumocystis infection)

Additional Treatments
Cyclosporin A
to prevent graft versus host (GVH)
(the transplanted cells attack the recipient)
Engraftment
Usually donor bone marrow cells begin to function in the recipient within 30 days.

Affected child in this case
Neutrophils were to target levels by day 17
Platelets were to target levels by day 30

Blood, 103:1147
Long-term
Affected child in this case
No acute or chronic GVH (she had a matched sibling donor)
Mild adenovirus gastroenteritis resolved by 3 mos
No other opportunistic infections developed
Mild drug related toxicity developed in the liver
All medications were discontinued by 24 months post transplant.

Molly Nash
Molly still needs treatment for some of her congenital defects (intestinal and spinal abnormalities)
Her risk of developing cancer other than leukemia remains high since the other cells in her body still contain mutations in FANCC.
Importance of a Matched Donor
2 year survival rates vary for FA patients who have received BMTs
matched sibling donor - 66 - 85%
match from bank 22 - 40%

What does a matched donor mean?
Our cells have molecules on their surface called human leukocyte antigens (HLA).
Our immune system uses to these molecules to distinguish between
our cells and invaders.
These molecules enable infected cells to signal and initiate an
immune response.

In a matched donor, the molecules on the surface of the donor cells
would be the same as those found on the surface of the recipient.
Why is it important for HLA type to match?
If the HLA antigens are the same between the donor and the recipient, neither with recognize the other as foreign.

If the HLA antigens are different...

Possibility 1
The donor bone marrow cells may recognize the recipient cells as foreign and attack the recipient. This can range from mild to fatal. It is known as Graft versus Host or GVH. GVH is a major risk in all BMT.

Possibility 2
Any remaining bone marrow cells in the recipient may recognize the transplant as foreign and destroy it.
There are two type of HLA: Major Histocompatibility Classes I and II

**MHC Class I antigens.** These antigens are found on the surface of all nucleated cells in our body. In humans the MHC Class I antigens are called HLA-A, HLA-B and HLA-C.

**MHC Class II Antigens**
These antigens are found on B-cells and macrophages. In humans these antigens are HLA-D, HLA-DR, HLA-DP and HLA-DQ
For transplant purposes
HLA-A, HLA-B and HLA-DR antigens are the most important.

Since you have two copies of the genes for each of these antigens (one from your mother, one from your father), there are 6 antigens that need to be matched. They are all co-dominant, meaning they are all expressed on the surface of cells.

A bone marrow transplant will not usually be done unless 5 out of 6 of these antigens match, and 6 out of 6 is considered best.

Matching of additional HLA antigens (beyond HLA-A, HLA-B and HLA-DR) is optimal and reduces chances of long-term complications.
HLA variability
HLA genes are highly variable in humans. This polymorphism represents a species response to maximize protection against diverse microorganisms.

This diversity in HLA antigens makes finding a transplant donor difficult.
# Chances of finding a matched donor

<table>
<thead>
<tr>
<th>Affected child’s HLA type</th>
<th>Frequency of HLA type in population</th>
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</thead>
<tbody>
<tr>
<td>HLA-A2</td>
<td>10 - 30%</td>
</tr>
<tr>
<td>HLA-A26</td>
<td>2 - 4%</td>
</tr>
<tr>
<td>HLA-B44</td>
<td>3 - 5%</td>
</tr>
<tr>
<td>HLA-B35</td>
<td>4 - 10%</td>
</tr>
<tr>
<td>HLA-DRB1 1001</td>
<td>?</td>
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<tr>
<td>HLA-DRB1 0402</td>
<td>?</td>
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</tbody>
</table>

A rough estimation of the probability of any given individual being a matched donor for the child:

\[
0.2 \times 0.03 \times 0.04 \times 0.07 \times 0.05 \times 0.05 = 0.0000000042
\]

42 out of 1 billion people will have this HLA type.

Currently around 3 million people in bone marrow donor registry.
Chances of creating an HLA-matched sibling

All HLA genes are located on chromosome 6
Recombination between the HLA loci is relatively rare

So, chances of any given sibling being a matched donor are just under 25%
In addition, the sibling will be matched at other HLA loci as well.
To create a sibling who could serve as a donor,
The case we are discussing goes beyond just HLA matching, we need to find an embryo that is FA-free and is HLA-matched. HLA matching is on chromosome 6, FANCC is on chromosome 9, So, we are looking at 2 chromosomes rather than one.

The genotypes of the family members are shown below. What are the chances of creating an HLA-matched, FA-free embryo?