# Myelodysplastic syndrome

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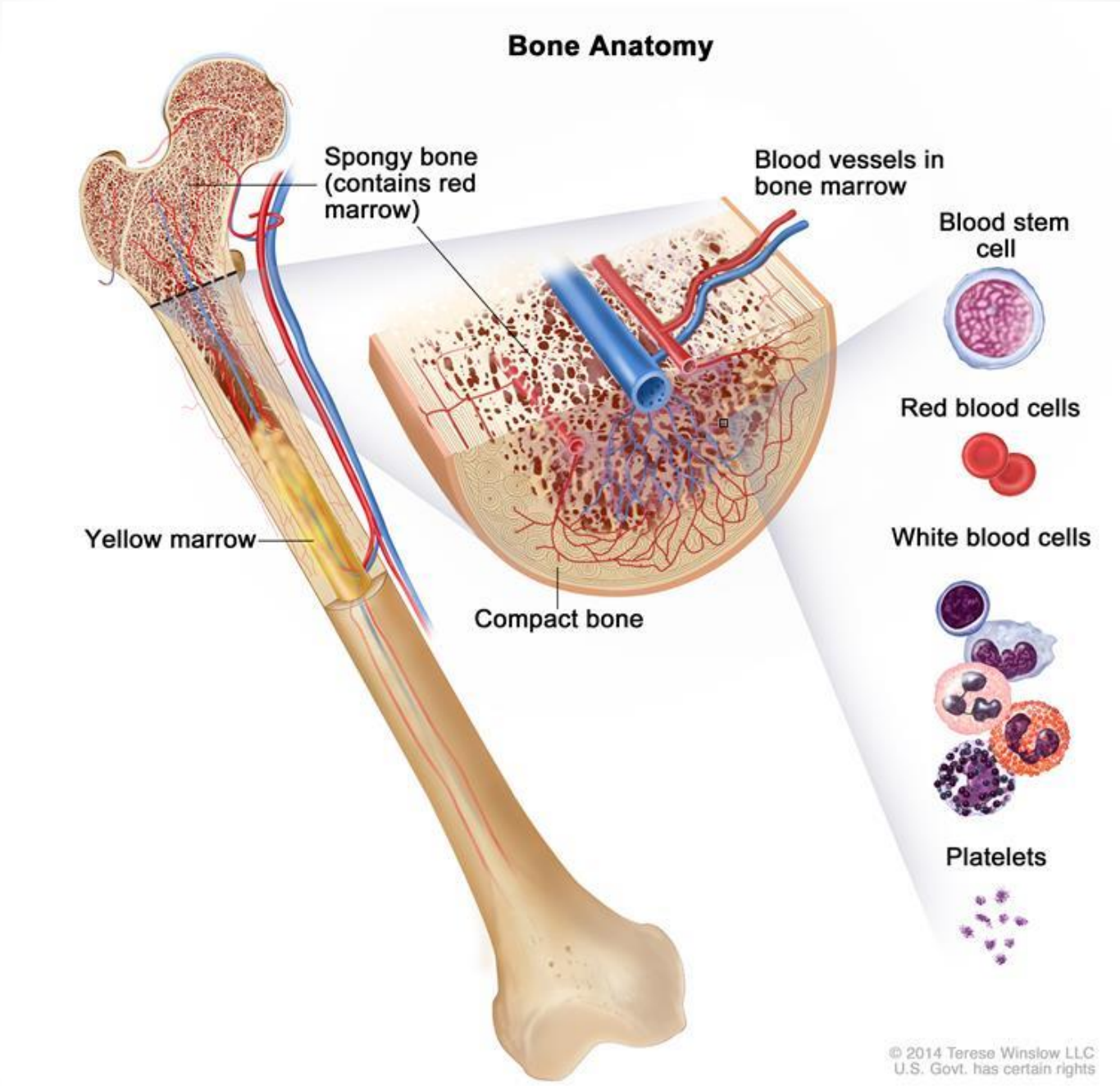
# What is Myelodysplastic syndrome?

- A disease where the bone marrow doesn't work appropriately

- What does that mean??


Bone Anatomy
Spongy bone (contains red marrow)
Blood vessels in bone marrow
Blood stem cell
Red blood cells
White blood cells
Platelets
Yellow marrow
Compact bone
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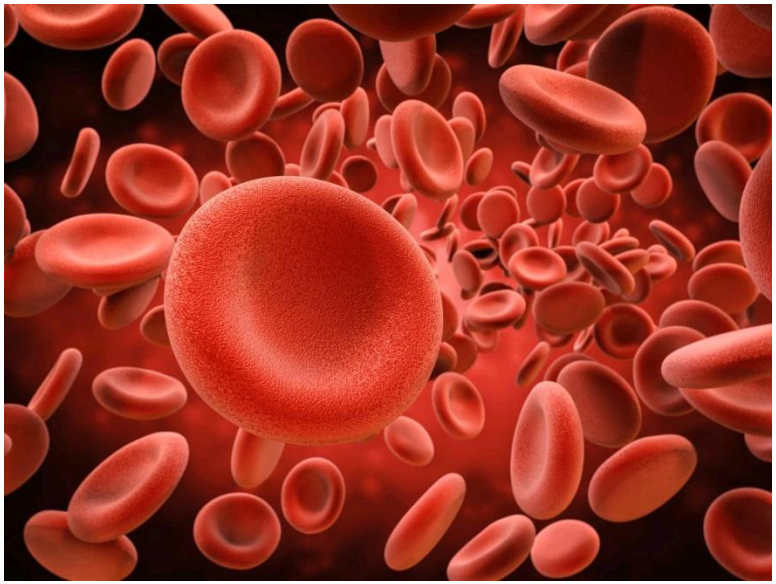
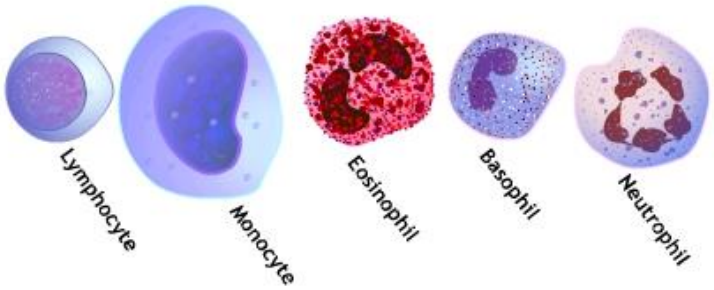
# Red blood cells



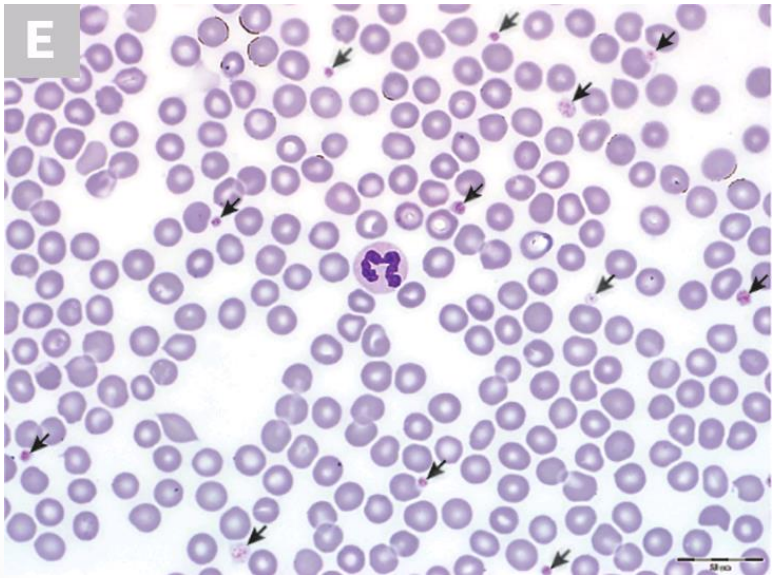
- Carry oxygen
- When low: anemia
- When not enough red blood cells
  - Fatigue
  - Shortness of breath
  - Difficulty concentrating

# White blood cells




- Fight infection
- When too low:
  - Increased risk for infection

# Platelets

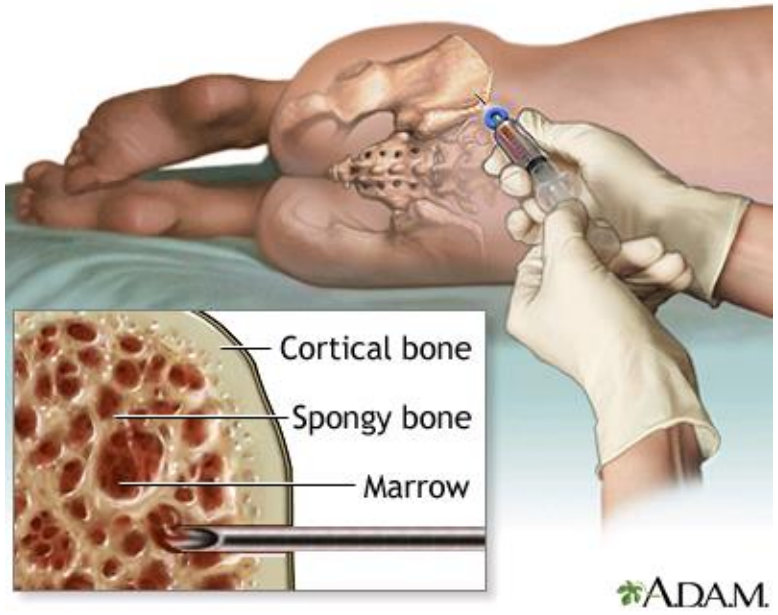



- Help blood clot
- When too low:
  - Increased bleeding

# The factory

# Diagnosis

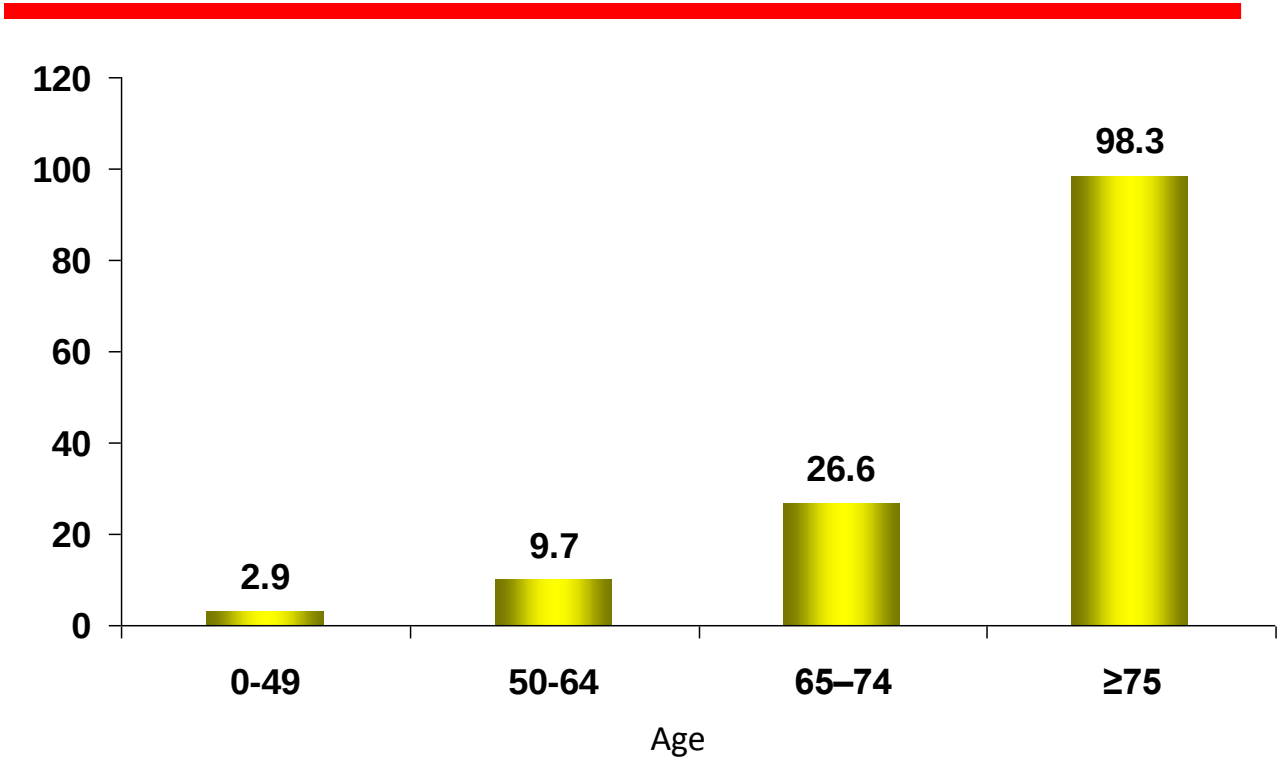
- Suspect when blood counts low
- Must rule out other causes
  - Nutritional deficiency (iron, B12, folate)
  - Liver disease
  - Autoimmune disease
- Bone marrow biopsy



# What causes MDS?

- Genetic mutations
- Exposure to toxic substances/radiation/chemicals

# MDS Rate/100,000




Ma X et al. *Cancer.* 2007:109:1536

# Treatment: depends on goals

- Curative:
  - Bone marrow transplant

- Improvement of counts/slow down progression to AML/prolong life
  - Azacitadine and decitabine both good options for treatment
  - Can consider lenolidomide (specially if 5q- present)

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# Now what??

Assess risk

# Cytogenetic scoring system

| Prognostic subgroups | Cytogenetic abnormalities | Median survival, y | Median AML evolution 25%,y |
|---|---|---|---|
| Very good | -Y, del(11q) | 5.4 | NR |
| Good | Normal, del(5q), del(12p), del(20q), double including del(5q) | 4.8 | 9.4 |
| Intermediate | del(7q), +8, +19, i(17q), any other single or double independent clones | 2.7 | 2.5 |
| Poor | -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities | 1.5 | 1.7 |
| Very poor | Complex: > 3 abnormalities | 0.7 | 0.7 |

Schanz et al. J Clin Oncol. **2012** Mar 10;30(8):820-9.

# Case Presentation

- 67 year old gentleman
- CBC:
  - Hb: 7.7 gm/dl
  - WBC: 1.8 x $10^9$/L ANC: 0.6 x $10^9$/L
  - Platelets: 20 x $10^9$/L
- BM biopsy: dysplasia with 8% blasts
- Karyotyping: Diploid
- PS: 1

# IPSS-R prognostic score value

| Prognostic variable | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| Cytogenetics | Very good | — | Good | — | Intermediate | Poor | Very poor |
| BM blast, % | ≤ 2 | — | > 2%- < 5% | — | 5%-10% | > 10% | — |
| Hemoglobin | ≥ 10 | — | 8- < 10 | < 8 | — | — | — |
| Platelets | ≥ 100 | 50-< 100 | < 50 | — | — | — | — |
| ANC | ≥ 0.8 | < 0.8 | — | — | — | — | — |

Score=6

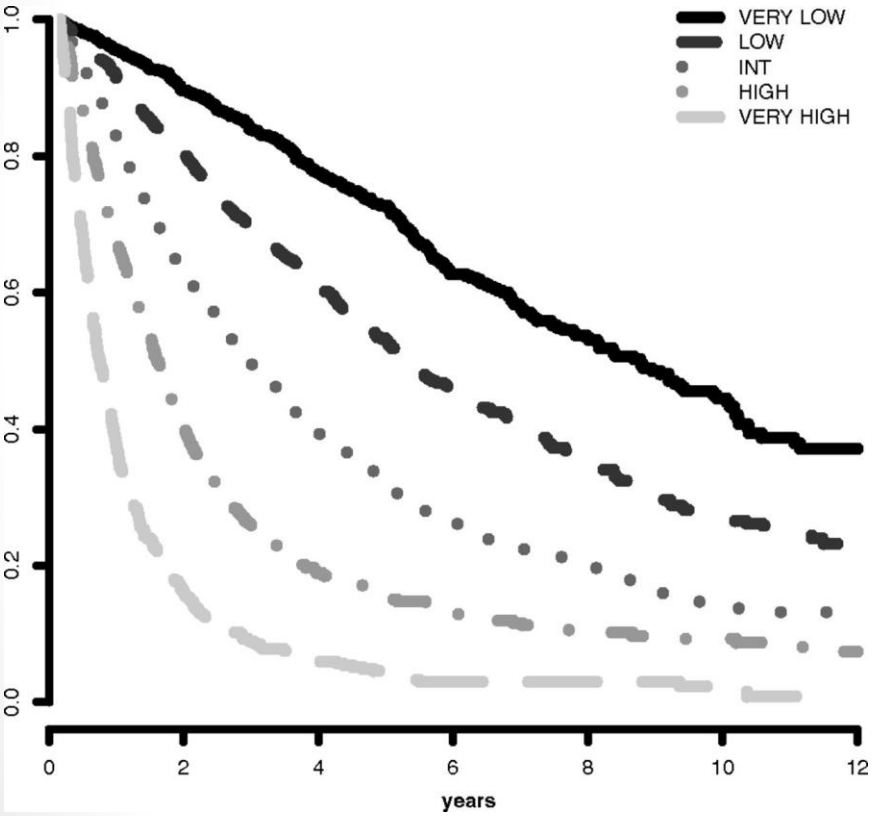
Greenberg P L et al. Blood 2012;120:2454-2465

# IPSS-R
# Risk Category by Score

| Risk category | Risk score |
|---|---|
| Very low | ≤ 1.5 |
| Low | > 1.5-3 |
| Intermediate | > 3-4.5 |
| High | > 4.5-6 |
| Very high | > 6 |

Greenberg P L et al. Blood 2012;120:2454-2465

# Survival based on IPSS-R prognostic risk-based categories.




| | Percent of patients | MS Years |
|---|---|---|
| Very low | 19 | 8.8 |
| Low | 38 | 5.3 |
| Intermediate | 20 | 3 |
| High | 13 | 1.6 |
| Very High | 10 | 0.8 |

Greenberg P L et al. Blood 2012;120:2454-2465

# Other ways of defining risk

- Next generation sequencing
- Molecular mutations that may define risk
- Transfusion dependence

# Goals of treatment

- Maintaining blood counts to help improve symptoms
- Prevention of progression to AML
- Curative?

# Treatments

- Clinical trials (clinicaltrials.gov)
- Observation
- Growth factors
- Hypomethylating agents (vidaza or dacogen)
- Bone marrow transplant
- Supportive care

# Blood count directed therapy

- Hemoglobin:
  - Transfusion:  to a hemoglobin of 7 or 8
  - Erythropoietin stimulating agents (Procrit ©, Aranesp©) to maintain hemoglobin greater than 10 or 11
  - When transfusion number >20- consider iron chelation

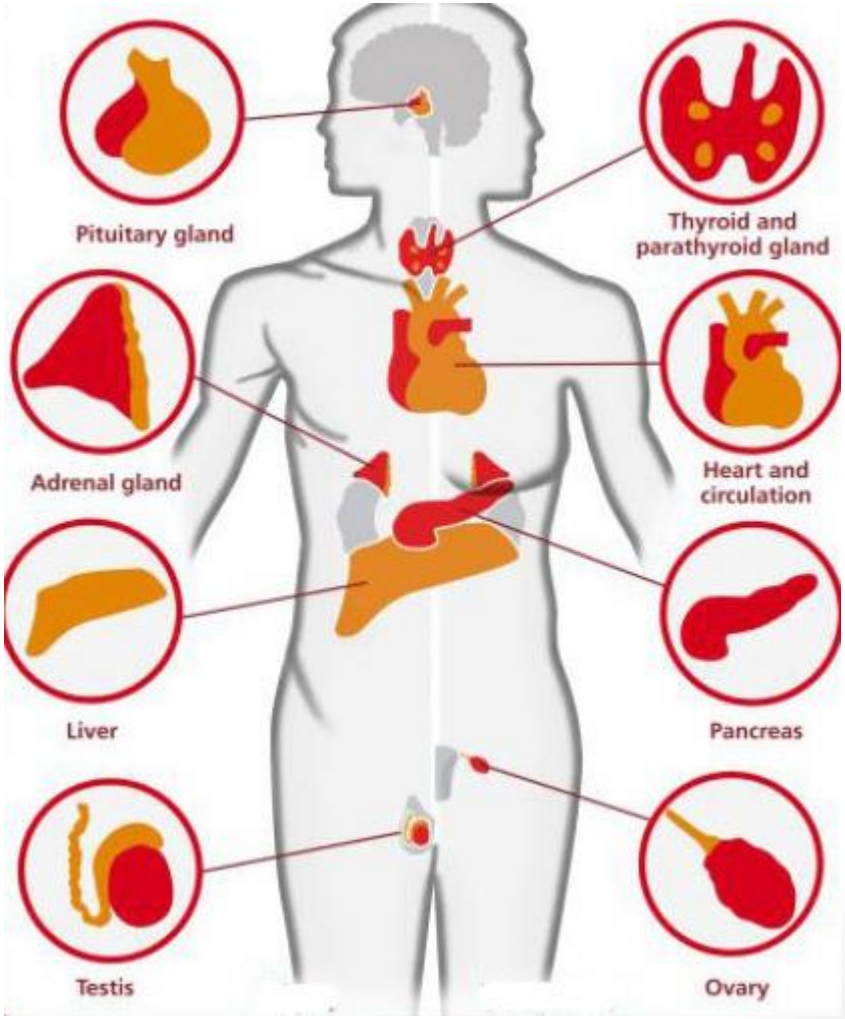
# Blood count directed therapy continued

- Platelets:  transfused to 10 or 20 (spontaneous bleeding more common in patients when platelets <10)

- White blood cells:
  - Neupogen (generally not recommended as therapy alone- may help erythropoietin stimulating agents work better)

# Iron overload

- Each unit of blood has 250 mg of iron
- After 20 units of blood start thinking about iron overload
- Ferritin >1000
- LIC >3



# Iron chelation

- Desferoxime:
  - Subcutaneous infusion overnight
  - Side effects: visual toxicity, otootoxicity
  - Renal + liver toxicity
- Deferasirox
  - Oral iron chelator
  - May cause decrease in blood counts, liver dysfunction, rash
  - ***use with caution if kidneys don't work***

# Hypomethylating agents

- They change the signaling in the bone marrow
- No head to head comparison
- Given 5-7 days once a month


- Decitabine: must be given IV
- Azacitadine: IV or subcutaneous

# More on hypomethylating agents

## What do they do?

- Improve survival
- Improve blood counts
- Slow down progression to leukemia

## When to use them

- High risk disease
- Poor risk chromosome
- Regular blood transfusions

# Revlimid- Lenalidomide

- Works best in patients with 5q- on cytogenetics
- Works in some patients with anemia

# Bone marrow transplantation

- Involves high dose/intermediate dose chemotherapy followed by hematopoietic stem cell infusion.
  - Chemotherapy helps reduce disease + suppress immune system
  - New blood system works better
  - New stem cells fight off underlying disease 'graft versus myelofibrosis'
- Historically, pt <55, however, now patients up to 75 years old will undergo transplant
- **Autologous:** uses patients own stem cells, allows use of high dose chemotherapy
- **Allogeneic :** uses donor stem cells, either related or unrelated

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# Alternative names

- Alternative names:
  - Peripheral blood stem cell transplant
  - Hematopoietic stem cell transplant
  - Bone marrow transplant
- Bone marrow vs peripheral blood
  - Refers to how the hematopoietic stem cells are collected:
    - Bone marrow: through bone marrow harvest, a procedure performed in the OR
    - Peripheral blood collection: collected after giving neupogen via leukopheresis

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# What to expect during a bone marrow transplant consultation

- Bring a family member/friend
- Be prepared to be scared
- If you can, record the consultation
- If you have any doubts get a second opinion

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# Who can be a donor?

- Brother or sister (same mom and dad):
  - Matched related donor (MRD) preferable - only 30% of the population will have one
- Matched unrelated donor (MUD)
  - Ideally full match- ie 10/10, 8/8
- A donor does not need to be the same blood type

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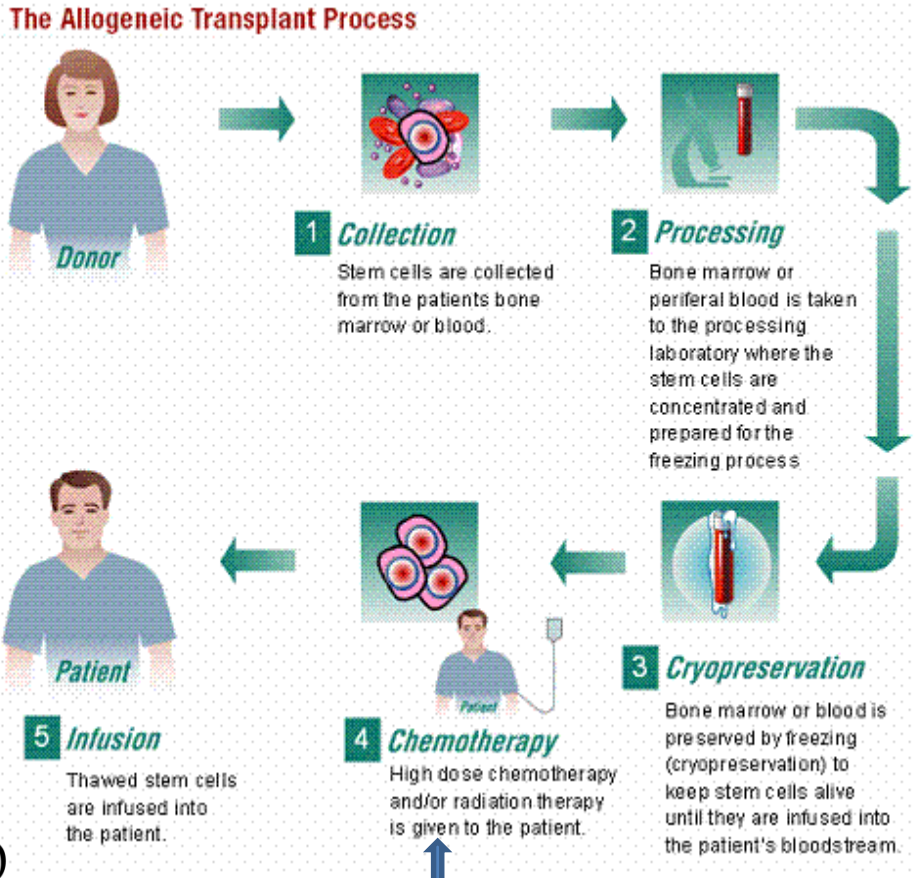
# How does transplant work

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Conditioning

http://biomed.brown.edu/Courses/BI108/BI108_2007_Groups/group07/stemcells/img/Allogenic_big.gif

# Risks of transplantation

- Graft versus host disease
  - New immune system attacking health tissues
  - Can be acute or chronic

- Infection
  - Bacteria/viruses/fungus inside your body
  - Exposure to viruses/bacteria/fungus
    - Many restrictions in place following transplant

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# What is required

- Live within 30-60 minutes from the transplant center for 100 days after the transplant
- Take 1 year off of work
- 24/7 caregiver for first 100 days
- Restrictions to prevent infections
  - Avoid crowds
  - Do not eat fast food/ buffet food/ salad bar

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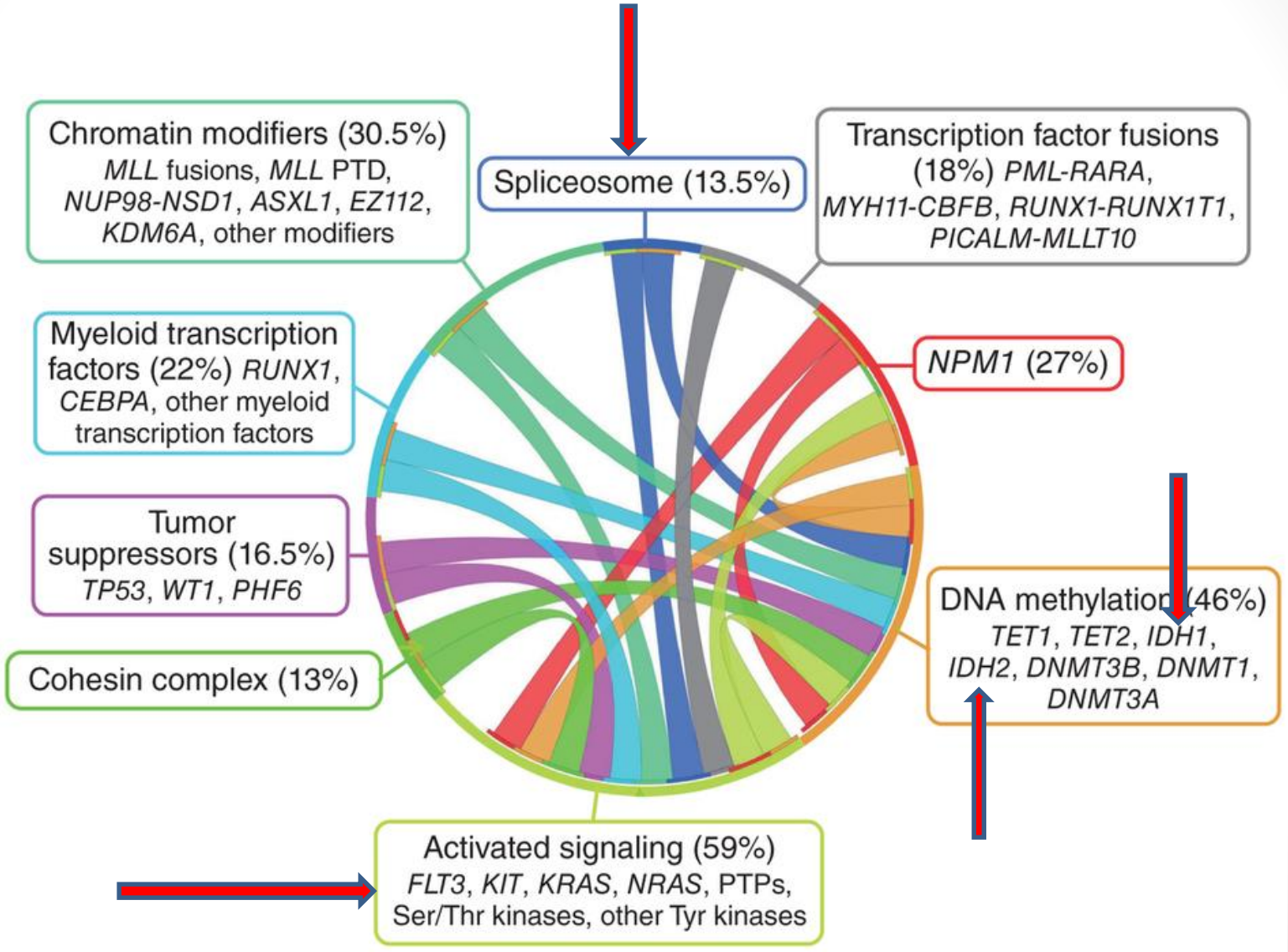
# Long term effects of BMT

- Quality of life
- Chronic GVHD
- Long term health risks

# Newer therapies

- Clinical trials using “targeted” agents
  - Spliceosome inhibitors
  - IDH1/IDH2 inhibitors
- Luspatercept (for anemia)
- Check point inhibitors
- Histone deacetylating agents

# MDS is a complex biological disease




*Sai-Juan Chen et al,Nature Genetics 2013; 45,586–587.*

# Summary

- MDS is a disease characterized by dysfunctional blood making
- Treatments can be supportive or curative
- Important to know your risk
- Consider bone marrow transplant when appropriate

# THANK YOU FOR YOUR ATTENTION