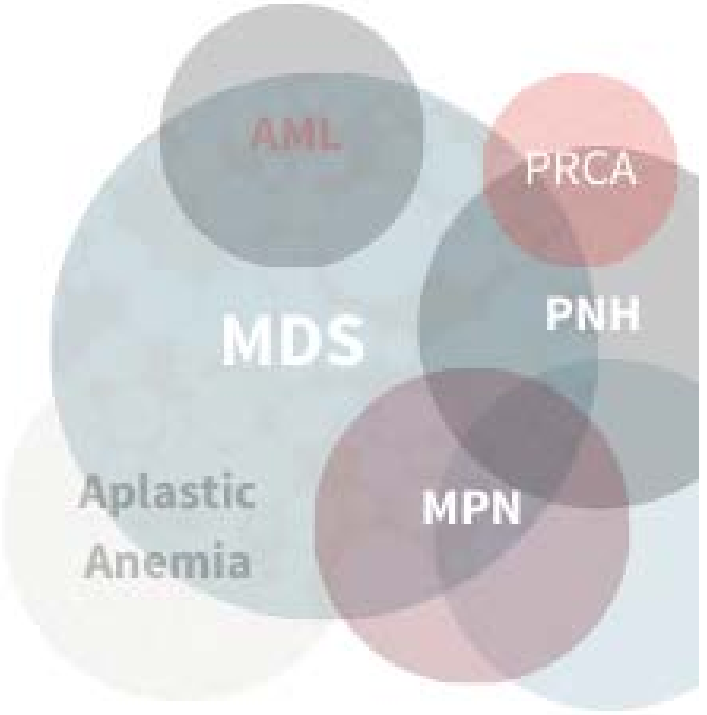
What are my Options with High Risk MDS/AML?



Nathan Punwani, MD
Cedars-Sinai

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INTERNATIONAL FOUNDATION

Our Mission

The Aplastic Anemia & MDS International Foundation is the world's leading nonprofit health organization dedicated to supporting patients and families living with aplastic anemia, myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria (PNH), and related bone marrow failure diseases. The Foundation provides answers, support, and hope to thousands of patients and their families around the world.

We are a patient-focused, patient-centered organization, serving patients and families throughout the three phases of bone marrow failure diseases:

- the life changing phase of diagnosis
- the life threatening phase of treatment
- the life long phase of living with a chronic disease

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Submitting Questions During the Presentation

1. Use the Q & A box on the bottom of your screen. Type your question into the box and press **ENTER**.
2. Please do not include private health information about the patient in your question. Our presenters cannot answer specific questions related to your diagnosis or treatment.
3. We will try to answer all questions during the webinar but may not be able to get to everyone.
4. If we do not get to your question, please send it to us via email at help@aamds.org, by calling the office at (800) 747-2820 x2 or by sending us a message on social media.

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Your Resource of Choice for Bone Marrow Failure Disease Education and Support

- For up-to-date guidance, webinar links, resources and Frequently Asked Questions on COVID-19, visit www.aamds.org/education/covid-19
- Contact AAMDSIF via e-mail to help@aamds.org
- Call AAMDSIF at (800)747-2820, ext. 2
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The AAMDSIF Medical Advisory Board and Staff are here to help you and your family, as we have for the past 36 years.

GUIDESTAR PLATINUM TRANSPARENCY 2021

AA·MDS INTERNATIONAL FOUNDATION

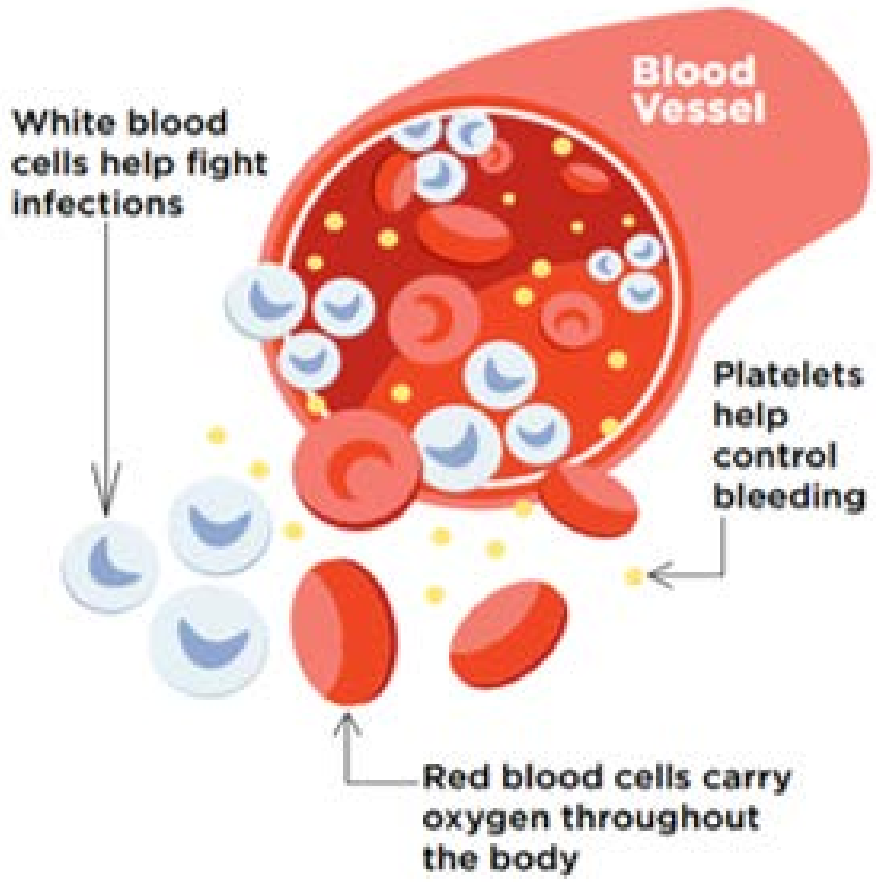
HIGH RISK MDS TO AML

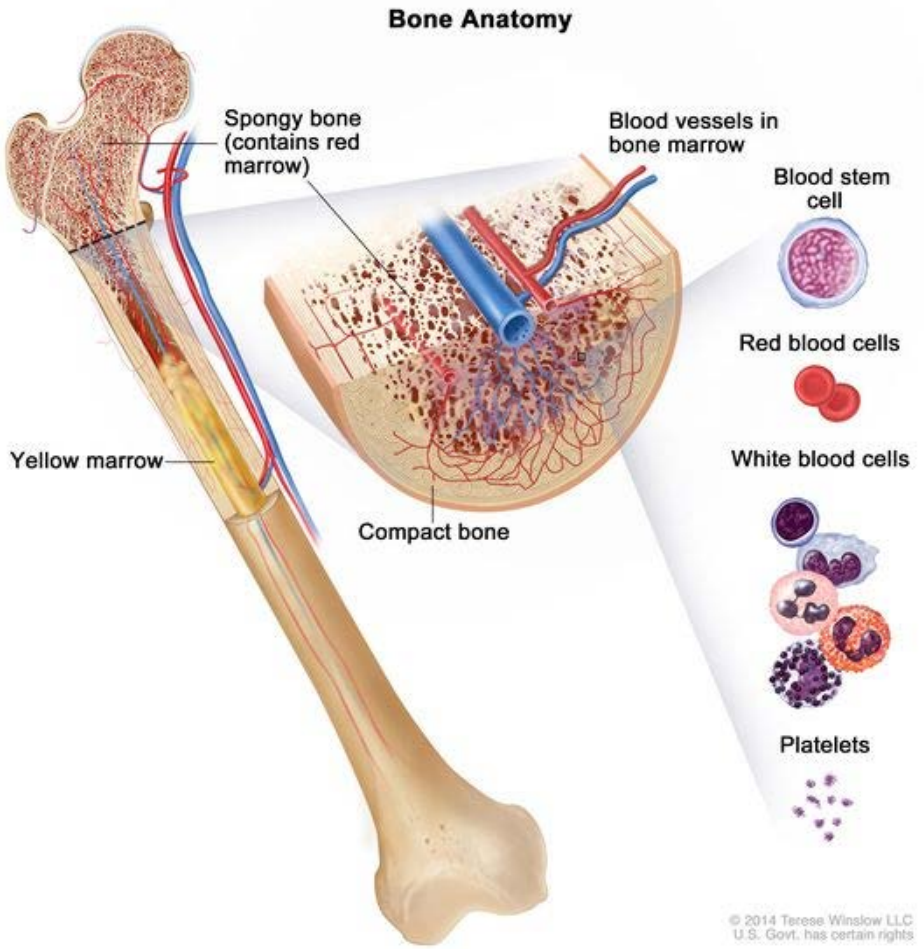
NATHAN PUNWANI, MD, MPH

CEDARS-SINAI

APRIL 10, 2021

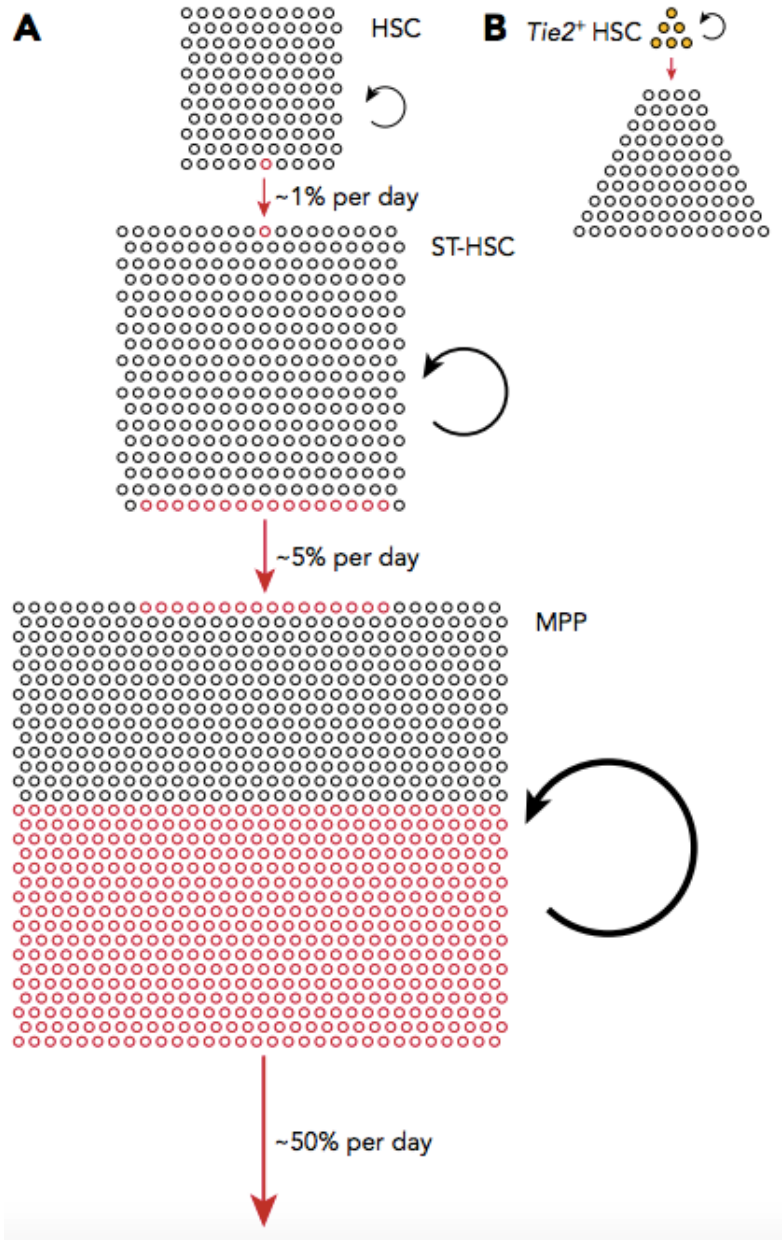
WHAT IS IN BLOOD AND WHERE DOES IT COME FROM





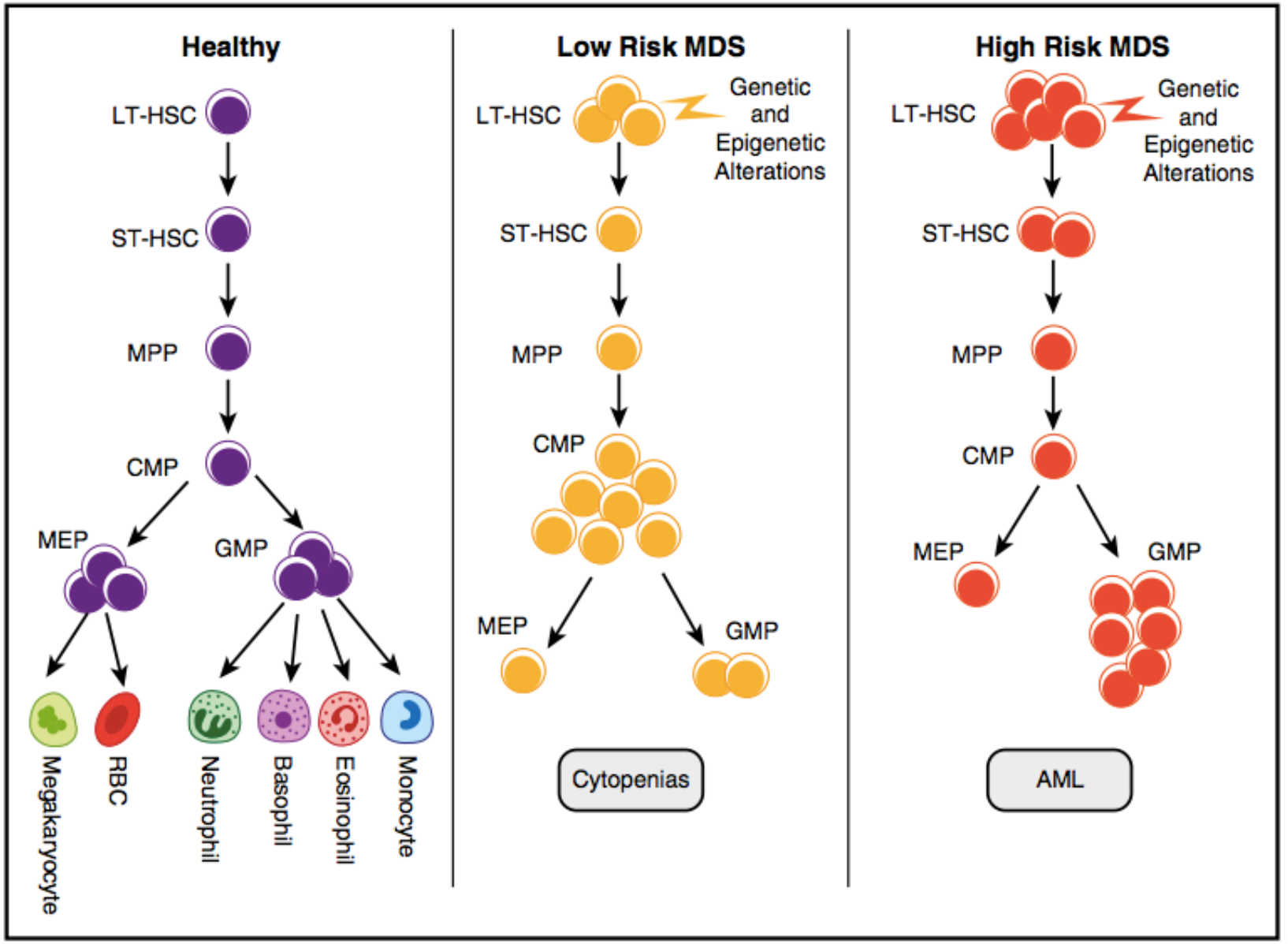
Courtesy of CureSearch and NCI

BONE MARROW STEM CELL HIERARCHY



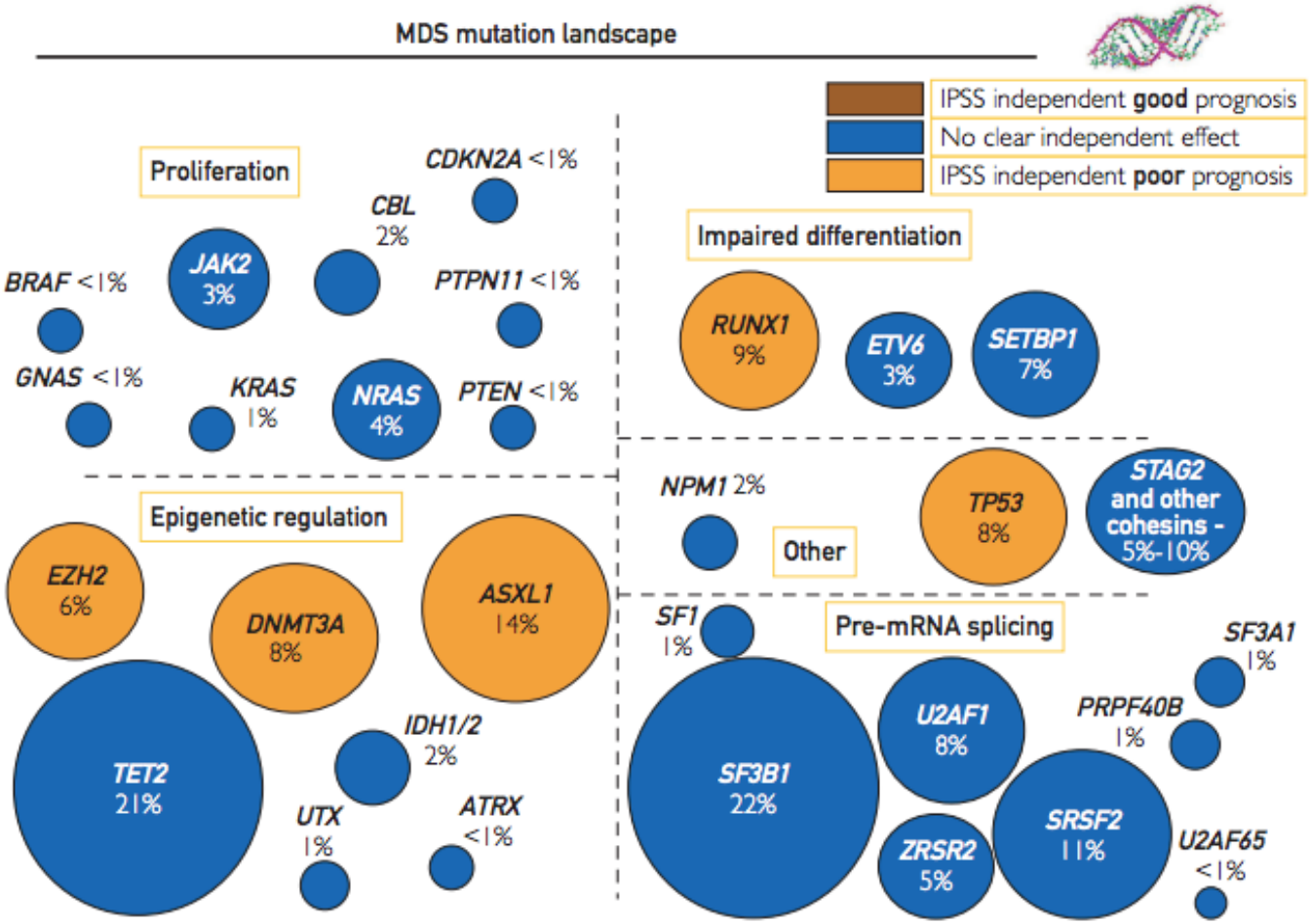
Höfer et al.Blood 2018 132:1106-1113

ANYTHING CAN GO WRONG WITH THE BONE MARROW STEM CELL "FAMILY TREE"



Shastri et al. Blood 2017 129:1586-1594

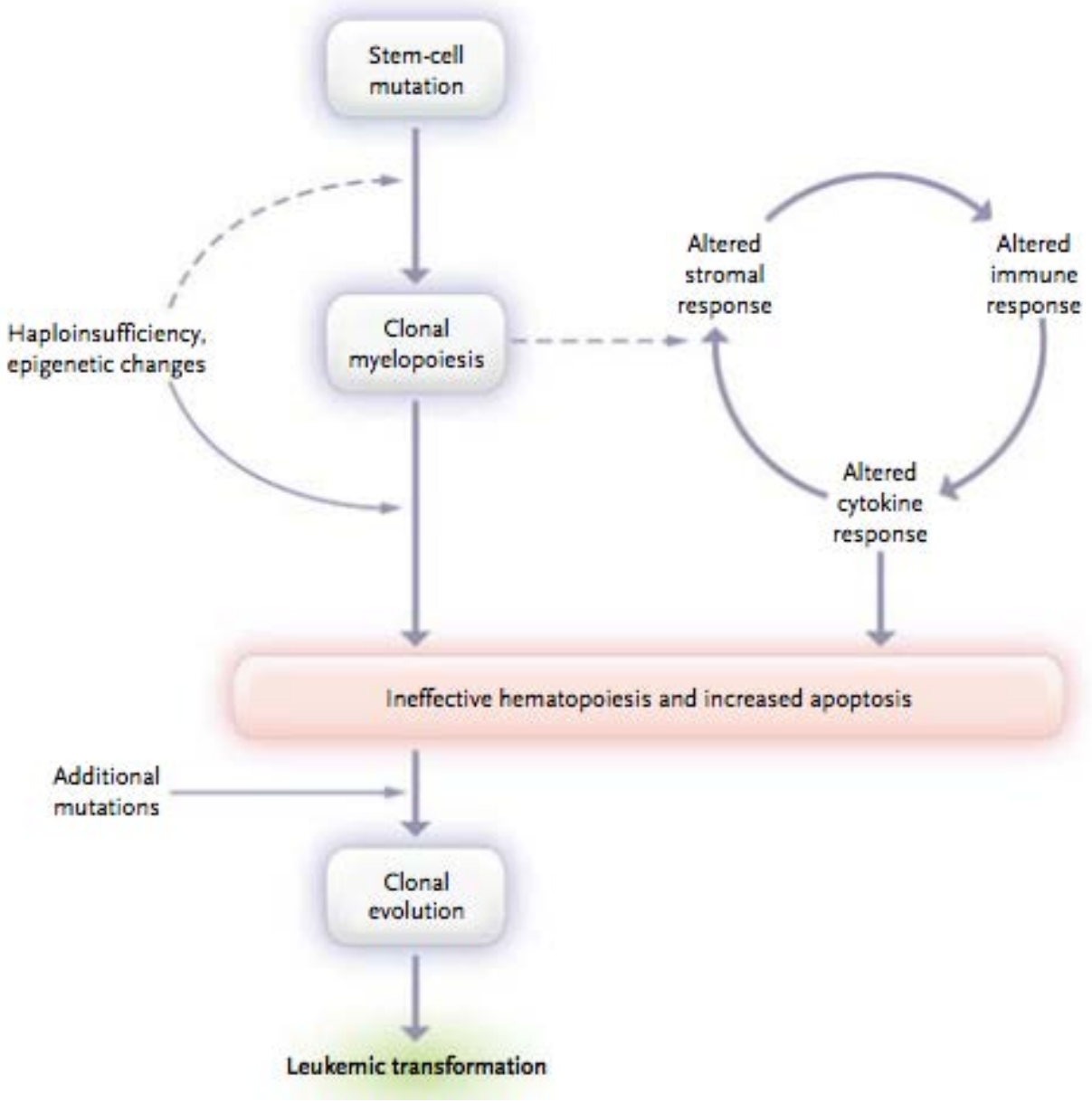
GENETICS OF MDS



Steensma. *Mayo Clinic Proceedings*. 2015;90:969.

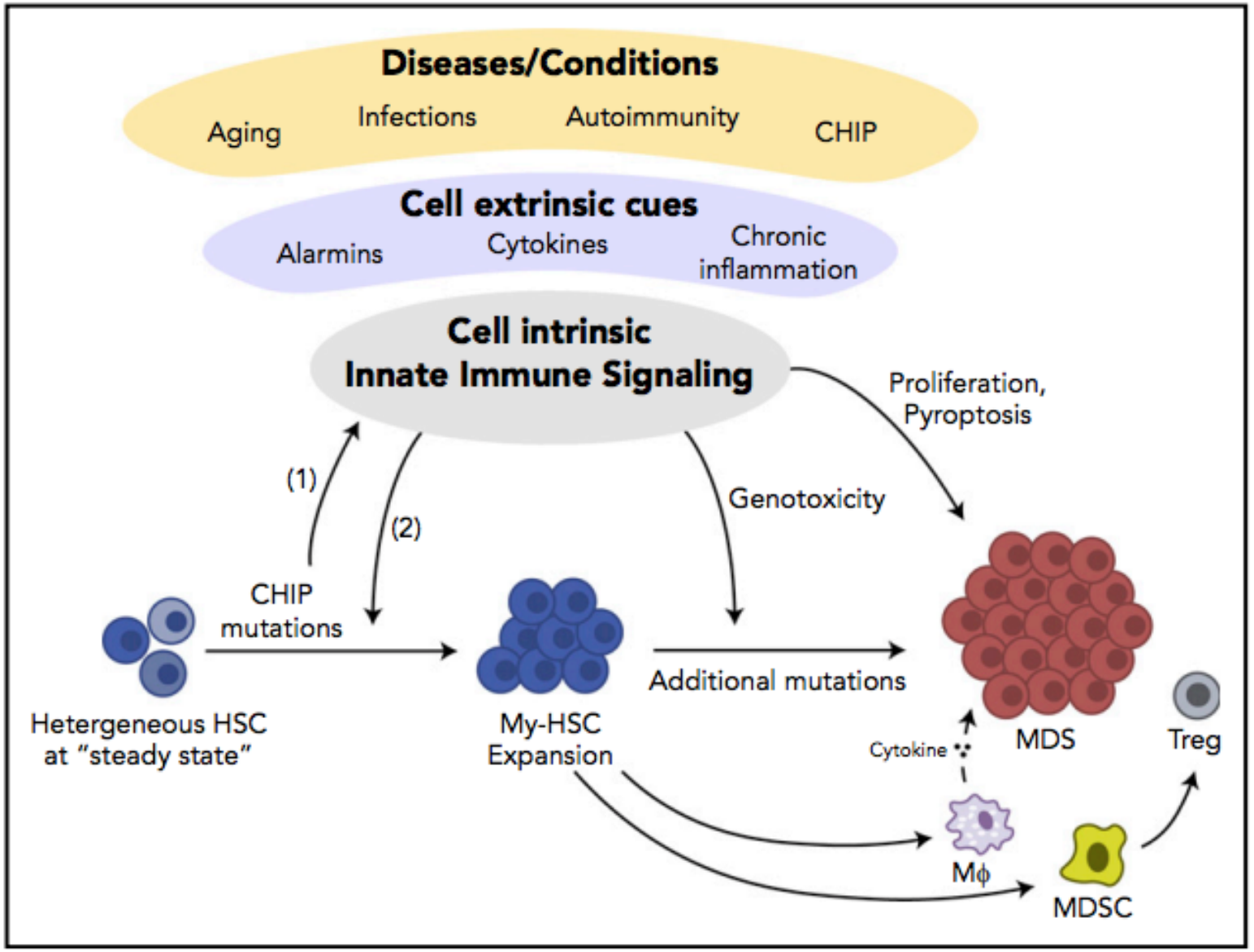
WHY MDS HAPPENS:

IT'S NOT ALL GENETICS



Tefferi et al, N Engl J Med 2009;361:1872-85

MANY FACTORS ARE CULPABLE FOR MDS



Barreyro et al. Blood. 2018;132(15):1553-1560

IMMUNE DYSREGULATION IN MDS

Low-risk disease: ↑ immune activation

- Less regulatory immune cells
- Immune cells are more aggressive and attack the corrupted bone marrow stem and progenitor cells
- More inflammation and increased bone marrow cell death

Late-stage, high-grade disease: ↓ immune activation

- More regulatory immune cells that "turn off" the immune system
- Dysfunctional immune cells
- Less inflammation and reduced bone marrow cell death

↓ immune activation → ↑ MDS progression and leukemia proliferation

TREATMENTS VARY BASED ON HOW AGGRESSIVE THE MDS IS

For low grade disease:

- Observation
- Transfusions
- Growth factors to boost blood cell counts
- Lenalidomide
- Immune suppression

For high grade disease:

- Only curative option is bone marrow stem cell transplant
- Hypomethylating agents (HMAs): decitabine, azacitidine

TRANSFUSIONS AND IRON CHELATORS

Courtesy of New Atlas

- 40% in lower-risk patients and 60% to 80% in higher-risk patients need transfusions
- Patients receiving regular transfusions have inferior survival compared with those who do not require transfusions
- RBC transfusions should be minimized and utilized only as necessary for symptomatic anemia or to maintain a safe hemoglobin of 7 to 8 g/dL
- Iron chelation therapy with oral deferasirox or parenteral deferoxamine can be considered in patients with a relatively good MDS prognosis who have evidence of tissue iron overload or elevated blood iron levels

GROWTH FACTORS

- Studies with recombinant ESAs (epoetin and darbepoetin) increase RBC production in 20-40% of patients
- An 8- to 12-week trial of an ESA at standard dosing schedules is appropriate for anemic patients
- G-CSF (filgrastim, tbo-filgrastim) have been evaluated in patients with MDS and increase the neutrophil/white blood cell counts in up to 60% to 90% of patients, which may help some patients who have recurrent infections
  - This practice is discouraged overall as survival was shorter in patients with "higher levels of pre-leukemia"
- TPO receptor agonists (thrombopoiesis-stimulating agents) can raise the platelet count in some patients with MDS and decrease platelet transfusions and bleeding events
  - Not FDA approved for MDS
  - Increases pre-leukemic cells, accelerates progression into full blown leukemia by 3-fold, esp in patients with higher risk disease!

LENALIDOMIDE & IMMUNE MODULATORS

- Lenalidomide is an immune modulator
- In certain types of MDS, 67% of patients on lenalidomide achieved transfusion independence
- Responses typically occur after 4 weeks with responses lasting more than 2 years
- Hemoglobin on average rise by over 5 g/dL
- If lenalidomide is given to all MDS patients then response rates fall
  - Only 26% of patients became red blood cell transfusion independent with a duration of response of no more than 10 months

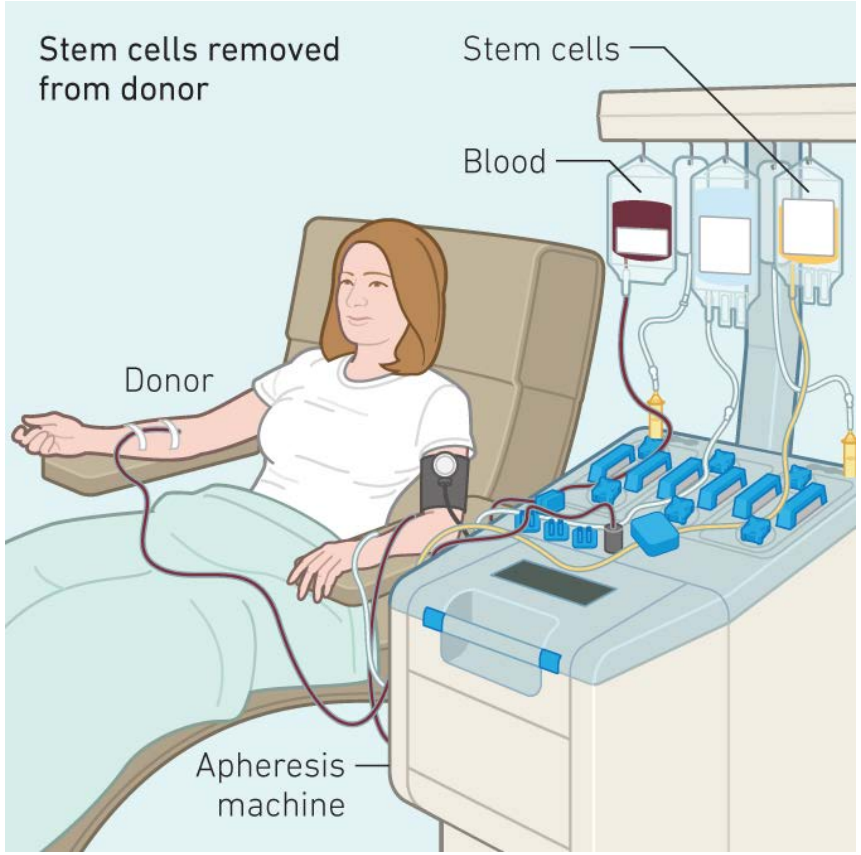
HYPOMETHYLATING AGENTS (AZACYTIDINE, DECITABINE)

- **Classical mechanism of action**: activation of cancer-fighting, tumor suppressor genes

- **Alternative mechanisms:**
  - Induces a more effective inflammatory response by the immune system
  - Encourages the most healthy stem cells to divide and differentiate into mature, functional blood and immune cells

- 17% of patients achieved a complete response
- 15% achieved a significant reduction in leukemia cells
- 18% experienced improvement in blood cells counts
- Clinical response requires at least 4-6 months of treatment

BONE MARROW STEM CELL TRANSPLANT



- <10% of patients with MDS currently undergo transplant due to older age, comorbid conditions
- Relapse rates are up to 50% even with transplant
- Reduced-intensity conditioning regimens (less chemo and radiation) is allowing for older, sicker patients to get transplants
  - Lower transplant-related mortality but higher relapse rate
  - Overall survival to more aggressive chemo, radiation conditioning

Courtesy of Lotus Hospital

IF MDS → AML: CHEMOTHERAPY

- Induction therapy (inducing a complete remission [CR])
  - 7 days of infusional cytarabine and 3 days of an anthracycline chemotherapy ("7+3")
  - CR in 60 to 85% of adults who are 60 years or younger
  - Patients older than 60 years have worse outcomes

- Consolidation therapy (preventing relapse)
  - Cytarabine chemo for 2-4 months
  - Bone marrow stem cell transplant

VYXEOS FOR THE FIT ELDERLY (S/T AML)

- VYXEOS is 7+3 encapsulated in "fat molecules"
- Vyxeos significantly improved median overall survival versus 7+3 (9.56 *v* 5.95 months)
- CR rates: 47.7% *v* 33.3%, favoring Vyxeos
- Early mortality rates with Vyxeos only 6%

AML IN THE GERIATRIC POPULATION

- Median survival 8-12 months in the best circumstances
- High frequency of genetic and chromosomal abnormalities
- No standard of care
- Hypomethylating agents can be considered
  - Can achieve CR in 10%-20% of patients
- Consider clinical trial for elderly with poor performance status or extensive co-morbidities

VENETOCLAX/HMA

- CR of 73% when combined with hypo-methylating agents
- The median duration of CR is 11 months
- Average survival almost 15 months
- The most frequent side effects were low white blood cell counts, infections, diarrhea, fatigue

Courtesy of NEJM

CONCLUDING REMARKS

- It's not all genetics
- MDS stems from "inflamm-aging"
- MDS can be classified into low-grade vs aggressive/high-grade forms
- Aggressivity of MDS is associated immune "down-regulation" → less immune surveillance allows leukemia to proliferate
- Treatments for MDS include transfusions, growth factor support, immune modulation, HMAs
- **Only curative option for MDS is bone marrow transplant**
- If MDS evolves into AML, treatment options include chemotherapy for fit patients or targeted agents with HMA for less fit patients

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THANK YOU! QUESTIONS?

Answers
Support
Hope

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Patient Support Group

TODAY: After the Conference! Virtual Support Groups!

4:00pm Eastern / 1:00pm Pacific

Aplastic Anemia - MDS – PNH – Caregivers

https://us02web.zoom.us/j/87341004741

Passcode: 2021

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