Stem Cell Transplantation for Severe Congenital Neutropenia

Kasiani Myers, M.D.

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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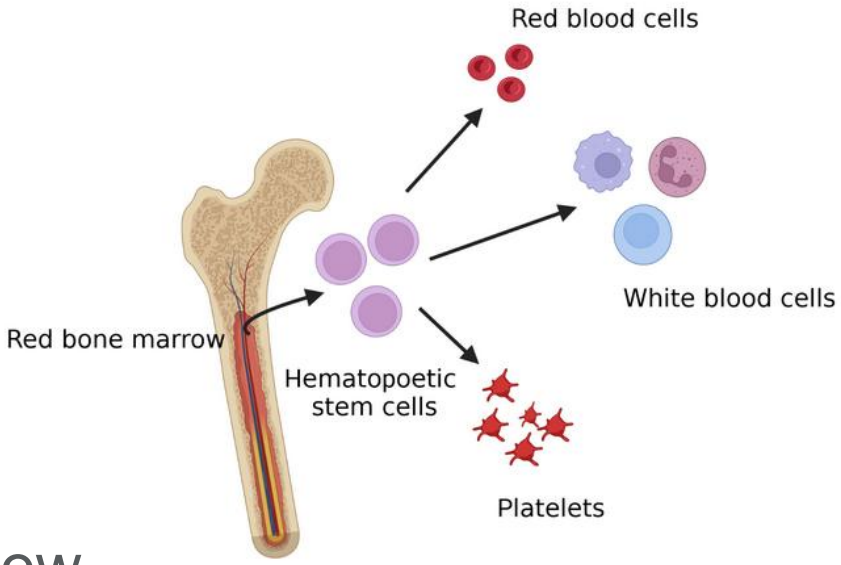
What are Stem Cells?

- All blood cells come from hematopoietic stem cells that live in the bone marrow
  - Red blood cells
    - carry oxygen
  - White blood cells
    - fight infection and form immune system
  - Platelets
    - stop bleeding forming clots
- Stem cells are like seeds
- Stem cells can grow a whole new bone marrow in a different person over time.



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Implications of SCN Diagnosis in considering HSCT

- HSCT is the only current potentially curative option for hematologic disease BUT
- The right *diagnosis* is critical
  - Why does it matter? SCN is SCN…
  - Transplant for SCN is challenging due to inherent but variable chemotherapy and radiation sensitivity across neutropenia syndromes
    - ELANE ≠ Shwachman Diamond Syndrome ≠ Barth's etc
- The right *timing* is critical
  - High risk therapy – preemptive transplant is not offered
- Decision to undergo HSCT should be made with a team experienced with SCN

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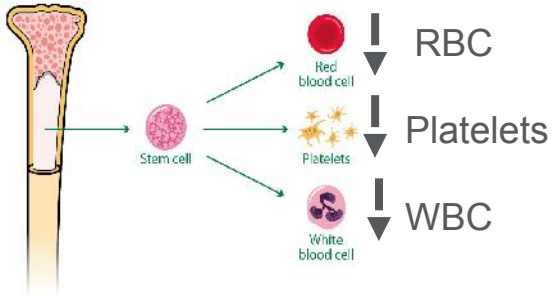
When do we consider HSCT in SCN

- Severe neutropenia (ANC <500)
  - not responsive to G-CSF, especially with recurrent infections
  - Severe pancytopenia/aplastic anemia: need for transfusions of red cells and/or platelets (rare)
- Myelodysplastic syndrome (MDS) **
- Acute Myeloid Leukemia (AML) **
- High risk markers
  - cytogenetic abnormalities
  - New/growing high risk mutations (needs expert interpretation)
- Consideration: Poor response to GCSF (requiring very high doses with ANC <1000-2000



**Challenge: how to predict who will get MDS/AML

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Goals of Transplantation for Patients with SCN

- Normalize the blood counts
- Achieve full engraftment
- Avoid graft rejection
- Minimize short-term and long-term toxicity
- Minimize risk of infection
- Prevent Graft *vs* Host Disease (GvHD)
- Destroy any clones, MDS or leukemia

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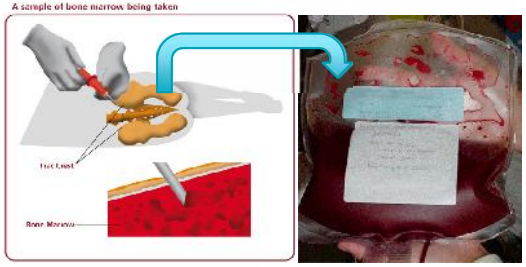
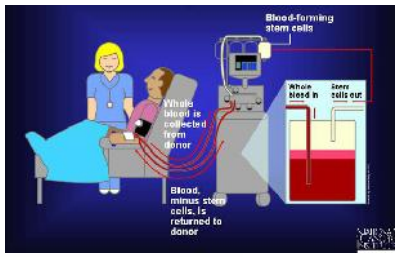
Multiple Factors Involved When Thinking About Transplantation

...It is not always an easy decision

1. How healthy is the patient?
   - Age
   - Organ function – heart, liver, lungs, kidneys
   - Other complications – such as infections
2. What kind of donor is available?
   - Matched sibling >> unrelated donor
3. What stem cell source is available?
   - Bone marrow >> cord blood or peripheral blood





4. What kind of conditioning can be used?
   - Full Intensity >> Moderate Intensity >> Minimal Intensity

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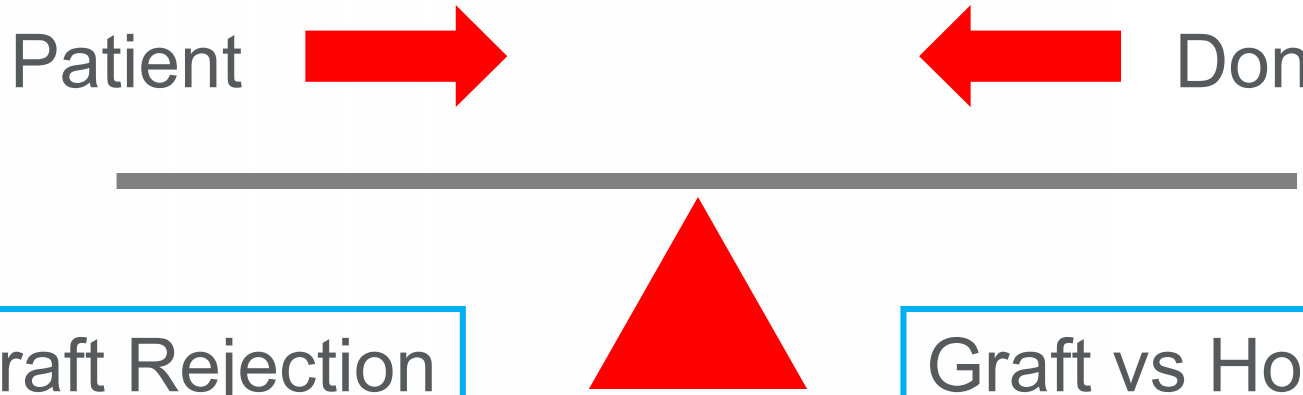
Two competing forces



Graft Rejection

Patient's immune system recognizes the donor's stem cells as foreign and "rejects" it

Graft vs Host Disease

Donor's stem cells recognize the patient as foreign and attack the patient

…we don't want either of these to happen

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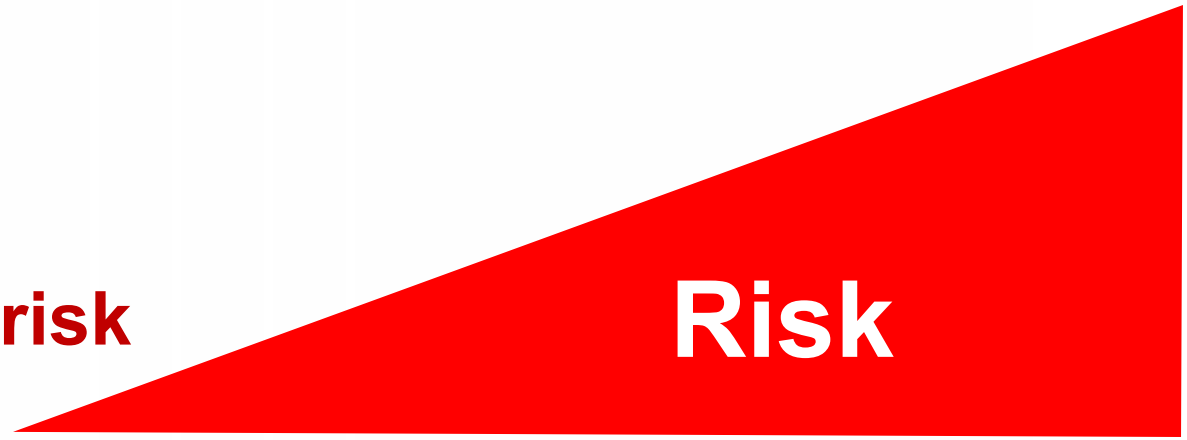
Transplant Risk



Donor:	Matched Sibling	Matched Unrelated	Mismatched Unrelated
Stem Cell Source:	Bone Marrow	Cord Blood ⟷	Peripheral Blood
Conditioning Regimen:	Minimal Intensity	Moderate Intensity	Full Intensity

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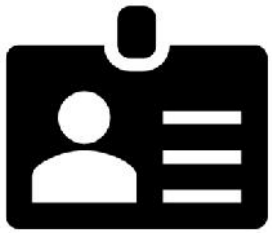
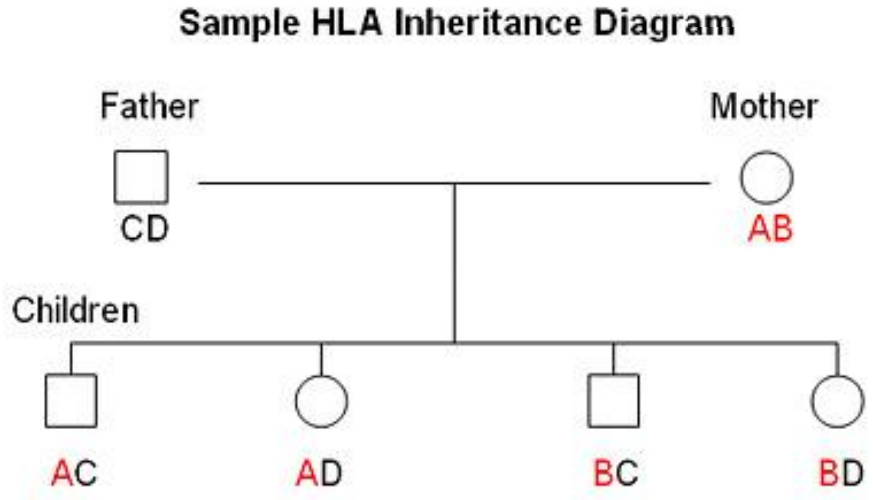
Is the sibling a “match”?

- Best match for transplant = patient’s brother or sister
- “HLA” (human leukocyte antigens – A, B, C, DR) are proteins on the surface of a cell that identify who the cell belongs to



- One in four chance that any brother or sister will be a HLA match to each other



What if the patient does not have a matched sibling donor?

- Unrelated donors = volunteers who have agreed to be tissue typed to help someone who needs a stem cell transplant
- The tissue types are stored in a large computer belonging to the National Marrow Donor Program/Be The Match in the US
- When a donor is needed the patient's tissue type is entered into the computer to see if there is match - called "running a search" through registries in the US and worldwide
- There are >19 million unrelated donors in the US registry & >29 million donors worldwide

Canadian Blood Services
it's in you to give

Registro Italiano
Donatori di Midollo Osseo

ABMDR
Australian Bone Marrow Donor Registry

Thai National Stem Cell Donor Registry

- Donations are anonymous; the patient doesn't know who the donor is until at least one year after a transplant.

Basic Principles of Transplantation:The Garden

1. Patient is given intensive drugs (called conditioning or preparative regimen) → destroy abnormal marrow, decrease the immune system → make room for healthy stem cells from donor

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4. About a year to get a normal immune system

Basic Principles of Transplantation: Preparative Regimen Intensity

- Myeloablative
  - Irradicates the bone marrow and immune system
  - Increased toxicity to the patient
- Reduced Intensity
  - Less toxicity→easier to use in sicker patients
  - May result in increased risk of donor cells not growing well in the patient receipent (graft failure)

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Transplant for SCN: Outcomes

- Most data is available for patients with ELANE mutations
- Very small series for patients with other SCN related diseases
- Typically myeloablative regimens historically
- HCT for patients with SBDS mutations leading to neutropenia are very different – discussed separately

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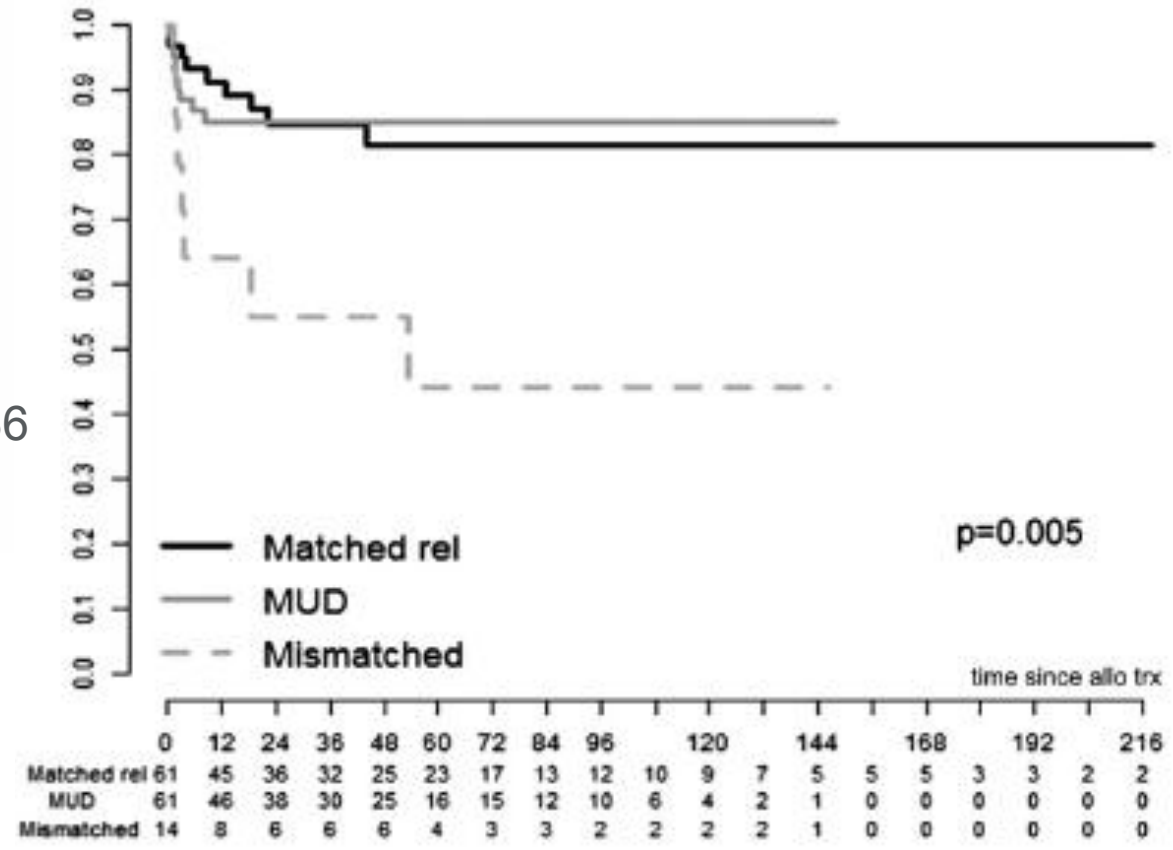
Transplant for SCN: Outcomes

- Improved with
  - Fully matched donor



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EBMT

blood

Stem cell transplantation in severe congenital neutropenia: an analysis from the European Society for Blood and Marrow Transplantation

Francesca Fioredda, Simona Iacobelli, Anja van Biezen, Bobby Gaspar, Phil Ancliff, Jean Donadieu, Mahmoud Aljurf, Christina Peters, Michaela Calvillo, Susanne Matthes-Martin, Giuseppe Morreale, Nelleke van 't Veer-Tazelaar, Liesbeth de Wreede, Amal Al Seraihy, Akif Yesilipek, Alain Fischer, Marc Bierings, Gulyuz Ozturk, Owen Smith, Paul Veys, Per Ljungman, Régis Peffault de Latour, José Sánchez de Toledo Codina, Reuven Or, Arnold Ganser, Boris Afanasyev, Robert Wynn, Krzysztof Kalwak, Judith Marsh, Carlo Dufour on behalf of the Severe Aplastic Anemia the Inborn Error, and the Pediatric Disease Working Parties of the European Society for Blood and Bone Marrow Transplantation (EBMT) and Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE)

Transplant for SCN: Outcomes

- Improved with
  - Healthier individuals and younger individuals

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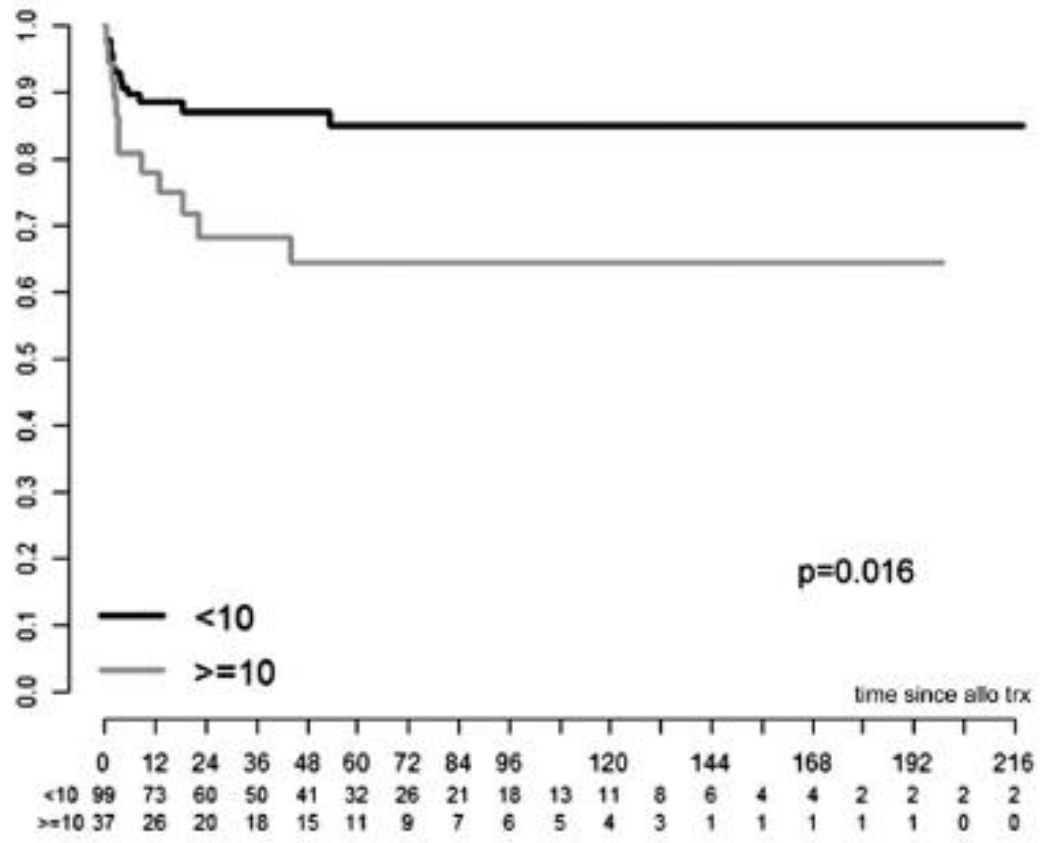

Transplant for SCN: Outcomes

- Improved with
  - More recent HCT → improvement of transplant procedures over time

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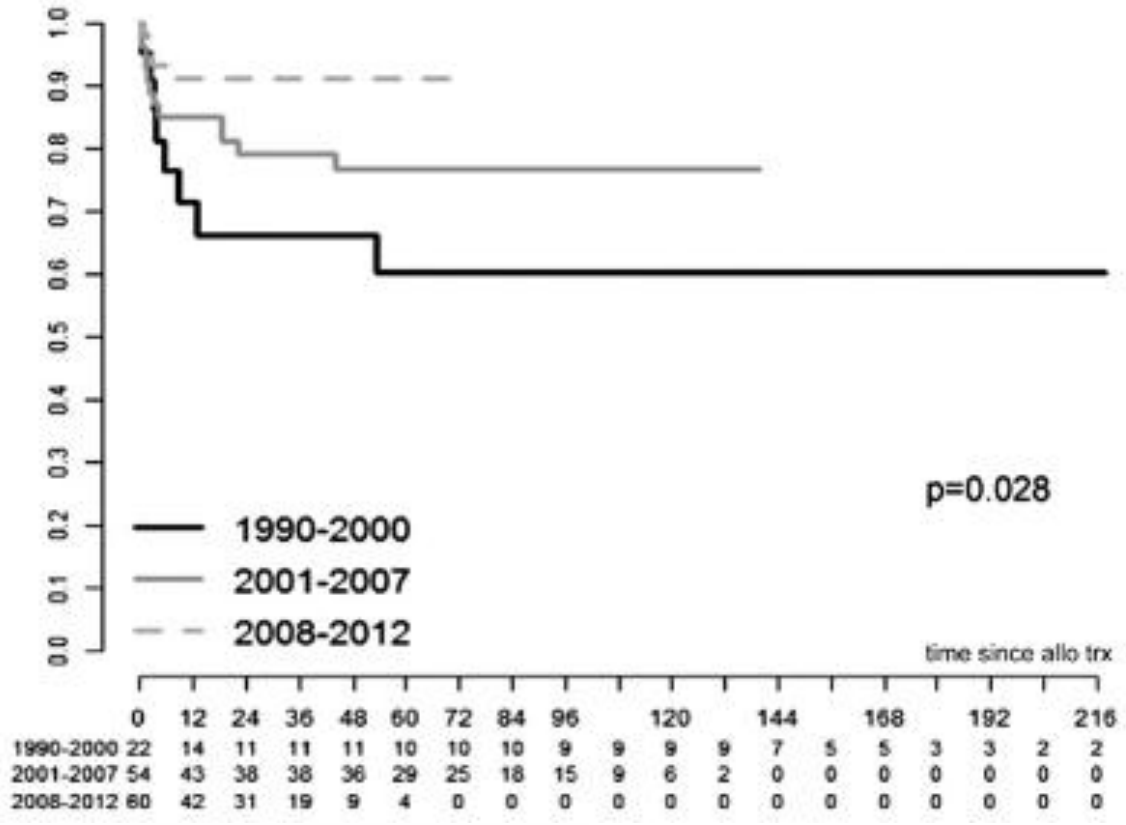

Transplant for SCN: Outcomes

- Improved with
  - Myeloablative vs Reduced Intensity

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Transplant for SCN: Outcomes

- Improved outcomes in in HCT without MDS/AML
  - Connely et al COH 2013
    - SCN without MDS/AML (n=65) 89% overall survival
    - SCN + MDS/AML (n=18) 39% overall survival
  - EBMT Fioredda et al 2017
    SCN without MDS/AML (n=73) 87% 3 yr overall survival
    SCN + MDS/AML (n=14) 79% 3 yr overall survival
  - Outcomes improving with MDS/Leukemia in SCN
    - Avoidance of excessive chemotherapy prior to conditioning regimen

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Final Thoughts

- HSCT is the only current curative treatment for hematologic manifestations (neutropenia, clonal evolution/MDS/AML) of SCN
- Decision to undergo HSCT should be made with a team experienced with SCN
  - HSCT approaches should be **disease and patient specific** to decrease early and late toxicities with experienced teams
  - Newer screening for **high risk features** with bone marrow somatic mutation testing (NGS for) consideration of early transplant referral prior to MDS/AML in some settings with expert consultation
  - Transplant outcomes overall are improving but significant treatment related mortality remains and may be higher in SCN
  - Consideration of late effects including fertility preservation

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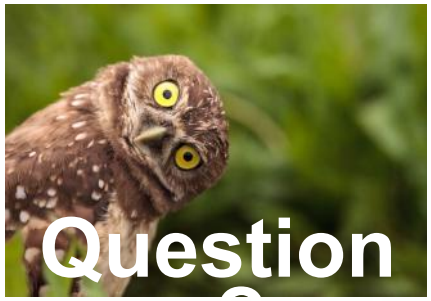

BMF/BMT Nurse:

Ali OConner Allison.Oconner@cchmc.org 513-636-3570

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