Transplant in MPN

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Setting the Stage

What will be covered

What is a bone marrow transplant?
When to start thinking about bone marrow transplant
Timing of transplant
Understanding disease risk

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’

- 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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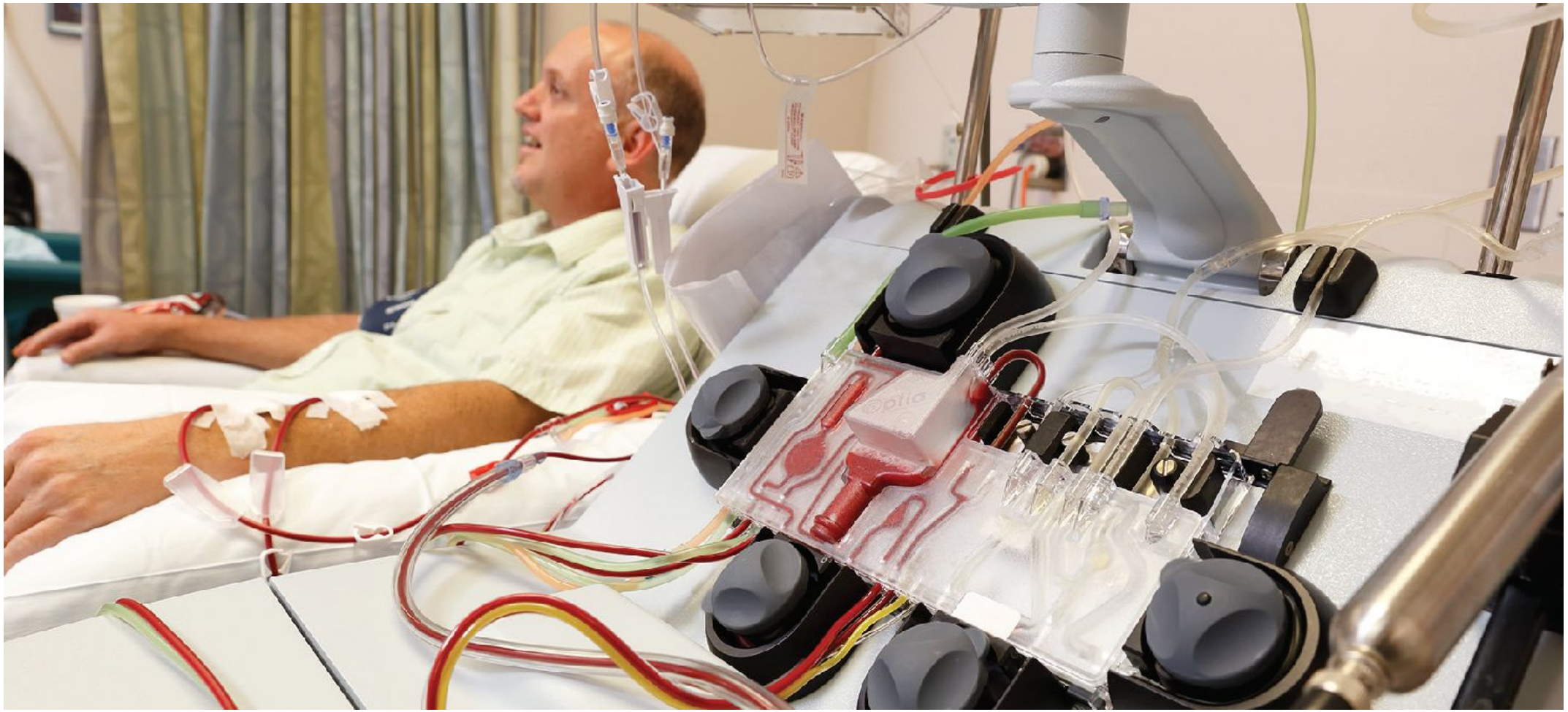
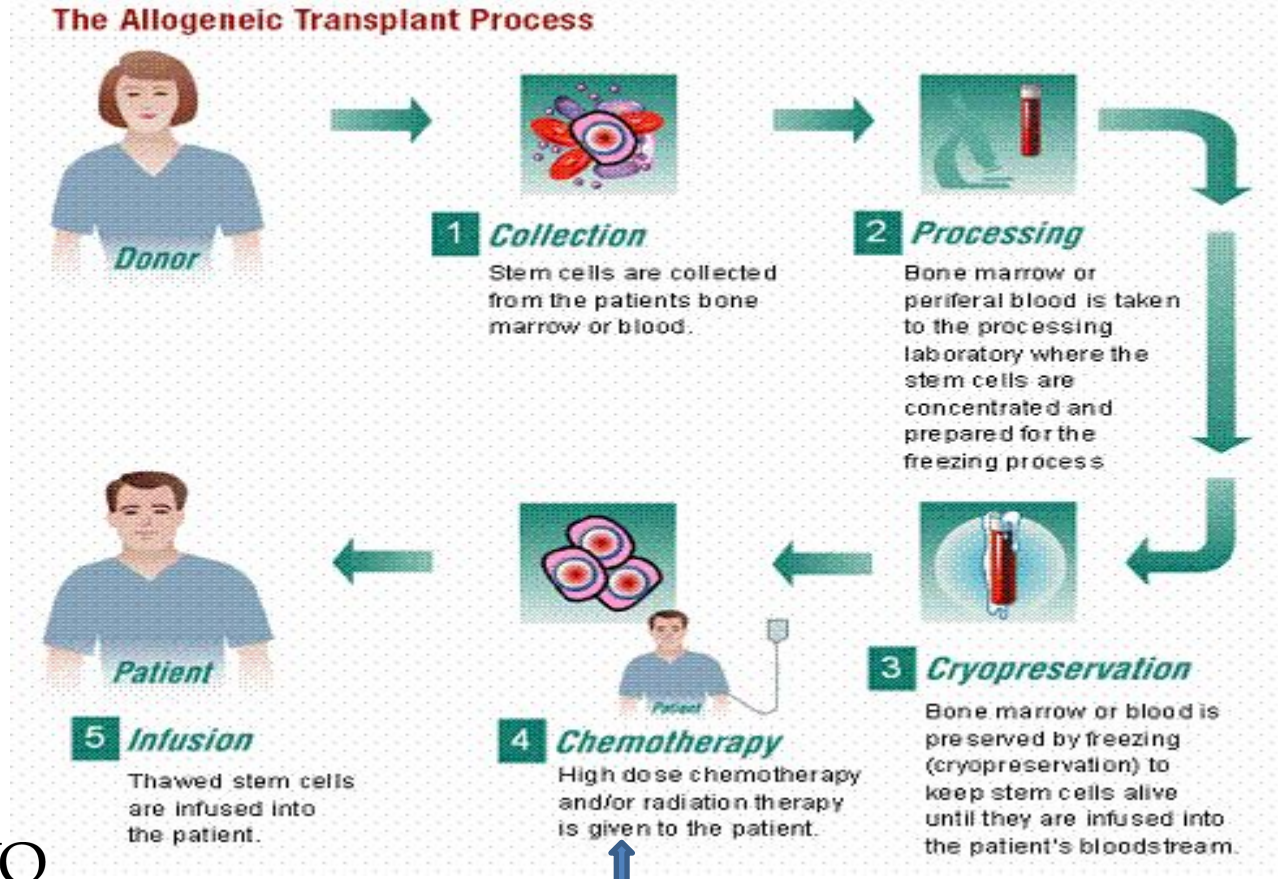
Leukopheresis



How does transplant work



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Conditioning

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

WHY WOULD I WANT TO DO THIS TO MYSELF?

SHOULD I PURSUE A CLINICAL TRIAL INSTEAD?

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What are common concerns about transplant?

- Survey done on patients with MPN
- Less than half the patients were referred for transplant
- Of those who saw a transplant specialist, less than half planned on proceeding with transplant due to the following concerns
  - Quality of life
  - Financial implications
  - Caregiver
  - Graft versus host disease
- WHY??
  - Further studies ongoing to understand the thought process around transplant

Other considerations

- Physicians are human and have biases as well
  - Transplant physicians
  - Hematologists

- Blogs
  - Everyone experiences transplant differently
  - People like to share their experiences

Clinical trials and medical treatment

- There are good clinical trials and treatments in MF
  - No curative options yet
- This is a very individualized decision

When do I see a transplant specialist?

- Important to see a transplant specialist early in the disease course– even if you aren't sure whether you will proceed with transplant or not
  - Understand and plan for the different resources needed for transplant
    - Caregiver
    - Financial
    - Lodging
  - Understand the process of transplant
  - Have time to **process** all the information related to transplant

Who should I see?

- Helpful to see a transplant specialist who has knowledge regarding transplants for MF
  - The timing of transplant is a **SHARED** decision making process
  - There is no one answer that is correct for anyone
- Even if you don’t get a transplant at the center, good to have the discussion/opinion

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
-

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So, when should I get a transplant?

- Generally transplant is reserved for higher risk patients
- It is important to KNOW YOUR RISK
- Can be dependent on life events

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HOW DO WE DEFINE RISK?

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Dynamic International Prognostic Scoring System

DIPSS scores/risk:

- 0 pts: low risk
- 1-2 pts: Intermediate – 1
- 3-4 pts: Intermediate – 2
- 5-6 pts: High risk

DIPSS	DIPSS plus
Anemia (hgb <10) (2 pts)	DIPSS score
WBC >25	Platelets <100
Blasts >1%	Transfusion dependant
Constitutional symptoms	poor risk cytogenetics: complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement
Age >60	

DIPSS plus scores/risk

- 0 pts: low risk
- 1 pt: intermediate-1
- 2-3 pts: intermediate-2
- 4-6 pts: high risk

Clarification of risks

- Anemia–low red blood cell count. Hemoglobin (hgb) is consistently less than 10
- Thrombocytopenia- low platelet (plt) count, less than 100.
- Leukocytosis – high white blood cell count (WBC), consistently greater than 25
- Blasts – immature white blood cells
  - Note this does not mean you have leukemia unless blast % greater than 20%
- Abnormal karyotype
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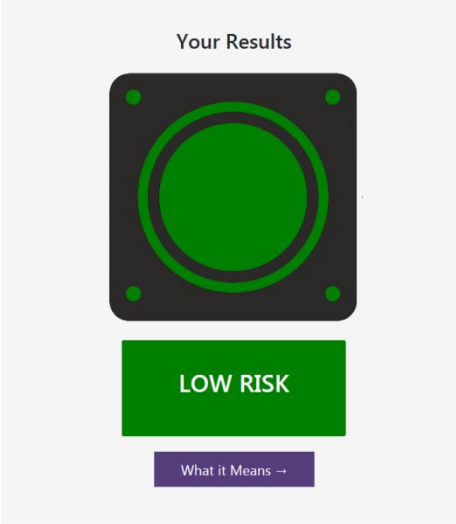
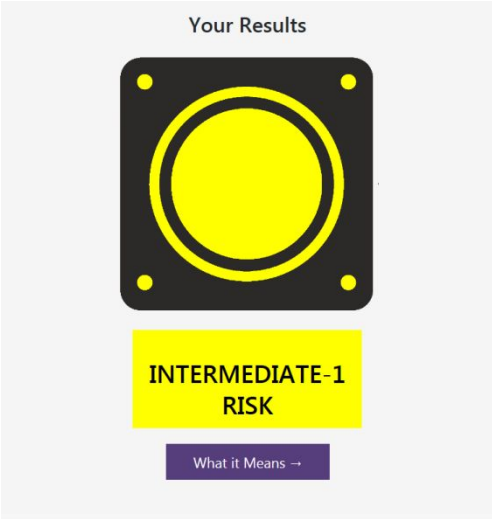
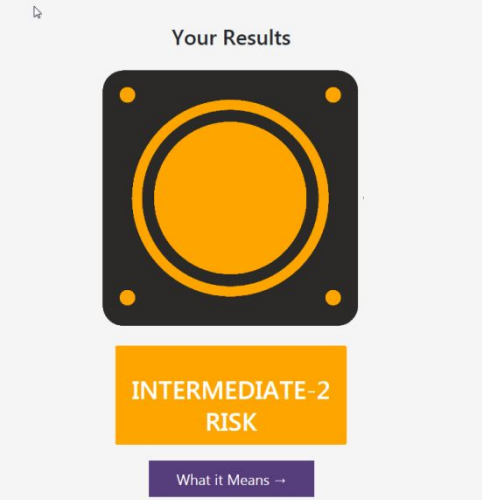
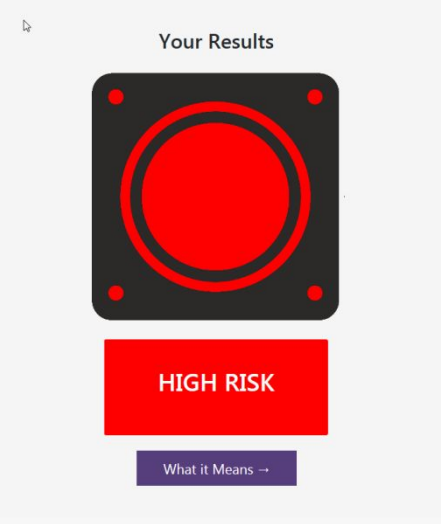
Stem cell transplant spectrum timing tool

- This tool uses DIPSS score to give a sense of when a transplant should be considered



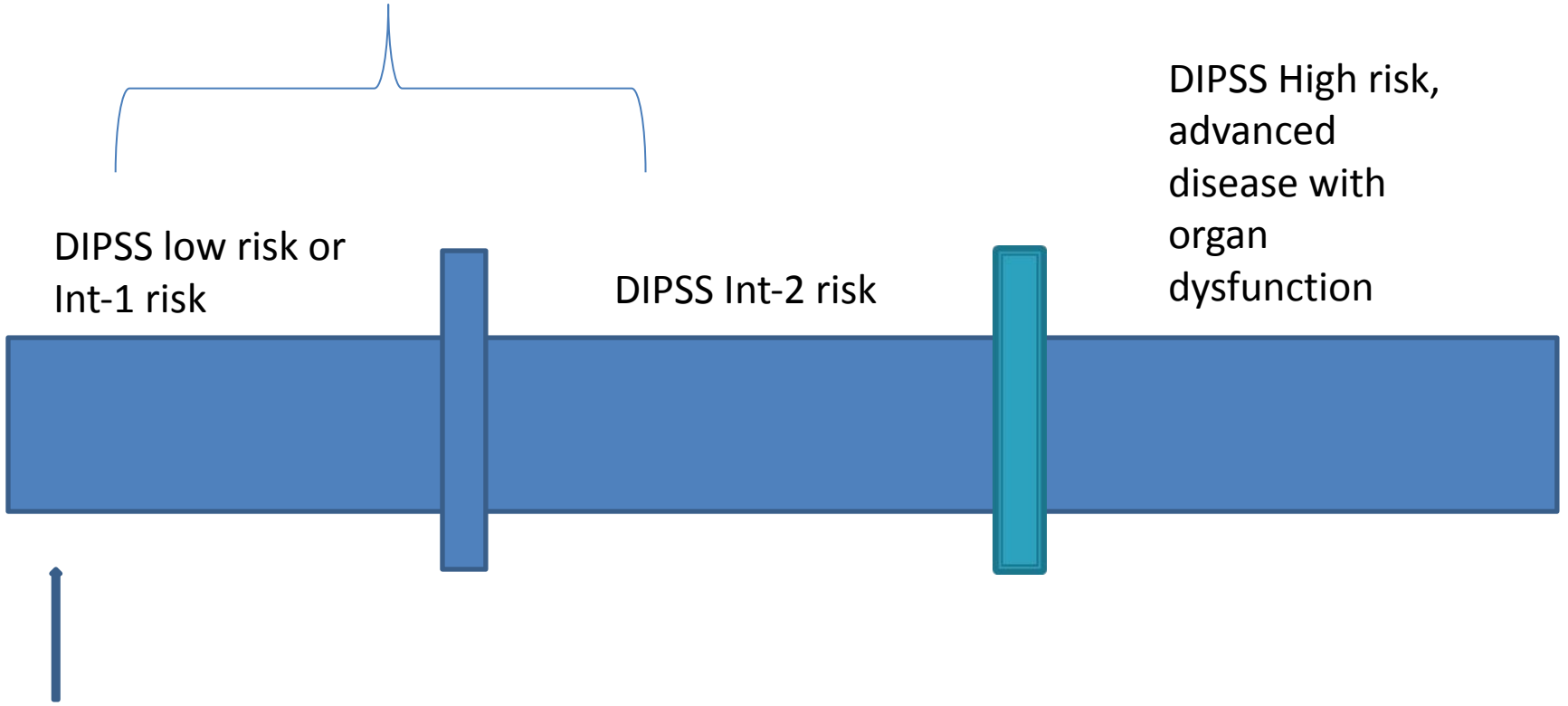






- Even in the case of low risk disease- good to start the conversation
- http://www.mpntransplant.com/

When to **think about a** transplant



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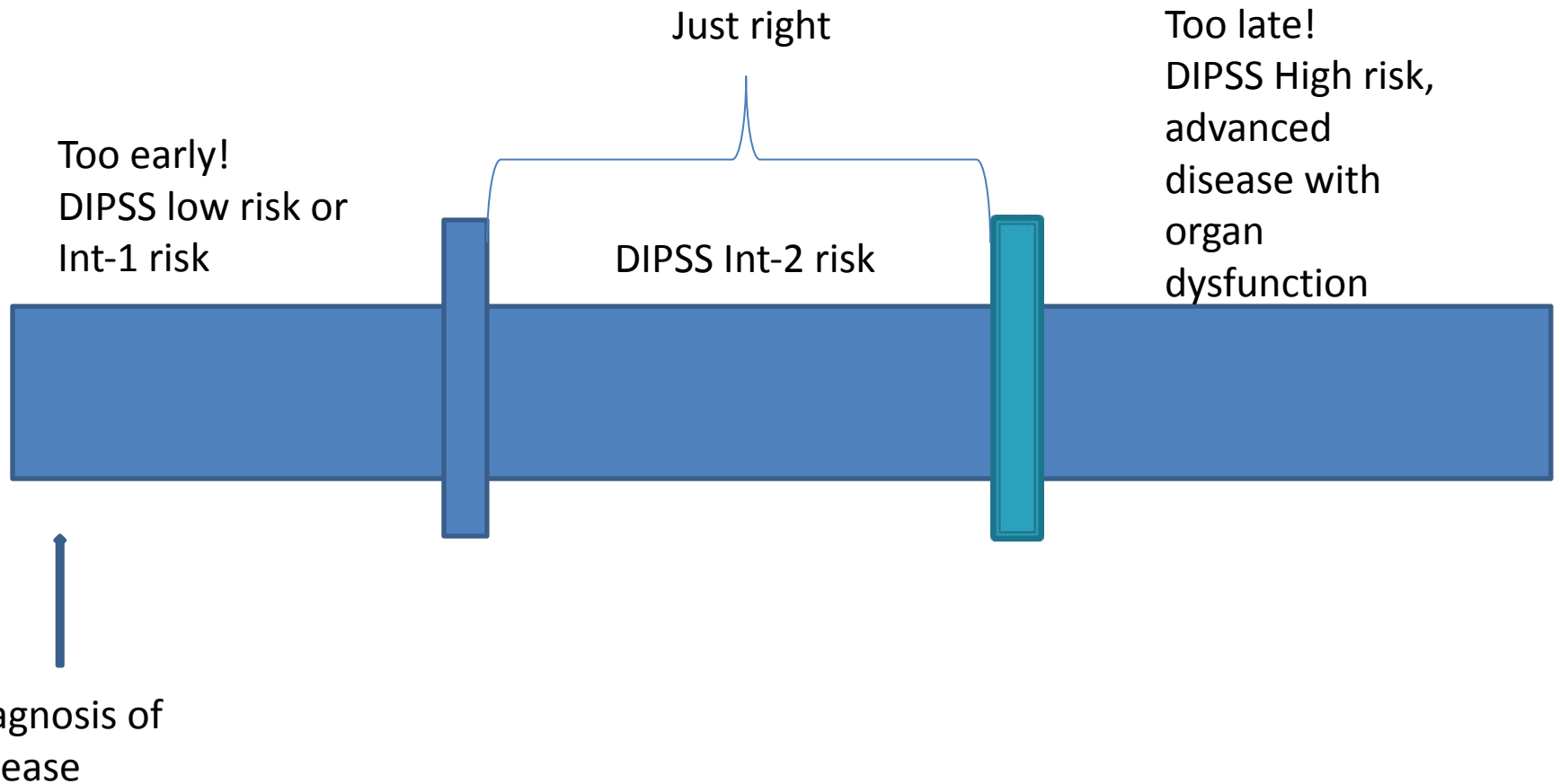
When to **do** transplant



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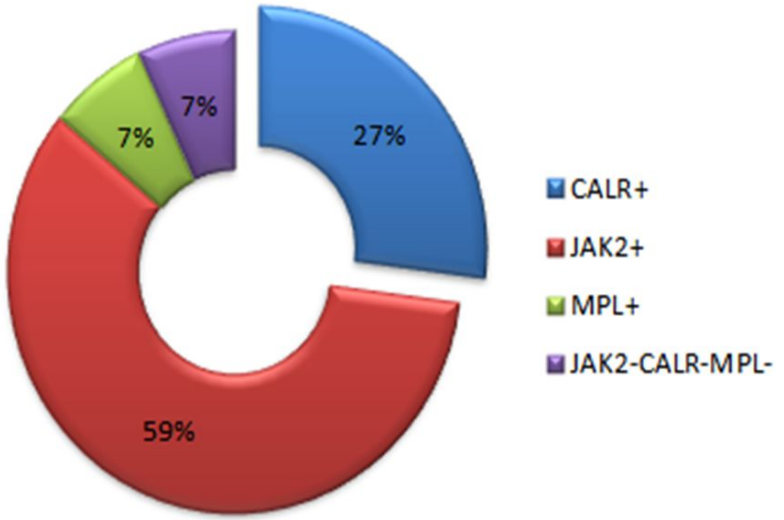
Other factors that contribute to risk

- Driver mutation
- Cytogenetics
- Molecular mutations

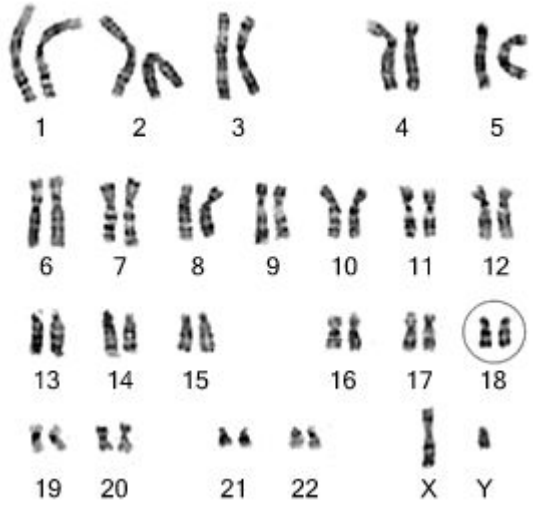
Driver mutation

- Mutations that CAUSE the disease
  - JAK-2
  - MPL
  - CAL-R
- CAL-R is GOOD
- No mutations is unfavorable



Cytogenetics

- Cytogenetics (abnormal chromosomes found in your bone marrow)
  - complex karyotype (3 or more abnormalities) or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement



These are not inherited… they are changes that occur only in disease cells

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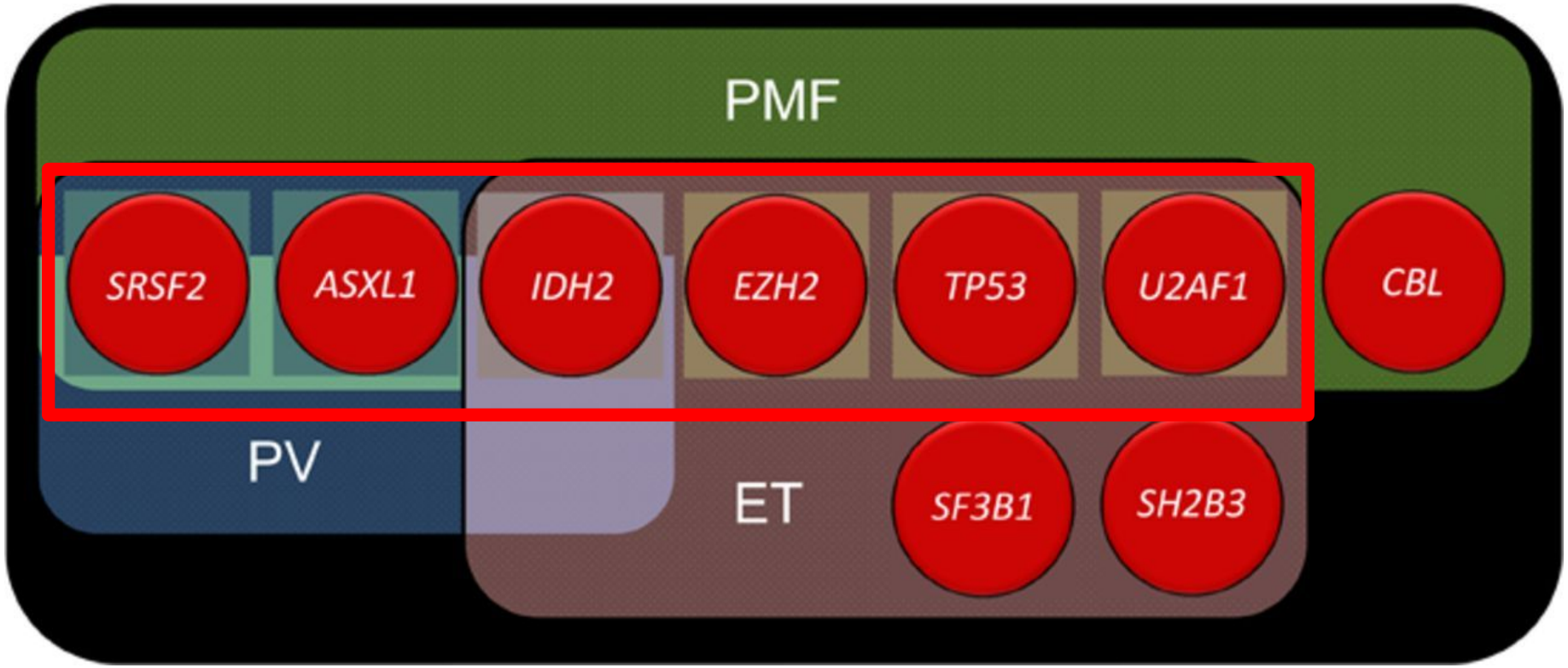
Molecular mutations
"next generation sequencing"

Prognostically important genes, other than *JAK2/CALR/MPL*, in essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)



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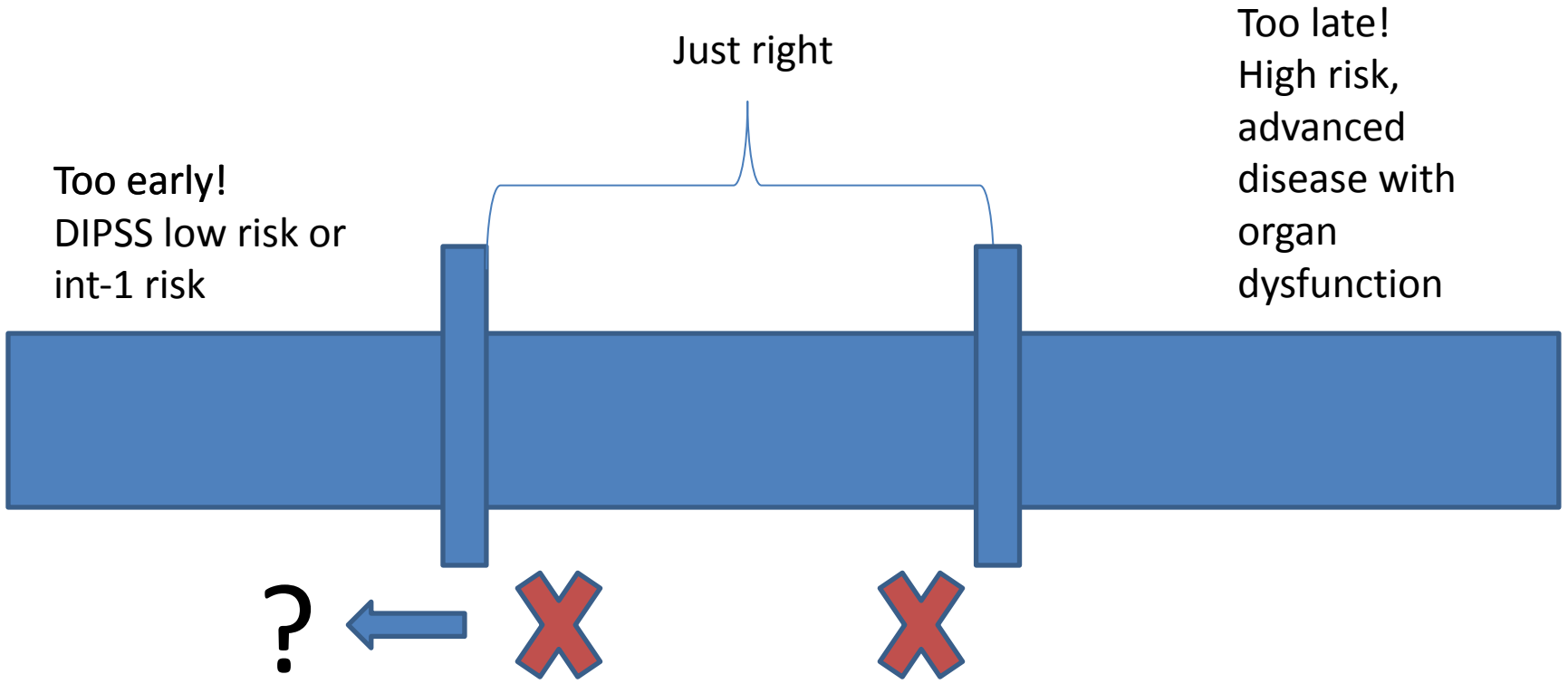
When to **do** transplant



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Other considerations

- Symptom burden
- Ruxolitinib (Jakafi©)
- Transfusion dependence
- What gives you points??

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Example #1

- 64 year old patient with primary myelofibrosis
- CAL-R positive
- On 1/5/19 WBC 23K, 2% blasts, hgb 9.7, platelets 115 (DIPSS: 3)
- On 2/5/19 WBC 26K, 0 blasts, hgb 10.2, platelets 150 (DIPSS: 1)
- Would this change if JAK2 positive?
- ASXL1 positive?

Example #2

- Patient is 58 year old female with post-essential thrombocythemia myelofibrosis
- MPL positive
- Hgb 7, requires transfusion every month, WBC 6.7, Blasts 0 DIPSS: 2

Example #3

- 65 year old male with primary myelofibrosis
- JAK2 positive
- Hgb 9.5, WBC 7.2, blasts 0, platelets 165 DIPSS: 3

- I feel SO good on Jakafi-- should I proceed with transplant??
- These newer agents in clinical trial may reduce my mutation burden and fibrosis- will these cure the disease?
- Should I do a clinical trial first, then transplant?

WHAT HAPPENS WITH A TRANSPLANT?

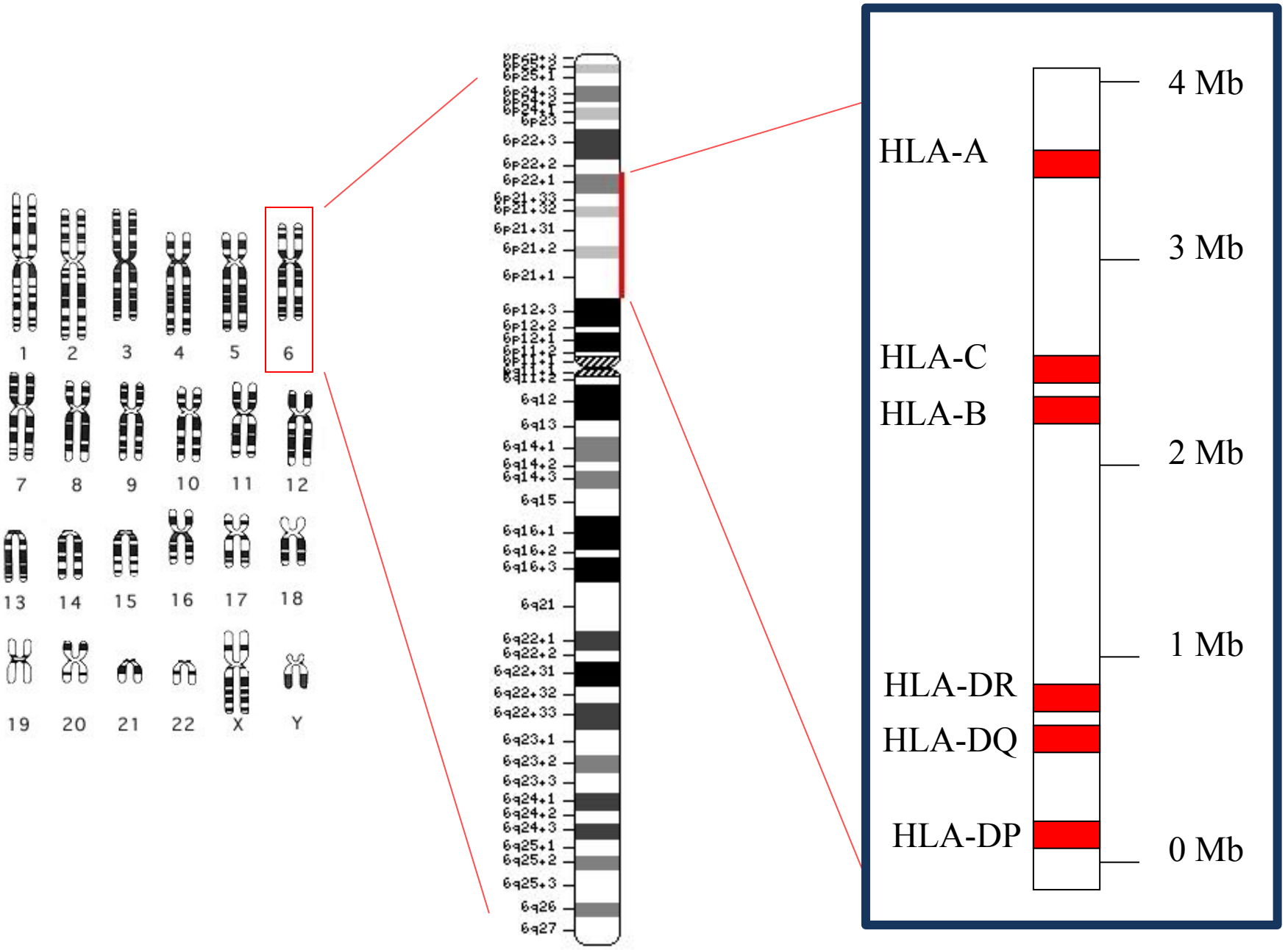
Important things to know ahead of time

- You will be seen daily for approximately 1 mo- some programs do this inpatient, others outpatient
- You will live near the transplant center at least 100 days following transplant (usually within 30-60 minutes)
- You need a full time caregiver (usually a spouse, relative or friend)
- You will have a lot of restrictions
- You will be off work for up to 1 year and sometimes more***

Finding a donor

- Donors can be related or unrelated
- As of the most recent data, there are over **40 million potential bone marrow donors** listed worldwide through various registries. Some of the largest global registries include:

1. **Be The Match** (run by the National Marrow Donor Program) in the United States, with over **11 million** donors.
2. **DKMS**, an international registry with over **9 million** registered donors.
3. **World Marrow Donor Association (WMDA)**, which supports and tracks the collaboration of bone marrow registries worldwide.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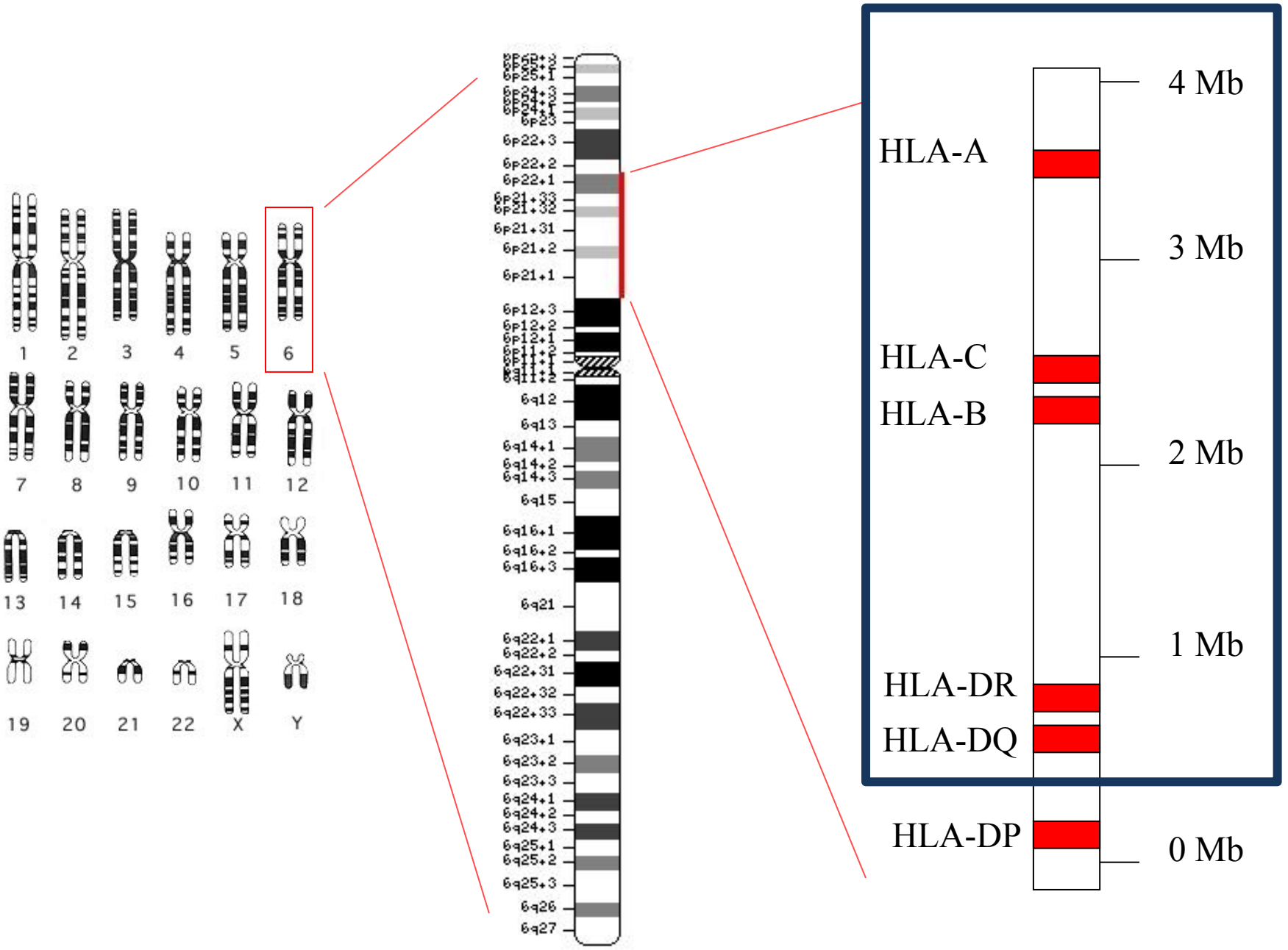
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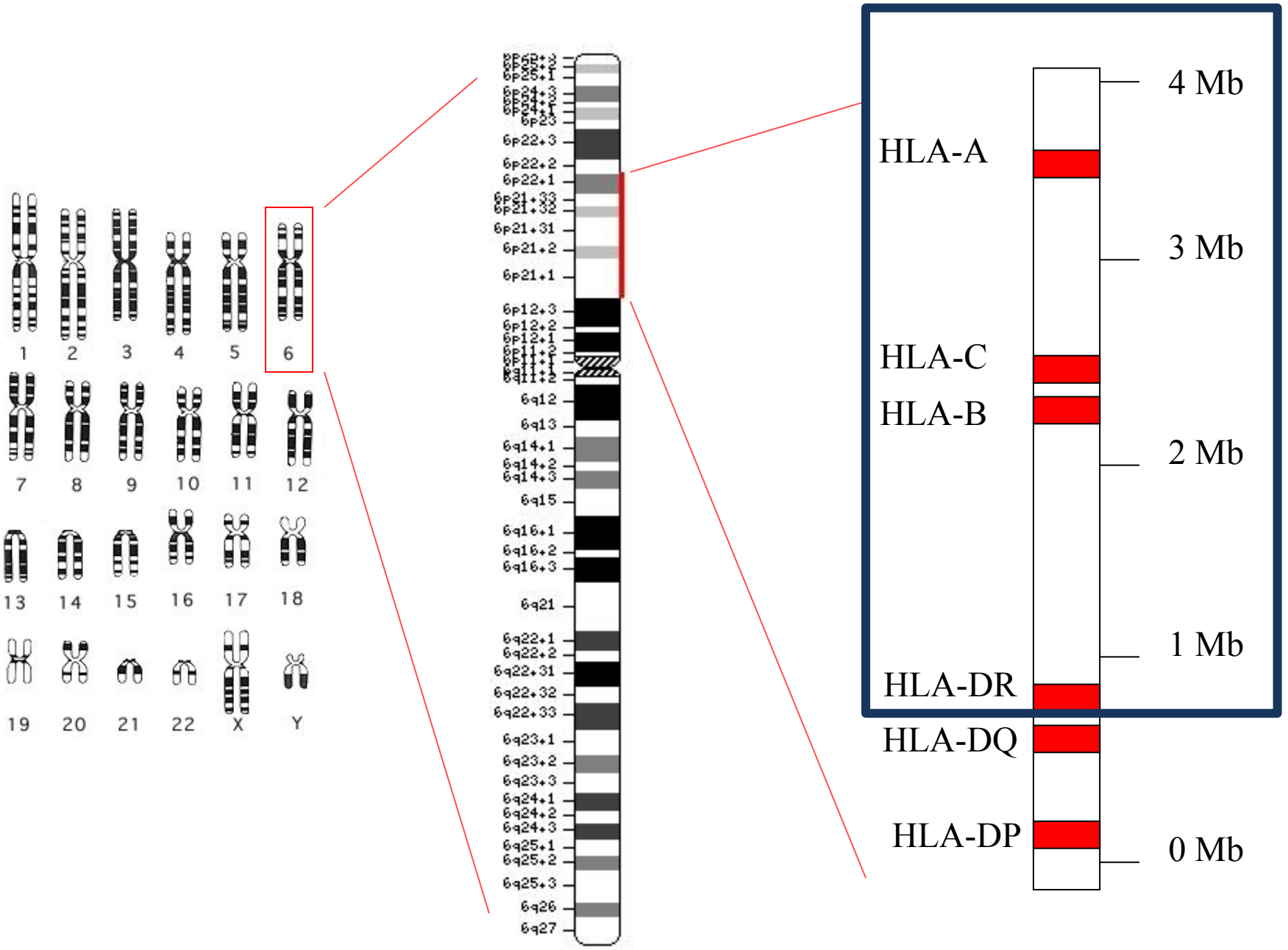
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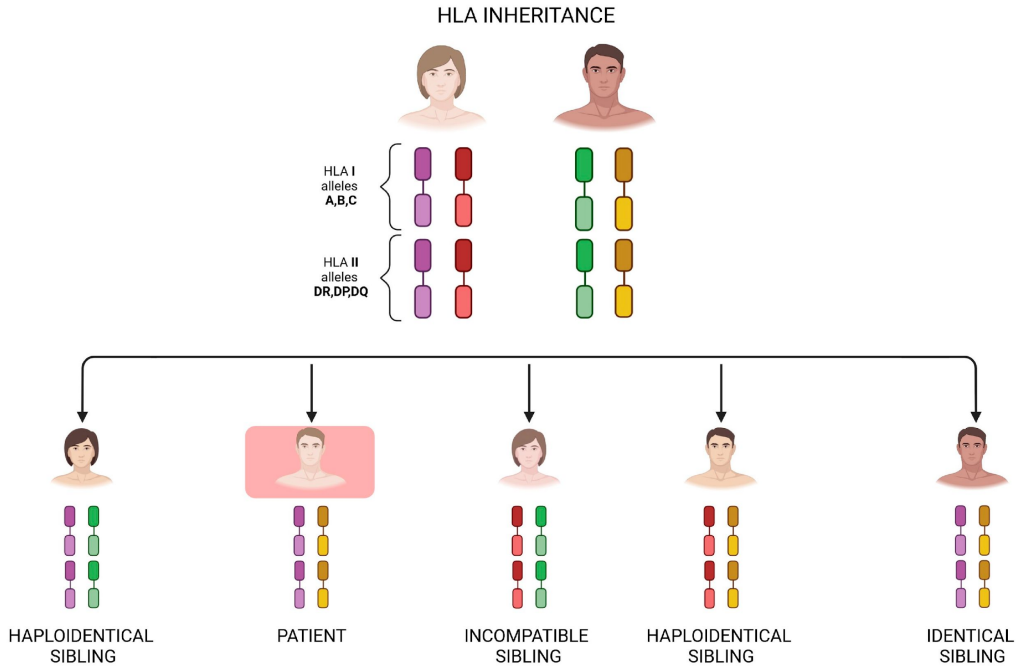
Should my relative be a donor?

- Each full sibling has:
  - 25% chance of being a full match
  - 50% chance of being a half match
  - 25% chance of not being a match at all
- Parents or children are ALWAYS a half match (unless donor egg or sperm)



Selection of a donor

Fully matched donor- can be related or unrelated:

- 10/10 or 8/8

- Mismatched unrelated donor
  - 9/10 or 7/8
- Haploidentical
  - 5/10 or 4/8
- Historically matched related donor and matched unrelated donor
- There appears to be some intolerance of mismatch
- HOWEVER, almost all donors can be utilized

What to do with a large spleen??

- Many studies are showing an advantage in the use of JAK inhibitor prior to transplant to shrink spleen, tapered off right before conditioning, or sometimes after transplant
- Splenectomy- must carefully weigh risks and benefits
- Splenic irradiation

- ***Individualized decision!!***

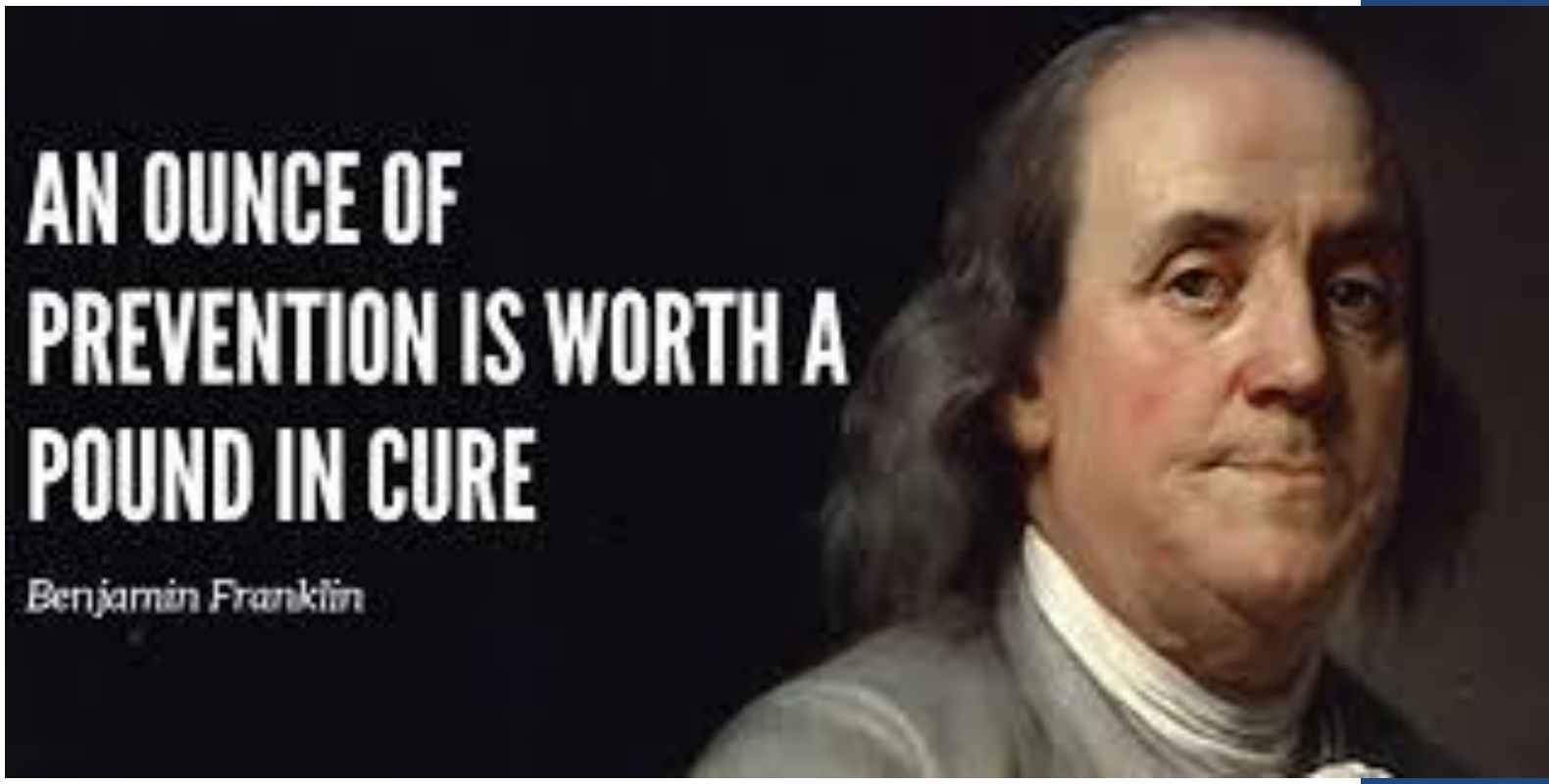
Conditioning regimens

- Myeloablative
- Reduced intensity
- Non-myeloablative

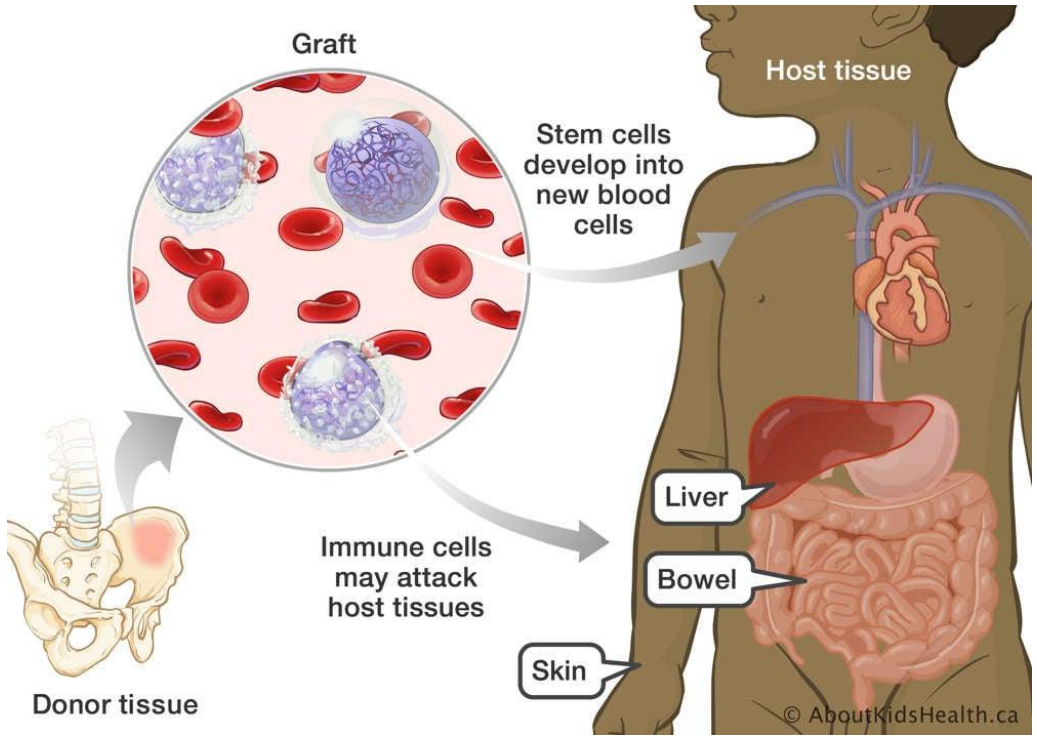
- Include a chemotherapy to suppress immune system, and one to attack disease

GVHD prevention

- Chemotherapy given after stem cells:
  - Methotrexate
  - Cyclophosphamide
- Immunosuppression medications:
  - Tacrolimus
  - Cyclosporine
  - Sirolimus
- Other interventions:
  - ATG
  - Campath
  - CD34 selection



Graft versus host disease



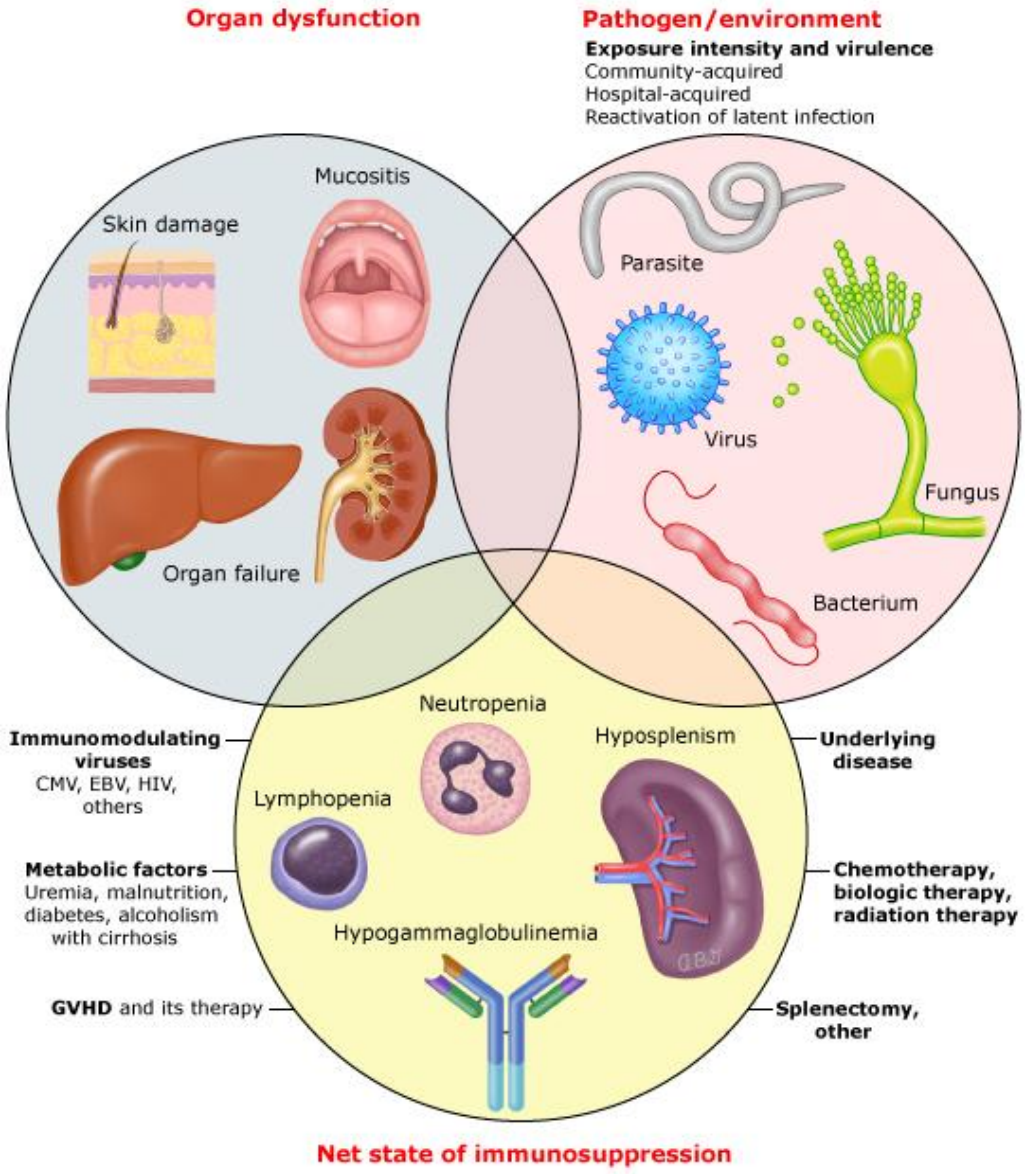
- Acute: typically involves the skin, liver and intestines
- Chronic: can involve almost any organ system in the body
- Differentiated by symptoms
- Occur in about 30% of transplant recipients
- TREATABLE!

The Holy Grail of Transplant

Graft vs host disease

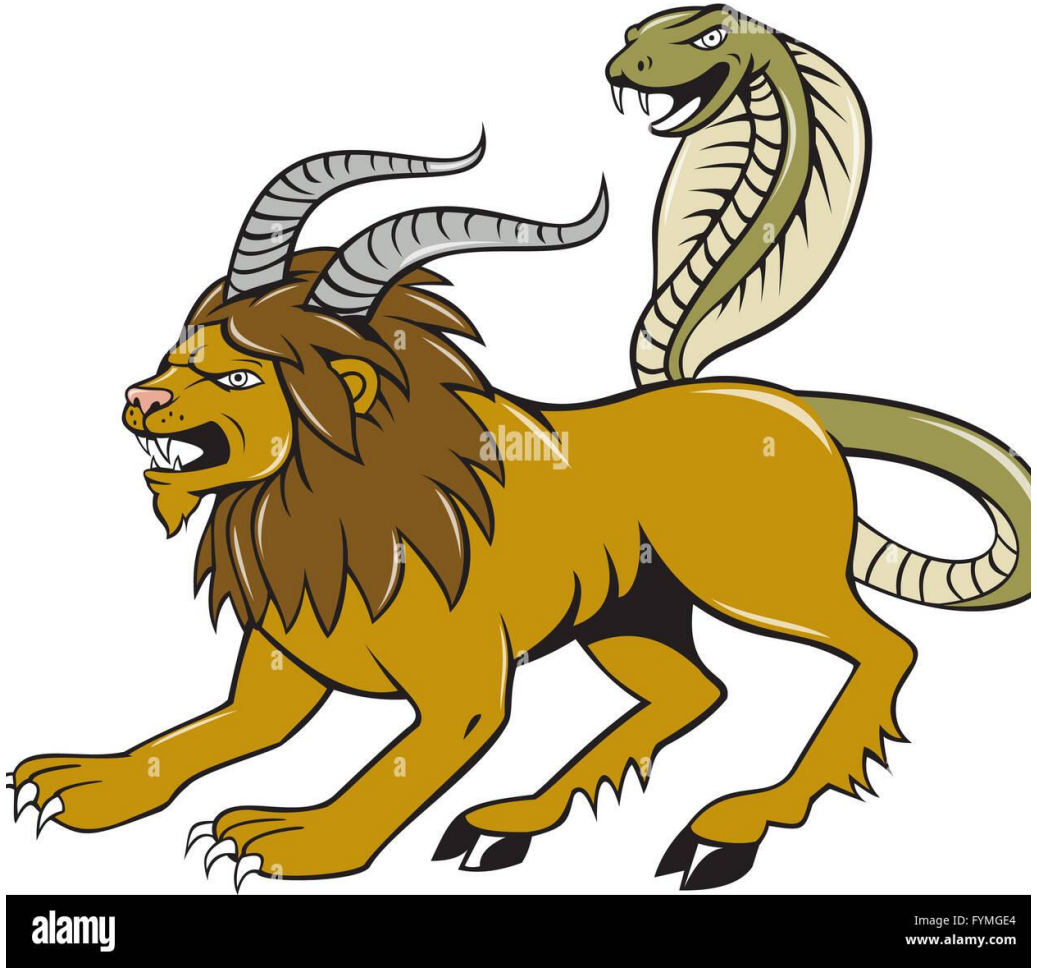
Graft vs myelofibrosis and infection

Infections


Organ dysfunction
Pathogen/environment
Exposure intensity and virulence
Community-acquired
Hospital-acquired
Reactivation of latent infection
Mucositis
Skin damage
Organ failure
Parasite
Virus
Fungus
Bacterium
Neutropenia
Hyposplenism
Lymphopenia
Hypogammaglobulinemia
Immunomodulating viruses
CMV, EBV, HIV, others
Metabolic factors
Uremia, malnutrition, diabetes, alcoholism with cirrhosis
GVHD and its therapy
Underlying disease
Chemotherapy, biologic therapy, radiation therapy
Splenectomy, other
Net state of immunosuppression

Monitoring after transplant

- Chimerism
  - How many cells are donor
  - How many cells are recipient (patient)
- Bone marrow aspirate
- Peripheral blood
  - CD33- neutrophils/monocytes etc
  - CD3- T cells (they cause GVHD and graft versus MF)



Common lab abnormalities after transplant

- Very slow recovery of red blood cells and platelets
- Kidney or liver dysfunction related to post transplant medications
- Low magnesium (related to immunosuppression)

Survivorship

Health maintenance is very important for BMT survivors

- Dental visits every 6 mo
- Routine cancer screening
- Management of cardiovascular risk factors:
  - Hypertension
  - Elevated cholesterol
  - Diabetes
- Yearly eye appointments
- Bone health
- Thyroid health

Relapse

- Can occur in up to 25-30% of BMT survivors
- Molecular relapse:
  - Decrease in chimerism
  - Recurrence of driver mutation
  - Blood counts stable
- Overt relapse
  - Decrease in chimerism
  - Recurrence of driver mutation
  - Blood count abnormalities

What do we do about relapse?

- Sometimes can give donor cells (donor lymphocyte infusion)
- If overt relapse, may come back in earlier stage, and treated like early myelofibrosis
- An area of unmet need!!

Summary

- Bone marrow transplant is a curative option for myelofibrosis
- When the best time to undergo transplant is still under investigation
- Know your risk! The risk of disease as characterized by cytogenetics, molecular mutations etc

More summary

- Transplant is a very complex process
  - Take your time digesting everything
  - Seek more education from groups like BMT infonet, NMDP
  - Talk to your BMT RN coordinator
  - Write down your questions
- Decisions such as donor choice, conditioning regimen and GVHD prevention vary- no clear right or wrong