Bone Marrow Transplant in MDS

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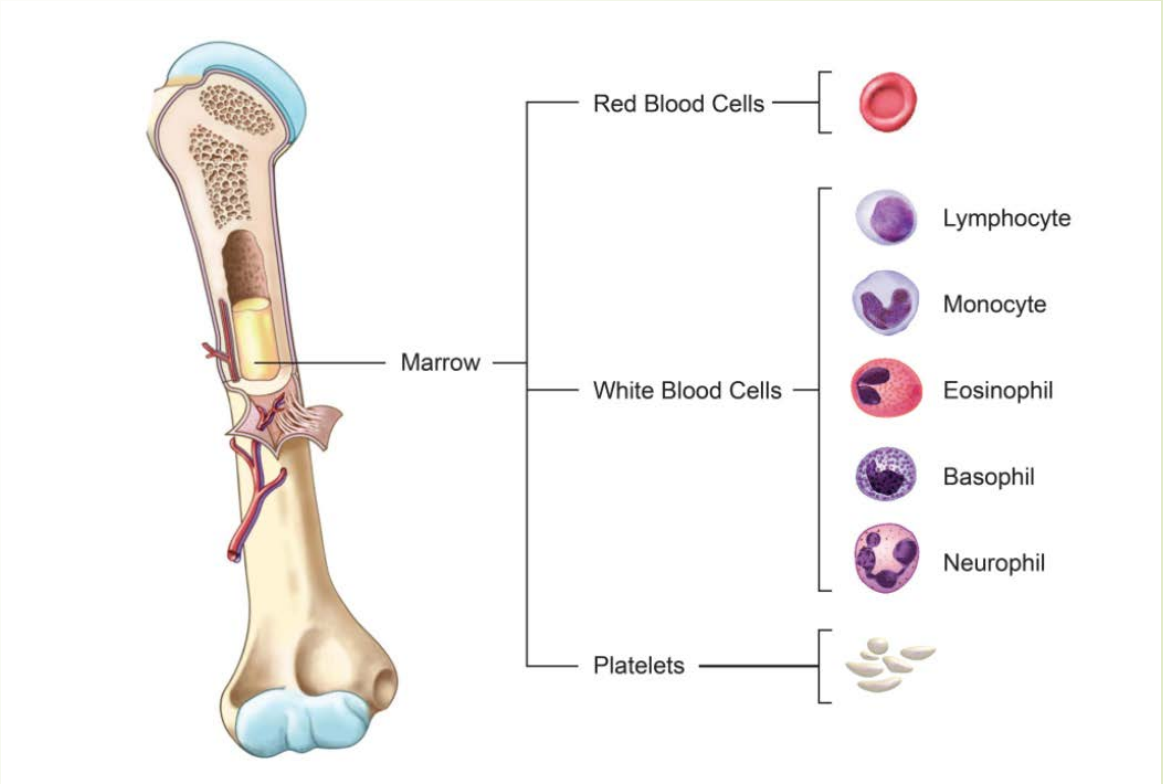
What is Bone Marrow?

- Marrow is the soft tissue inside bones that produces blood forming cells that mature into red blood cells, white cells and platelets (factory)
  - **Red Blood cells** – carry oxygen through our body
  - **White Blood cells** – help fight infection
  - **Platelets** – help control bleeding



What is a Bone Marrow Transplant (BMT)?

- Healthy marrow and blood cells are required to survive
- Disease's such as MDS can affect the marrow's ability to function properly, a transplant can offer a potential cure
- A bone marrow transplant replaces unhealthy blood forming cells (aka stem cells) with healthy cells
- Two types of transplant : **Autologous** and **Allogeneic**

Autologous transplant – Uses your own cells which are collected and stored for your transplant

Allogeneic transplant – Uses cells donated by a family member, unrelated donor or umbilical cord blood unit

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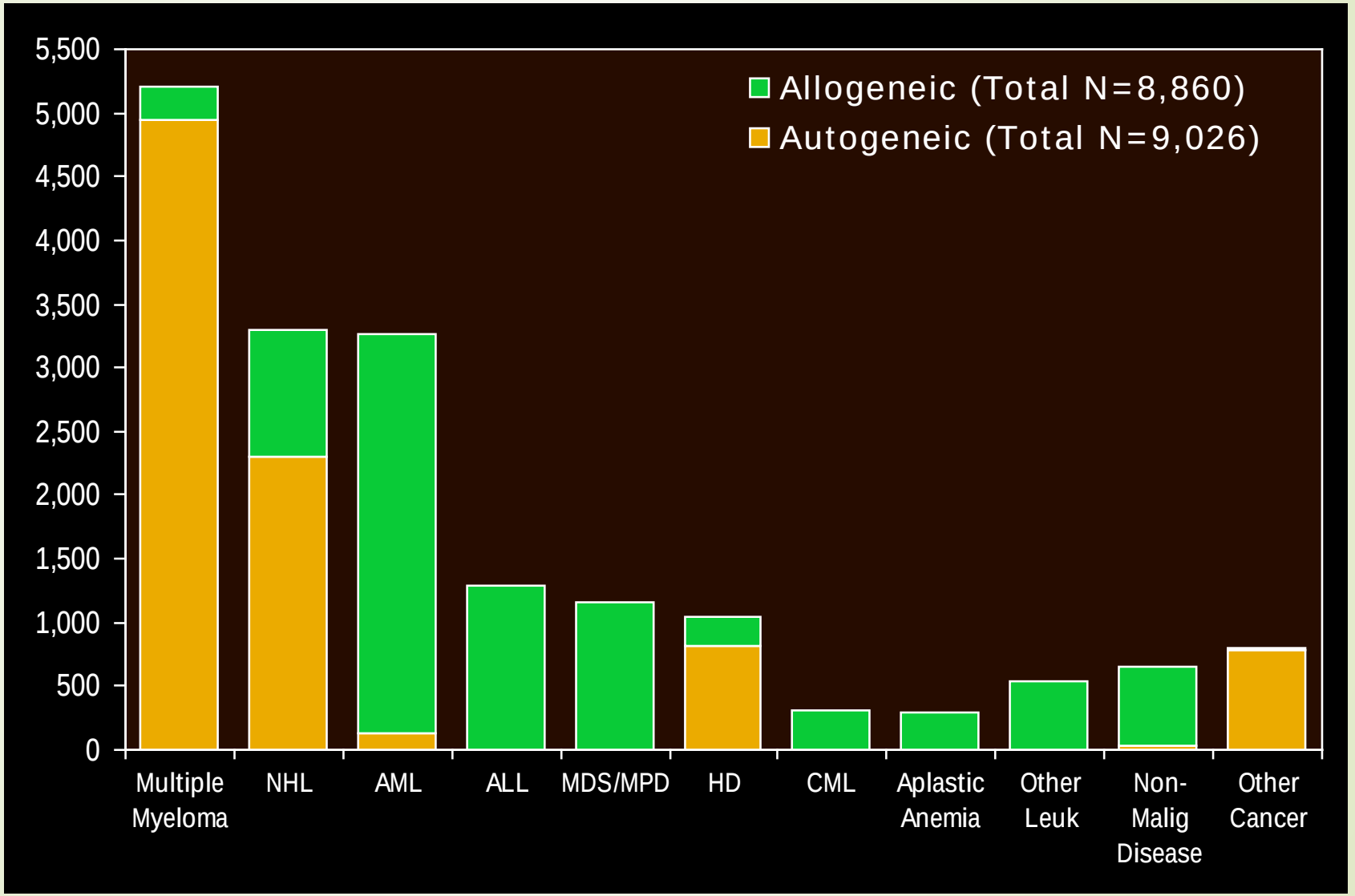
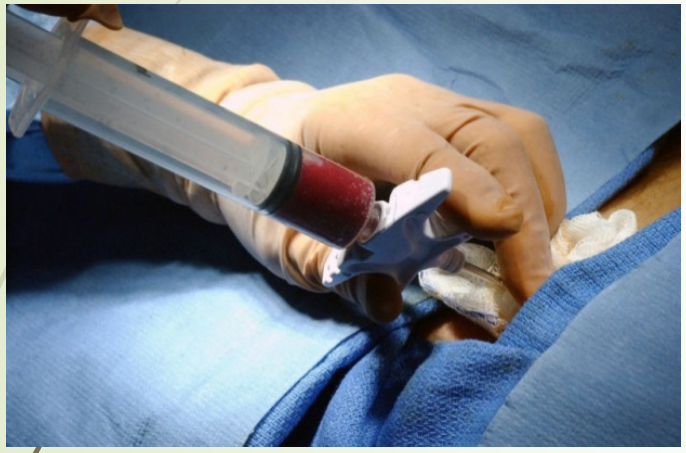
Indications for Hematopoietic Stem Cell Transplants in the United States, 2010

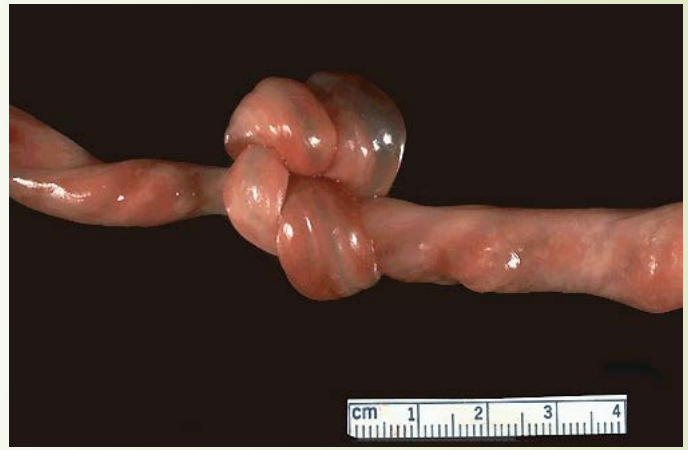


Sources of Stems Cells for Transplant



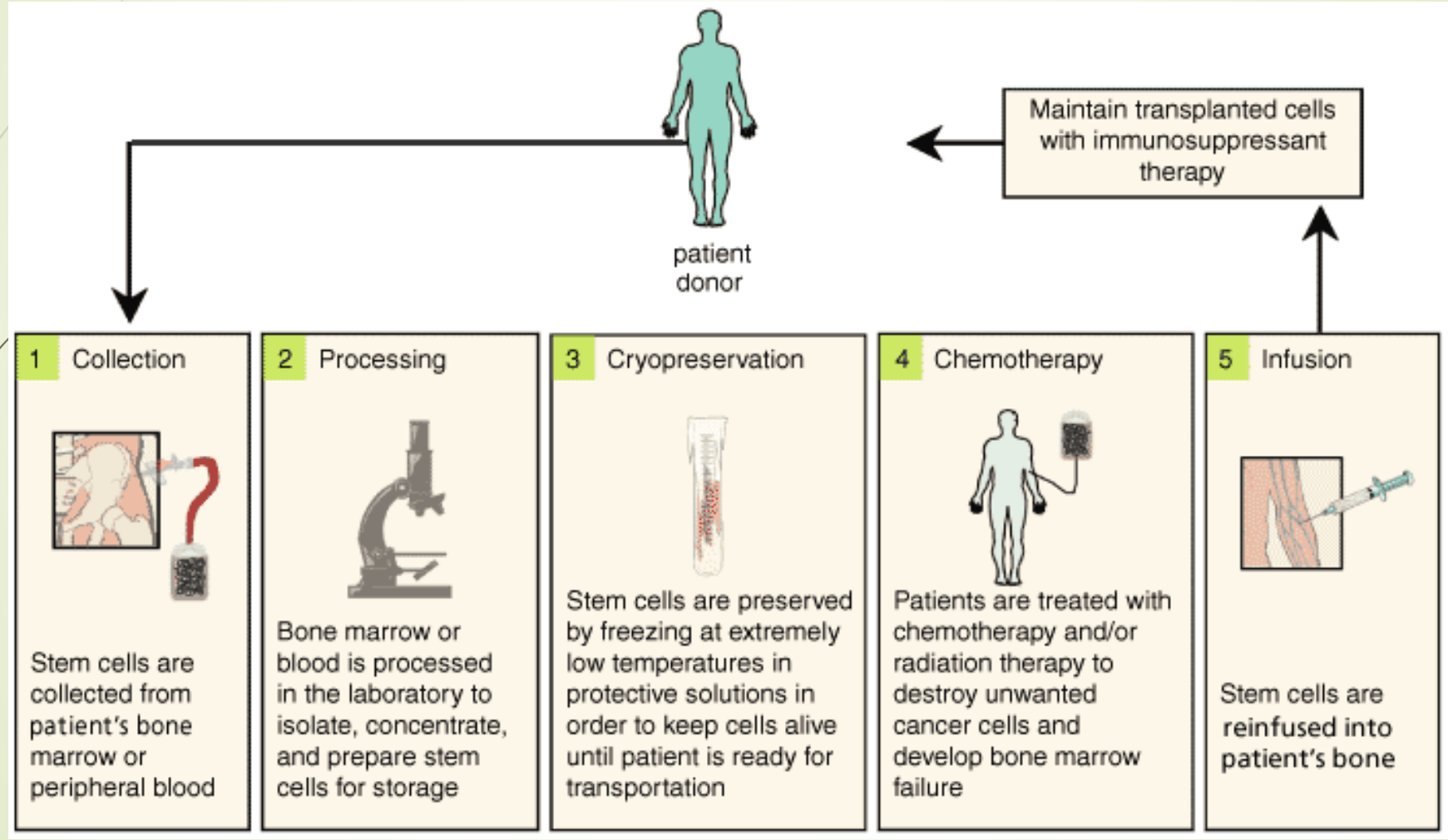
BONE MARROW

PERIPHERAL BLOOD



CORD BLOOD

How Allogeneic transplant works



Transplant Process (5 Steps)

1. Conditioning (1-7 days). Chemotherapy or radiation to suppress the patient's immune system from rejecting the donor's stem cells and to eliminate the residual tumor cells
2. Stem cell infusion (hours)
3. Neutropenic phase (10-20 days)
4. Engraftment phase (2-3 weeks)
5. Post-engraftment period

Which MDS patients should be considered for transplant?

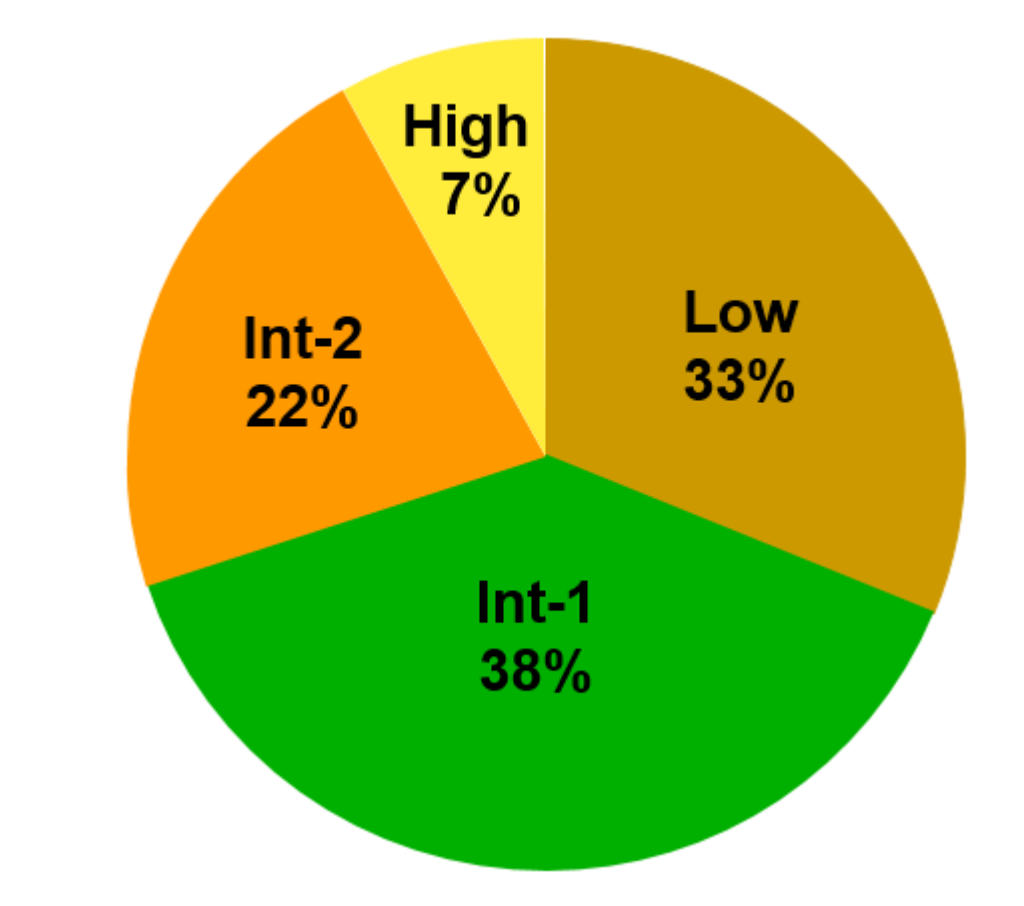
	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Bone marrow blasts	< 5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

	Low Risk			High Risk		
	0	0.5	1.0	1.5	2.0	≥ 2.5
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yr	5.7	3.5		1.2		0.4

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1800/μL; platelets < 100,000/μL.

International Prognostic Scoring System (IPSS): Most frequently used risk stratification scoring system

IPSS: Distribution of Risk Groups in MDS



Greenberg P, et al. Blood 1997;89:2079–88

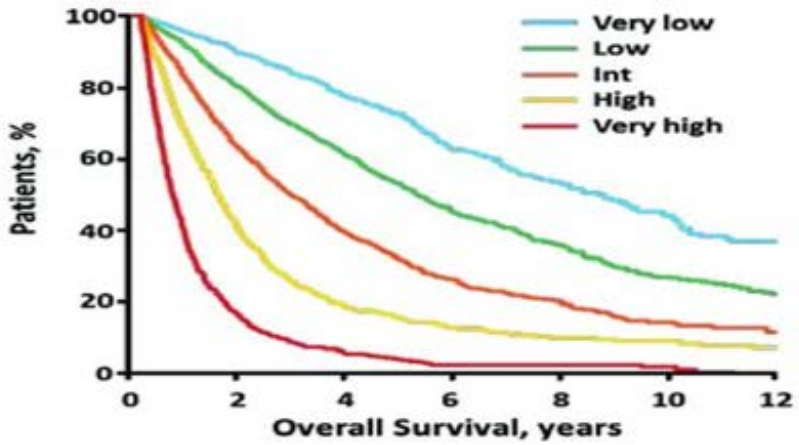
Revised International Prognostic Scoring System (R-IPSS)

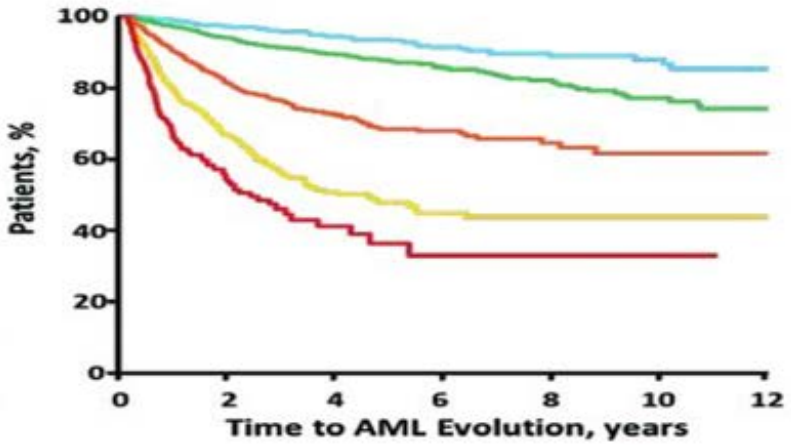
Prognostic Category	IPSS-R Prognostic Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Int	Poor	Very poor
BM blasts, %	≤ 2		> 2-< 5		5-10	> 10	
Hemoglobin, g/dL	≥ 10		8-< 10	< 8			
Platelets, × 10^9/L	≥ 100	50-< 100	< 50				
ANC, × 10^9/L	≥ 0.8	< 0.8					

Cytogenetic groups

Very good: –Y, del(11q)
Good: normal, del(5q), del(12p), del(20q), del(5q) + 1 additional
Intermediate: del(7q), +8, +19, i(17q), other abnormalities not in other groups
Poor: -7, inv(3)/t(3q)/del(3q), -7/del(7q) + 1 additional, complex (3 abnormalities)
Very poor: complex (> 3 abnormalities)

Risk Category	Risk Score (for age 70)
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6





Transplant for High Risk MDS Patients

1. Allogeneic hematopoietic stem cell transplant is the only curative approach for MDS patients, however it is associated with high risk of severe and life threatening complications

2. To be considered for transplant a patient should meet following criteria:

   a) To be in relatively good health (transplants typically done for patients younger than age 70, however no definitive age limits exists)

   b) Do not have acute severe illness (poorly controlled infections, etc.)

   c) Preferably have well HLA matched donor

   d) Do not to have rapidly progressing and poorly controlled MDS

   e) Have a reliable and dedicated caregiver

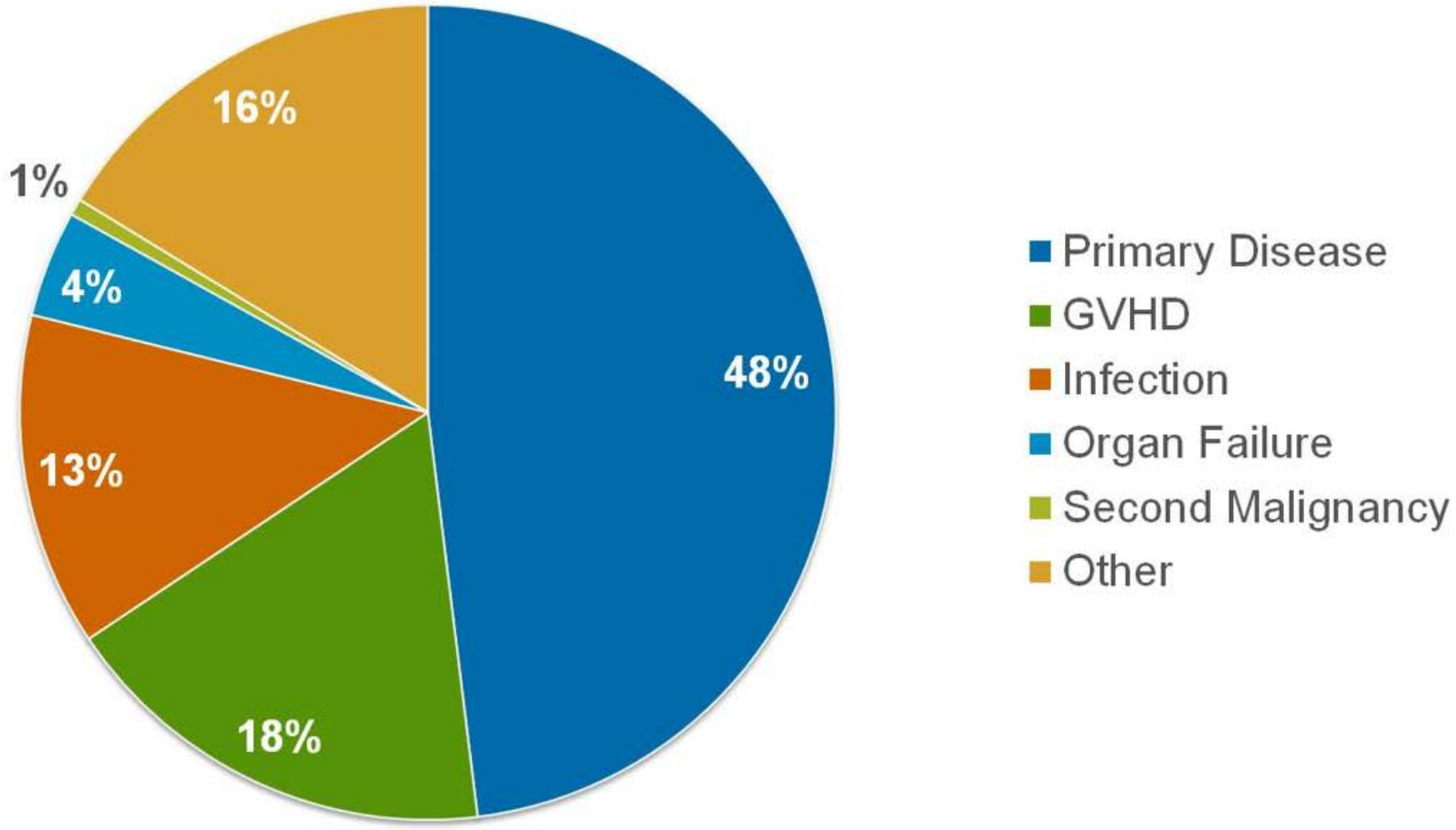
Efficacy of BMT for MDS

- Survival benefit in Intermediate-2 and High risk patients
  - 20-30% progression free survival (PFS) at 5 years in older patients
  - 30-40% PFS in Center for International Blood and Marrow and Transplant Research (CIBMTR)
  - Quality of life improved with transplant in high risk patients

Potential Risks of BMT for MDS

- Allogeneic transplant is one of the higher risk procedures in medicine
- Higher IPSS increases relapse risk and transplant related mortality (TRM)
- Average age 60s → increases comorbidities/TRM

Causes of Death after HLA Match Sibling Transplants done in 2011-2012



CIBMTR
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Graft vs Host Disease (GVHD)

- Only happen with allogeneic transplant
- Condition occurs when donor stem cells that make up new immune system see host body (tissues and organs) as foreign and attack it

- **Acute GVHD**
  - **Skin rash, GI and Liver**
  - **Generally occurs within 100 days of transplant**
  - **Prevention: CSA or tacrolimus**
  - **Treatment: Steroids, Mycophenolate, ATGAM**
  - **Risk Factors**
    - **MSD>MUD>Mismatched related or unrelated**
    - **Parous female for male**
    - **Older>Younger**

- **Chronic GVHD**
  - **Resembles autoimmune disorders**
  - **Protean manifestations**
  - **Major cause of long-term morbidity and late mortality**
  - **Treatment: Steroids are first line so infection major cause of death**
  - **In vast majority>Resolves so no life-long immunosuppression**

Other Risks

Deaths during cytopenia (low counts)

- Uncommon
- Less than 5%

Failure to engraft

- Rejection, also uncommon and approx. equal to 5%

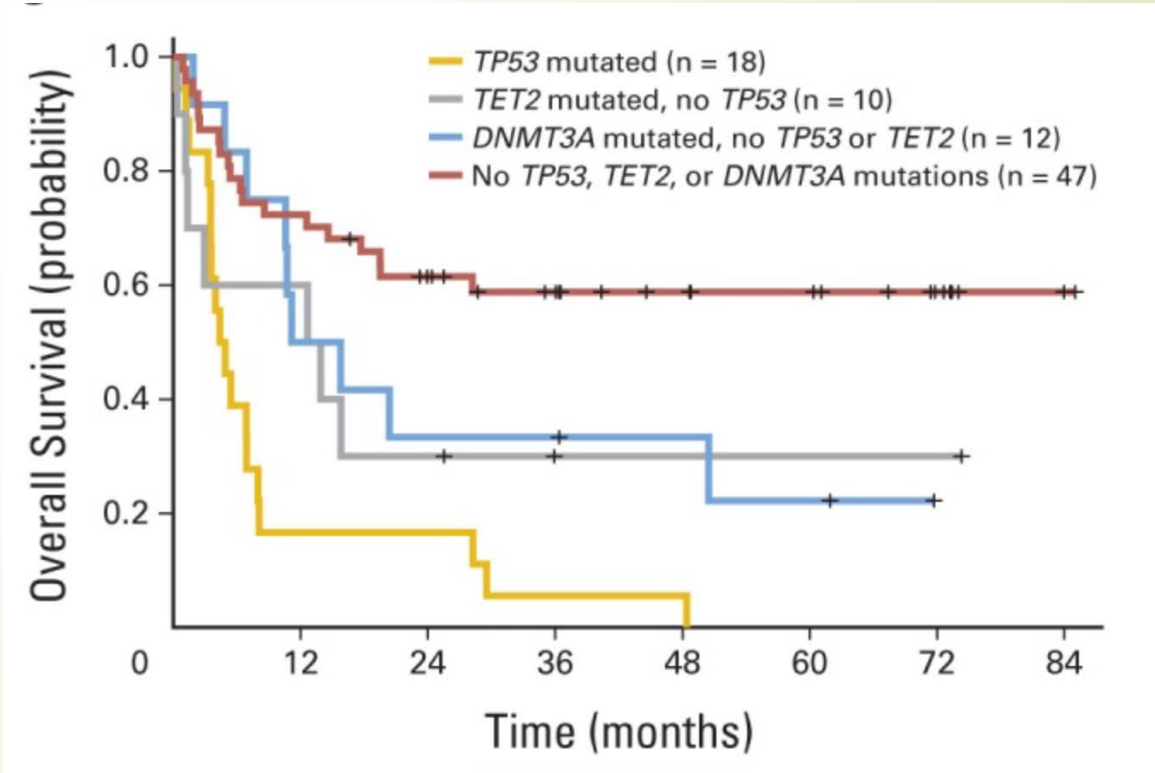
Organ failure

- Heart, liver and lungs

What Mutations in MDS Predict a Poor Outcome After Transplant?

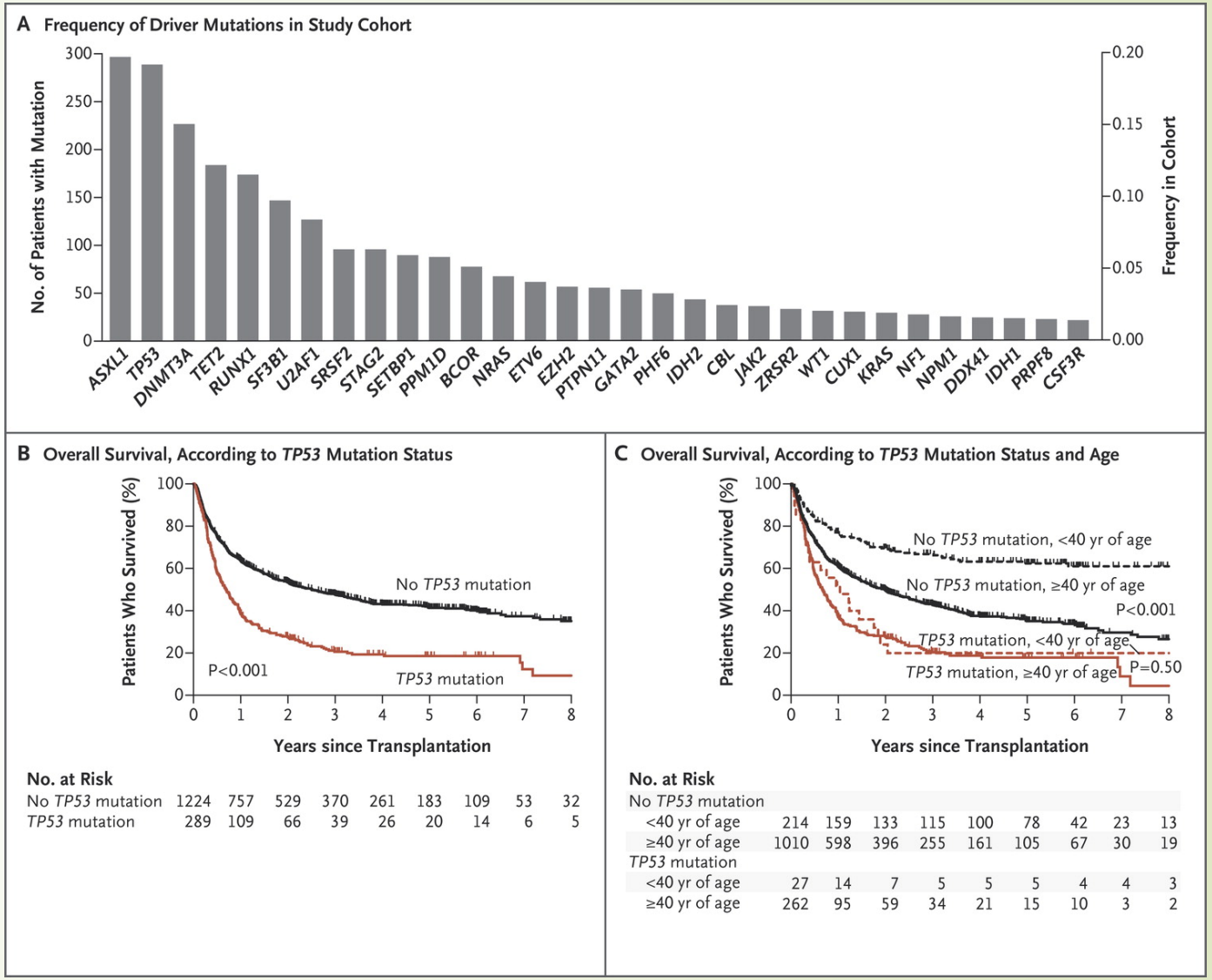
- Tumor samples from 87 pts were sequenced prior to transplant to look at what mutations predicted a poor outcome after transplant

- TP53 mutation (21%), DNMT3A (18%), TET2 (13%)
- Pt's who carried these mutations represented 64% of deaths in this study
- Three year overall survival in patients without these mutations was 59% vs 19% for those with these mutations



Bejar R, et al. J Clin Oncol 2014

- 1520 patient samples with MDS enrolled from CIBMTR database
- TP53 mutations were present in 19% of pts and were associated with shorter survival and a shorter time to relapse than absence of TP53 mutations
- Adverse effect of TP53 was similar in patients who received reduced intensity conditioning (RIC) vs myeloablative conditioning regimens
- Presence of JAK2 mutations was associated with shorter survival than absence of JAK2
- Among pts>40yrs who did not have TP53, RAS was associated with shorter survival
- The effect of RAS on relapse only evident in RIC regimens



Lindsley RC, et al. NEJM 2017

Thank You!

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