UNIVERSITY of MARYLAND MEDICAL CENTER

How long do I have to live? Understanding Prognosis for Bone Marrow Failure Diseases

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How long do I have to live?

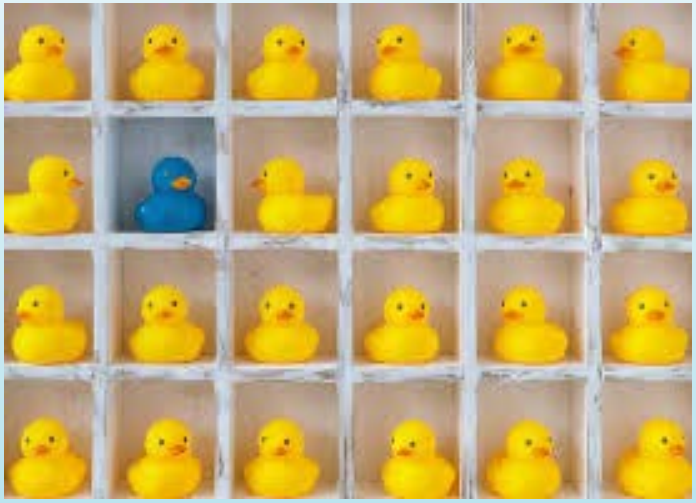
- Outline
  - How to make prognosis
  - Making a prognosis
    - Bone marrow biopsy
    - Flow Cytometry
    - Cytogenetics
    - Identifying Mutations
  - Prognosis in Aplastic Anemia
  - Prognosis in MDS
  - Being Prepared for Clinic appointments

How long do I have to live?

- Prognosis
  - An educated guess about the likely course of your disease from beginning to end
  - Trying to answer how long you might live with your disease

Prognosis Can Be Difficult to Make

- Each person is unique



- Each person's disease is unique and different
- How a disease progresses over time is unpredictable
- We have less information on rare diseases compared to more common cancers

https://lookeducation.com.au/marketing-your-unique-school/

How do we make a Prognosis

- Blood work
- Severity Symptoms
- Bone marrow biopsy results
- Previous clinical research
- Risk Assessment Tools

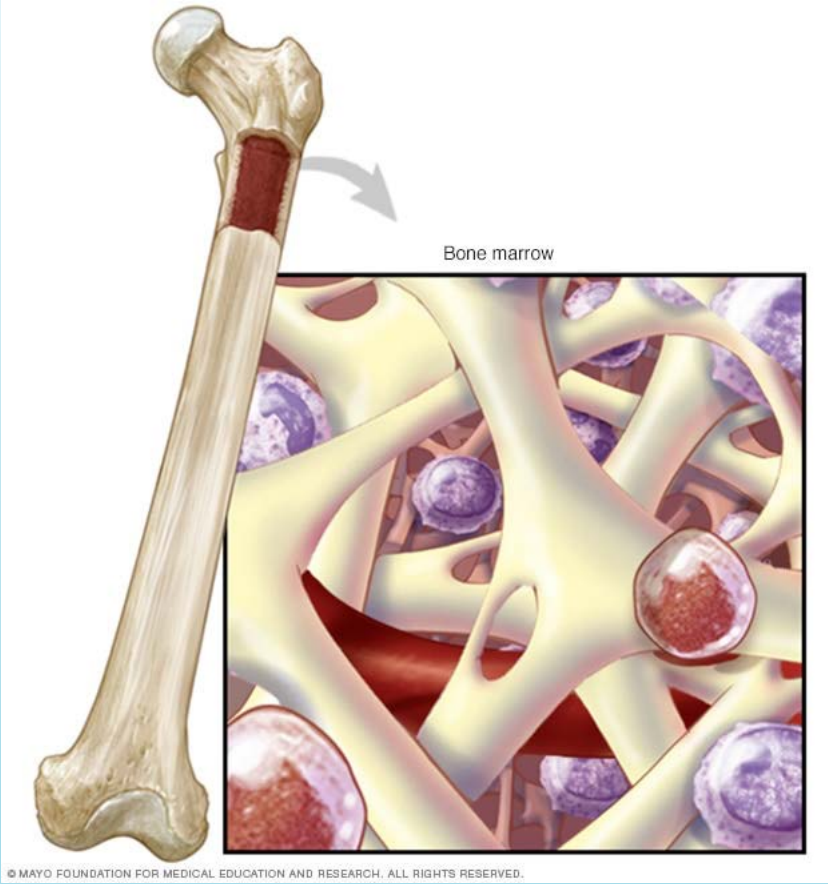
How Do We Diagnose Bone Marrow Failure Diseases?

Medical History- We ask questions about any health events, health problems, and medications that you have taken in the past and present.

Physical Exam- We examine you from head to toe to identify any symptoms suggesting cancer

Labs- We take blood work to evaluate your blood counts and complete testing to diagnose your cancer

Bone marrow biopsy and aspirate- Critical to making the diagnosis



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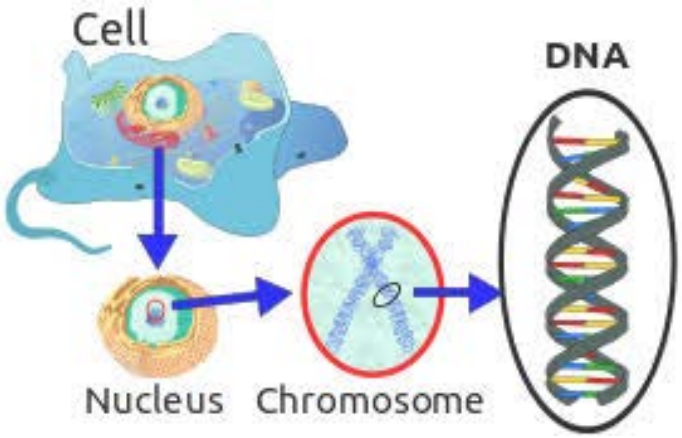
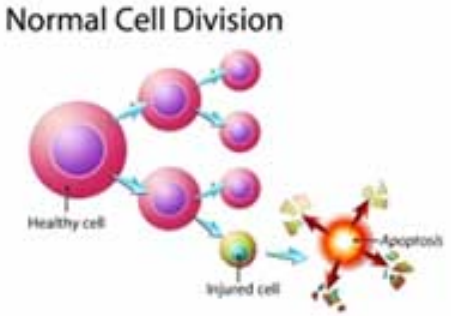
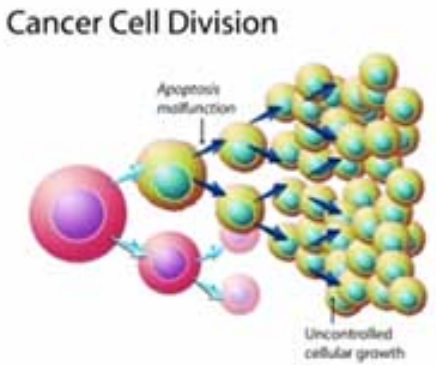
Cancer Cell Growth





Death of cell



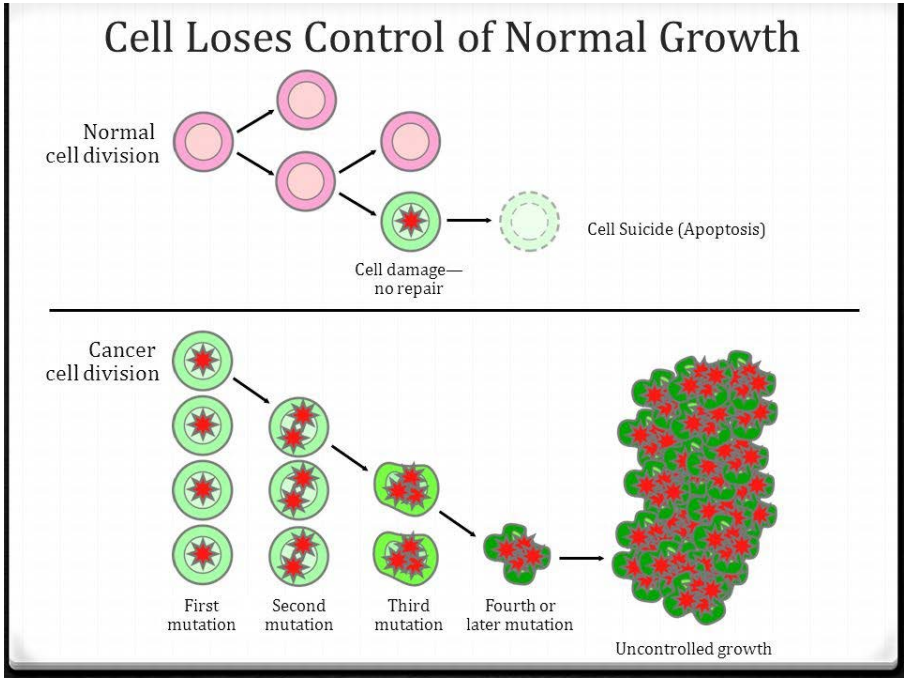
Uncontrolled Cell Growth Leads to ***cancer***

- Inside all cells are instructions for building new cells and controlling how cells are made and behave. These instructions are called **genes**.
- **Genes** are a part of our DNA
- DNA is grouped together in long strands called **chromosomes**
- These **chromosomes** in cancer cells are examined using FISH or cytogenetics as part of the bone marrow biopsy.

- We all have blasts in our bone marrow
- Changes or mutations in genes can cause normal ***blasts*** to ***become cancer cells***
- Researchers are working to learn what causes **genes** to change and cause cancer.

Courtesy: https://www.anylogic.com/resources/articles/the-effect-of-cellular-interactions-on-cancer-cell-growth-using-evolutionary-game-theory/

Cancer Cells versus Normal Cells



Abnormal ***myeloblasts*** ("***blasts***") are the cancer cells resulting in MDS or AML

Cancer Cells vs Normal cells

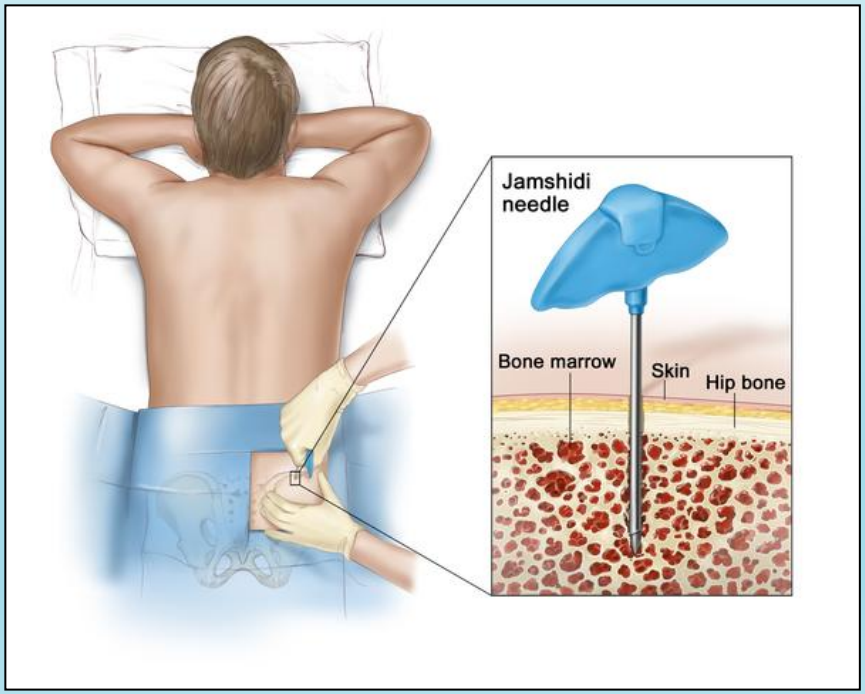
- ***Blasts*** grow more quickly and live longer than normal cells
- ***Blasts*** divide and copy themselves to make more blasts
- ***Blasts*** cells can spill out of the bone marrow into the blood stream. They can spread to other parts of the body including collecting in the spleen, thymus, lymph nodes, liver, testicles, skin, and area around the brain and spinal cord.

Image Courtesy of National Cancer Institute

Bone Marrow Biopsy

Bone marrow biopsy and aspirate are *essential* to establish the diagnosis, determine the subtype, and determine risk

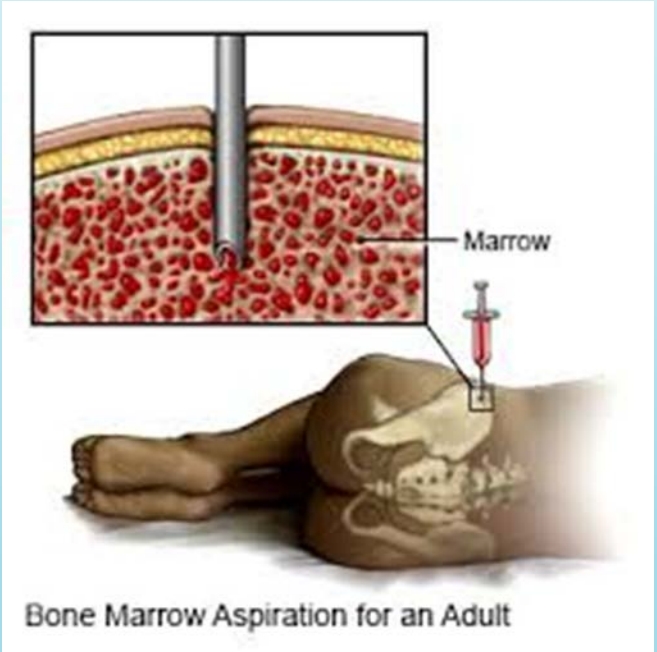
- Morphologic evaluation
- Chromosome analysis (karyotype/cytogenetics)
- Flow cytometry – detect cells with abnormal markers
- Molecular mutations



https://www.healthtap.com/

Bone Marrow Biopsy and Aspirate

Tests from blood or bone marrow
Pathology review of bone marrow to confirm diagnosis
Cytogenetic Testing
Flow cytometry
FISH (Fluorescence in situ hybridization)
PCR (polymerase chain reaction)
Mutation Testing

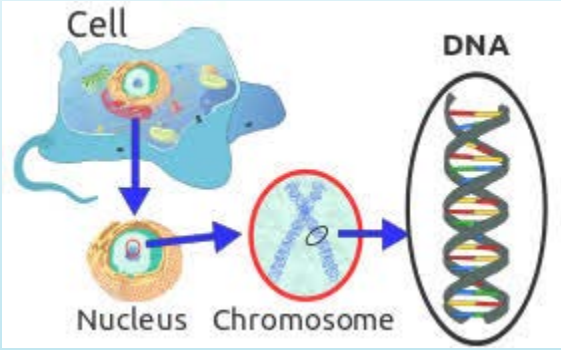


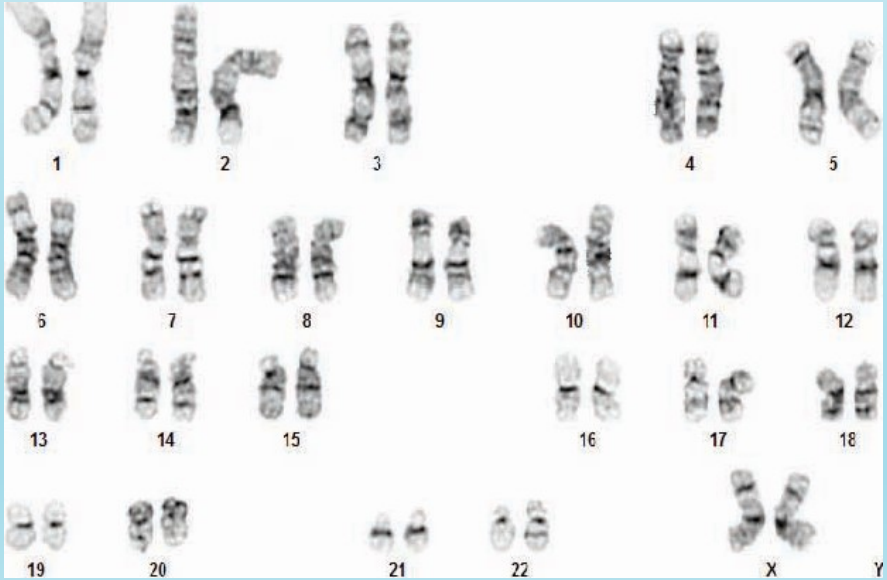
Bone Marrow Aspiration for an Adult

Image from Drugs.com Bone Marrow Biopsy

Genetic Tests: Cytogenetic testing

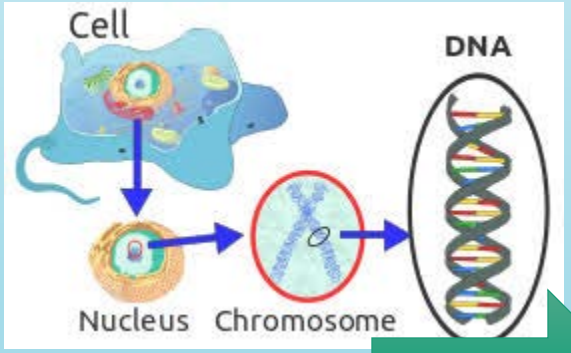
- Cytogenetics uses a microscope to look at the chromosomes inside the leukemia cells to identify the abnormal changes. Completed by a pathologist.
- It is best done from the bone marrow biopsy sample
- Certain chromosome changes in the leukemia cells can affect treatment options including decision on whether a patient needs a bone marrow transplant, what is the best treatment to use, and important for prognosis.
- It can be repeated to evaluate response to treatment (if there is no evidence of the leukemia cells and the chromosome abnormalities are no longer detected, it suggests a great response to treatment)

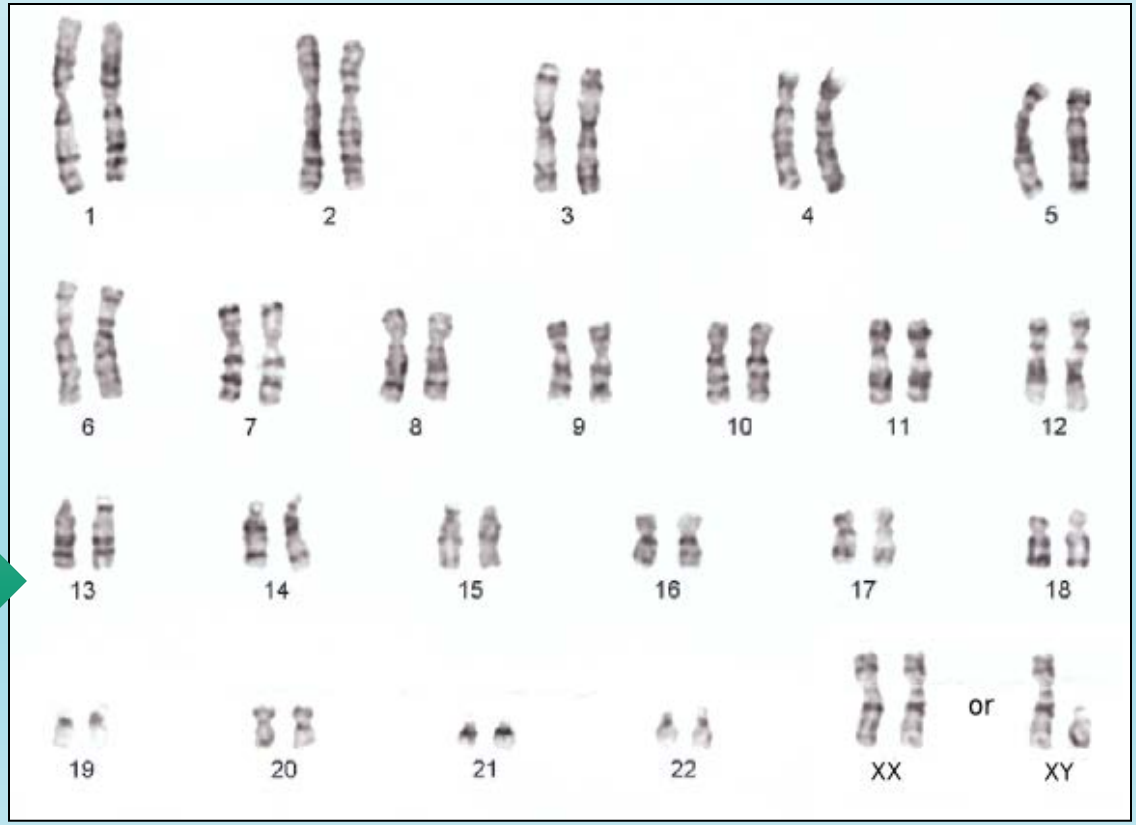




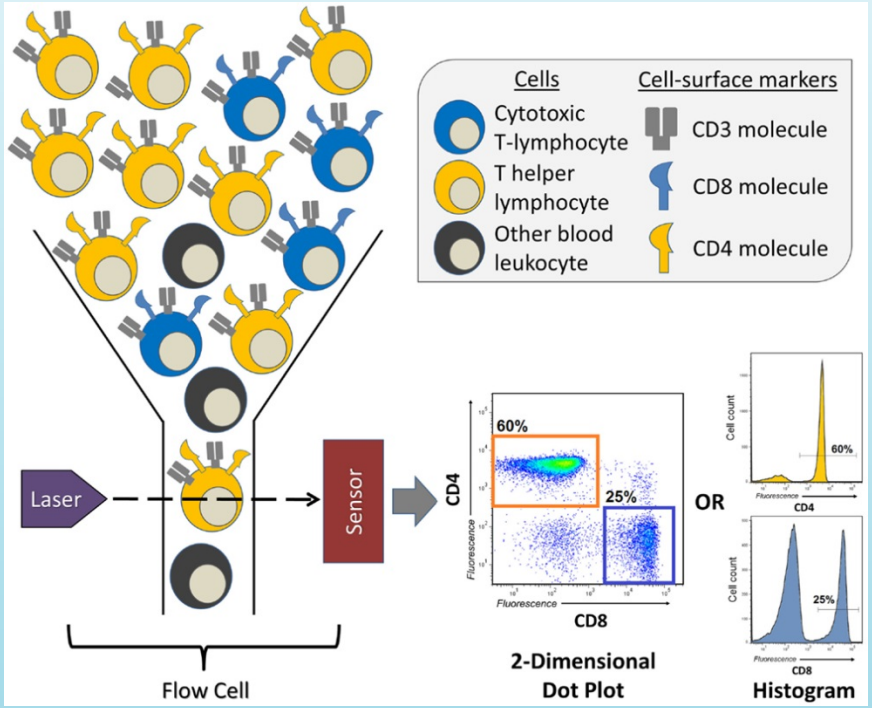
Karyotype/Cytogenetics

- Cells are cultured
- Chromosomes isolated





Flow Cytometry



- Test used to identify and count the different blood cell types in a patient blood sample including percent **blasts**.
- It can help us tell the difference between MDS and other types of leukemia/blood cancers.
- The test helps to confirm the diagnosis of MDS versus AML.
- Flow cytometry can also be used to evaluate whether a patient is responding to treatment.

Image from Frontiers in Immunology
https://www.frontiersin.org/articles/10.3389/fimmu.2015.00380/full

Molecular Studies: Identifying Mutations

- Detects abnormal gene and chromosome changes (mutations) in bone marrow cells that are common for bone marrow failure diseases.
- These tests are used to decide treatment as well as prognosis
- We now have specific drugs that target certain mutations and chromosome changes that are often oral drugs

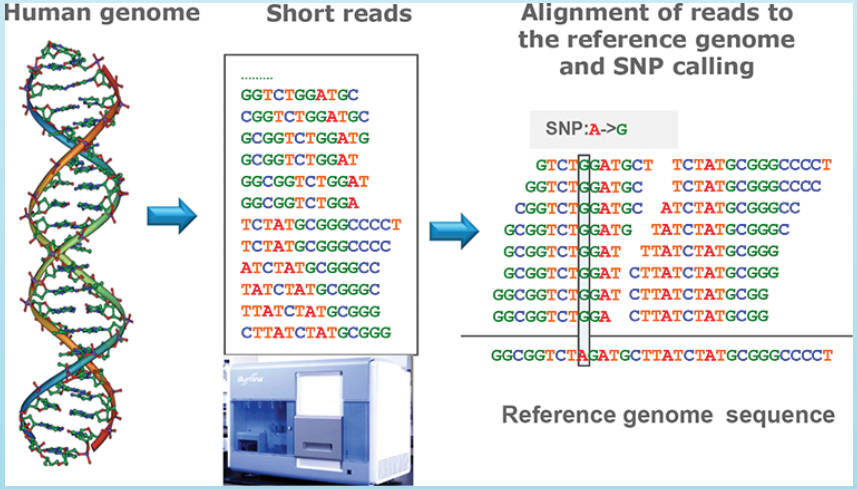


Image Courtesy of Cloud Computing-Architecture and Applications Edited by Jaydip Sen

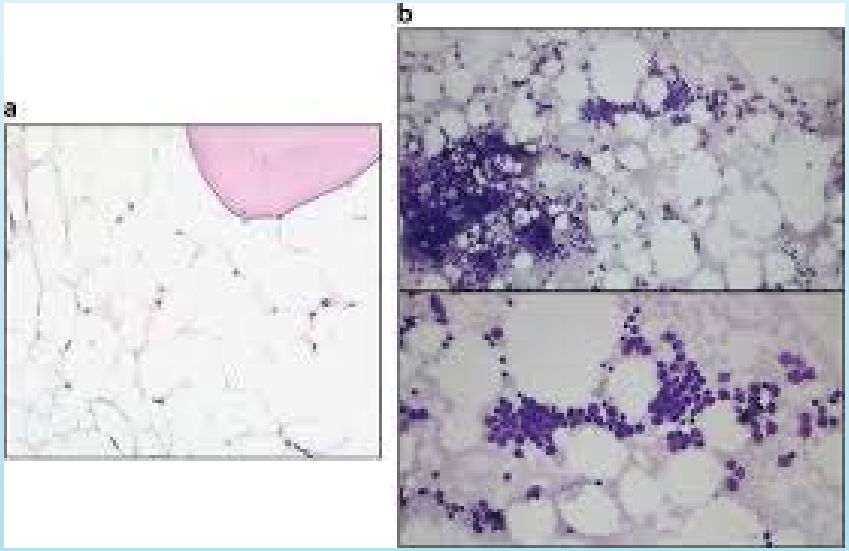
Summary of How To Diagnose Bone Marrow Failure Diseases

- A complete exam with a physician Blood tests are required to help make a diagnosis as well as plan treatment.
- A **bone marrow biopsy** removes blood from the bone marrow as well as a core bone sample to evaluate your marrow for disease.
- From the bone marrow bone biopsy and blood sample, very complex and technical tests are completed **in order to identify and learn more about the type of bone marrow failure disease you have**
- **Molecular testing** is identifying abnormal genes. Genes tested include TET2, DNMT3A, CEBPA, IDH1, IDH2, TP53, KRAS, and NRAS which helps **us classify what type of bone marrow failure disease and answer questions on prognosis.**

Test name
Medical History and Physical Exam
CBC with differential (blood counts)
Other Critical Blood testing
Bone marrow biopsy and aspirate (Key)
Flow Cytometry
Cytogenetics with karyotype and FISH
Molecular testing
HLA typing for bone marrow transplant
Imaging scans
Echocardiogram or MUGA

What is Aplastic Anemia

- Rare and serious condition where the bone marrow fails to make enough blood cells (red blood cells, platelets, and white blood cells)
- Can be acquired (develop any time in life) or hereditary



Rovó, A., Tichelli, A. & Dufour, C. Diagnosis of acquired aplastic anemia. *Bone Marrow Transplant* **48,** 162–167 (2013). https://doi.org/10.1038/bmt.2012.230

Classification of Aplastic Anemia by Severity

- Severe Aplastic Anemia
  - Bone marrow cellularity less than 30%
  - Decrease of at **least two** of the following three cell lines (the 3 cell lines are: red blood cells, white blood cells, and platelets)
    - **Absolute neutrophil count** less than 0.5 X 10^9/L
    - **Platelet count** less than 20 X 10^9/L
    - **Transfusion dependence** with absolute reticulocyte count less than 60 X 10^9/L

Classification of Aplastic Anemia by Severity

- **Severe Aplastic Anemia**
  - Bone marrow cellularity less than 30%
  - Decrease of at **least two** of the following three cell lines
    - **Absolute neutrophil count less than 0.5 X 109/L**
    - **Platelet count less than 20 X 109/L**
    - **Transfusion dependence with absolute reticulocyte count less than 60 X 10^9/L**
- **Moderate Aplastic Anemia**
  - Decreased Bone marrow cellularity
  - Decrease of at least two of the following three cell lines but does not meet the criteria for severe aplastic anemia

Classification of Aplastic Anemia by Severity

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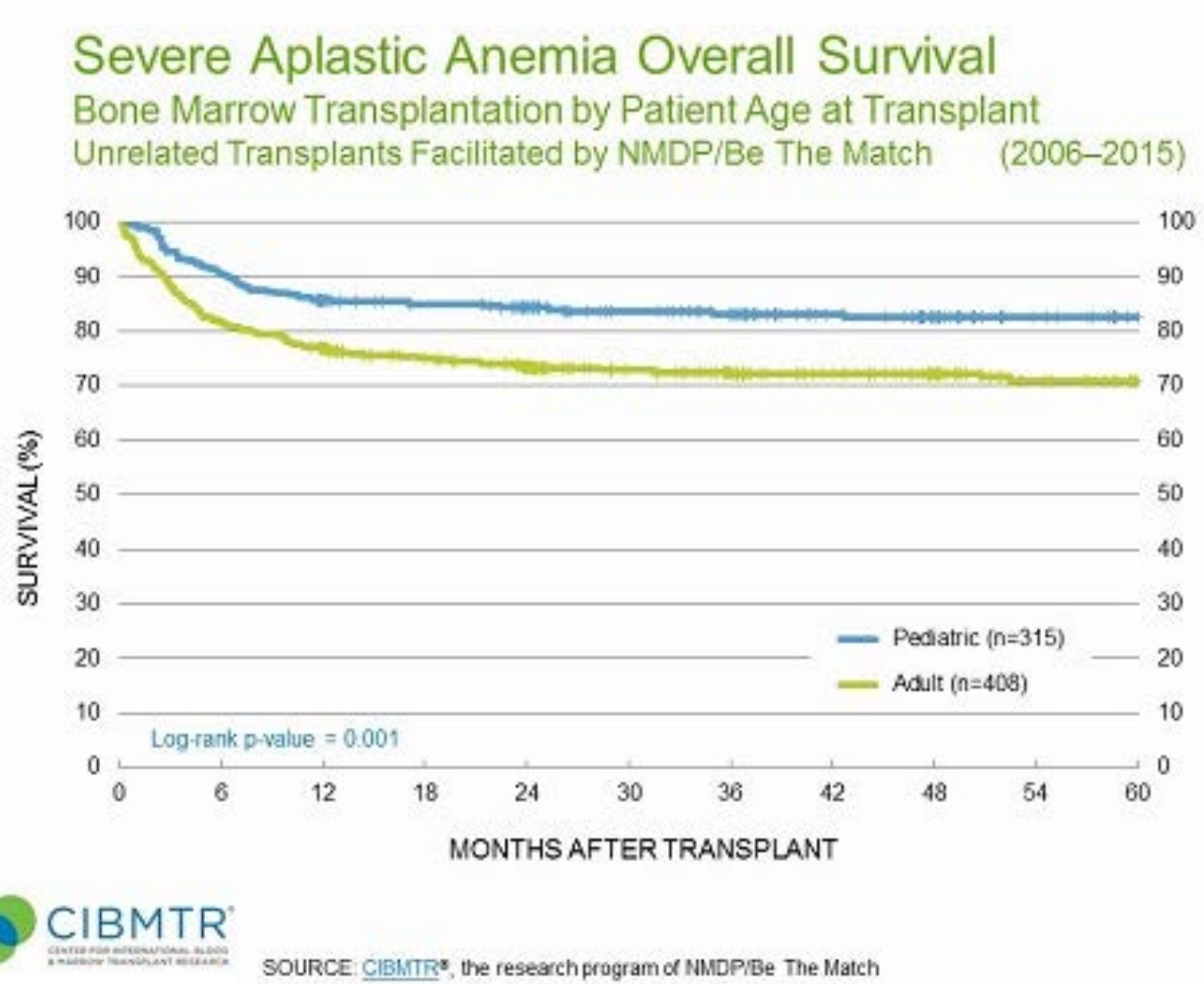
- **Moderate Aplastic Anemia**
  - Decreased Bone marrow cellularity
  - Decrease of at least two of the following three cell lines but does not meet the criteria for severe aplastic anemia
- **Very Severe Aplastic Anemia**
  - Patients who fulfill criteria for severe aplastic anemia but have an **absolute neutrophil count less than 0.2 X 10^9/L**

Prognosis with Aplastic Anemia



With standard treatments 8 out of 10 patients with aplastic anemia get better. Chance for recovery depends on many factors including how severe your disease and how you respond to treatment.

What is Myelodysplastic Syndrome (AKA MDS)

- MDS is a group of malignant bone marrow stem cell cancers
  - Atypical appearing cells (cytologic dysplasia)
  - Impaired maturation (ineffective hematopoiesis)
  - Low blood counts (cytopenias)
- MDS is a cancer
- Increased risk of progression to acute myeloid leukemia (AML), an aggressive blood cancer

What is Myelodysplastic Syndrome (MDS)

- MDS uncommon before age 50, risk increases as a person gets older
- Most commonly diagnosed in people in their 70s
- There are several types of MDS
- Characterized by bone marrow that cannot produce blood cells effectively and many of the blood cells formed are abnormal and defective
- Bone marrow fails to produce healthy cells

2016 WHO Classification

Classification	Dysplastic Lineages	Cytopenias	Ring Sideroblasts	BM and PB Blasts	Karyotype
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS) MDS-RS with single lineage dysplasia (MDS-RS-SLD) MDS-RS with multilineage dysplasia (MDS-RS-MLD)	1 2 or 3	1 or 2 1-3	≥15%/≥5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM<5%, PB<1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del (7q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%*	BM<5%, PB<1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with excess blasts (MDS-EB) MDS-EB-1 MDS-EB-2	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U) With 1% blood blasts	1-3	1-3	None or any	BM<5%, PB=1%, no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM<5%, PB<1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1-3	<15%	BM<5%, PB<1%, no Auer rods	MDS-defining abnormality

*If SF3B1 mutation is present.

International Prognostic Scoring System (IPSS)

Your MDS Prognostic Score is calculated from:

- Your blood counts at time your MDS is diagnosed
- Number of abnormal immature cells or blasts in the bone marrow at diagnosis
- Chromosome results from your bone marrow at diagnosis

	0	0.5	1.0	1.5	2
BM blasts (%)	<5	5-10	--	11-20	21-30
Karyotype*/ Cytogenetics	Good	Intermediate	Poor		
Cytopenias (number abnormal blood counts)	0/1	2/3			

*Good Karyotype/Cytogenetics: normal, -y, del(5q), del(20q)
*Poor Karyotype/Cytogenetics: complex (more than 3 abnormalities) or chromosome 7 is abnormal
*Intermediate: all others Karyotype/cytogenetic abnormalities

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

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*Intermediate: all others Karyotype/cytogenetic abnormalities

	Median Survival (yrs)
Low (0)	5.7
Int-1 (0.5-1)	3.5
Int-2 (1.5-2)	1.2
High (≥ 2.5)	0.4

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

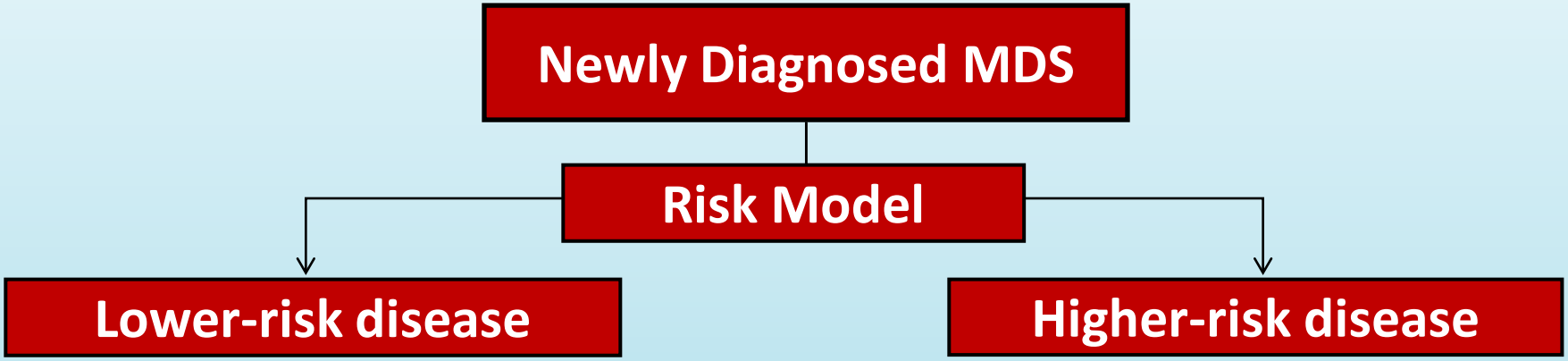
Revised IPSS

Prognostic Subgroup	Cytogenetic Abnormality	Median Survival, y
Very Good	-Y, del(11q)	5.4
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7
Poor	-7, inv(3)/t(3q)/del(3q), double including-7/ del(7q), complex: 3 abnormalities	1.5
Very Poor	Complex: > 3 abnormalities	0.7

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	--	Good	--	Int	Poor	Very Poor
BM blast, %	≤ 2	--	>2 - <5	--	5 - 10	>10	--
Hemoglobin, g/dL	≥ 10	--	8 - <10	< 8	--	--	--
Platelets, K/μL	≥ 100	50 - <100	< 50	--	--	--	--
ANC, K/μL	≥ 0.8	< 0.8	--	--	--	--	--

Greenberg P. Blood 2012;120: 2454-2465

Risk Assessment



Treatment Goal:

- Decrease the number of blood transfusions to less often or none at all
- Improve symptoms
- Improve quality of life

Treatment Goal:

- Alter natural history of disease
- Prevent progression to AML
- Improve overall survival

Revised IPSS: The Hard Numbers

Category	Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Less Aggressive Disease

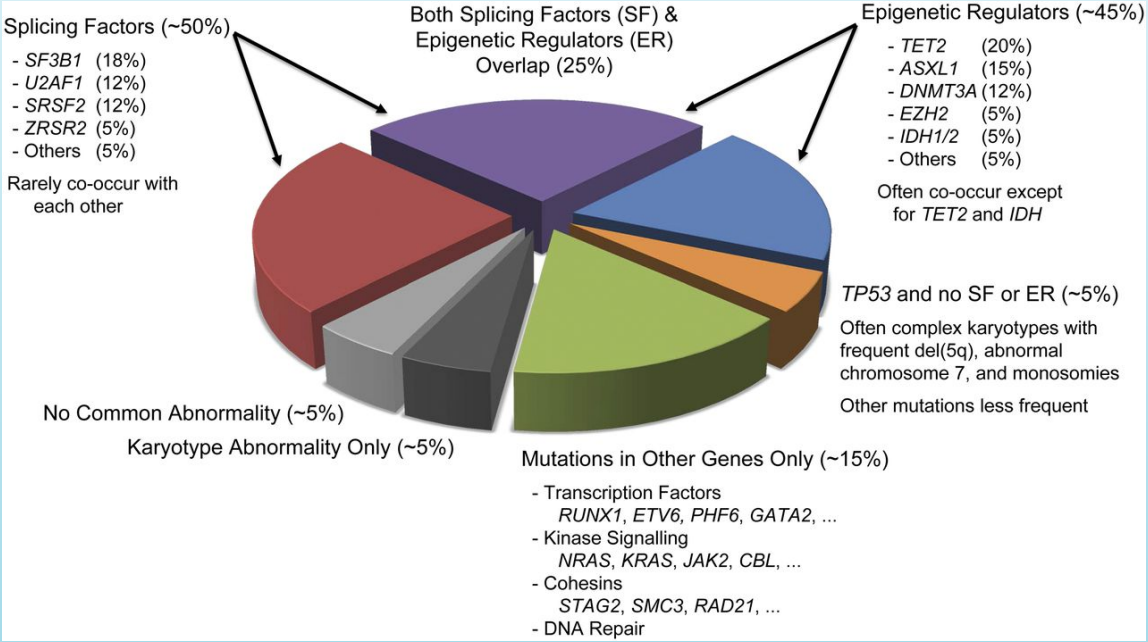
Very Aggressive Disease

	Survival, y	HR for OS
Very low	8.8	0.5
Low	5.3	1.0
Intermediate	3.0	2.0
High	1.6	3.2
Very High	0.8	8.0

Greenberg P. Blood 2012;120: 2454-2465

Mutations in MDS

- >90% of patients with MDS have at least 1 mutation or abnormal gene



- Some mutations are associated with more aggressive disease: TP53, RUNX1, ASXL1, etc.

Bejar R and Steensma D, Blood 2014

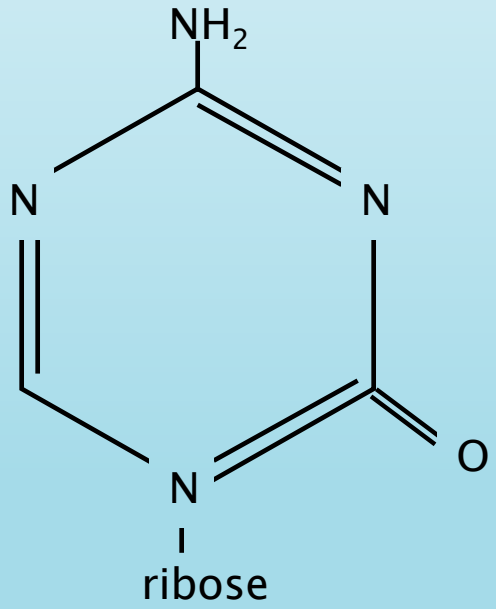
How Prognosis Influences Treatment in MDS

- **Lower Risk Disease**
  - Observation
  - Growth Factors
  - Immunosuppressive Therapy
  - Lenalidomide
  - Hypomethylating Agents
- **Higher Risk Disease**
  - Hypomethylating Agents: **Azacitidine** (Vidaza®) and **Decitabine** (Dacogen®)
  - Intensive Chemotherapy
- Bone Marrow Transplantation

Hypomethylating Agents

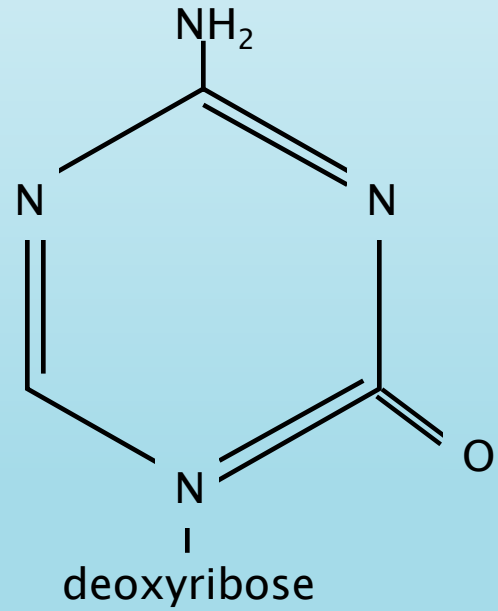
5-Azacitidine

(Vidaza®)

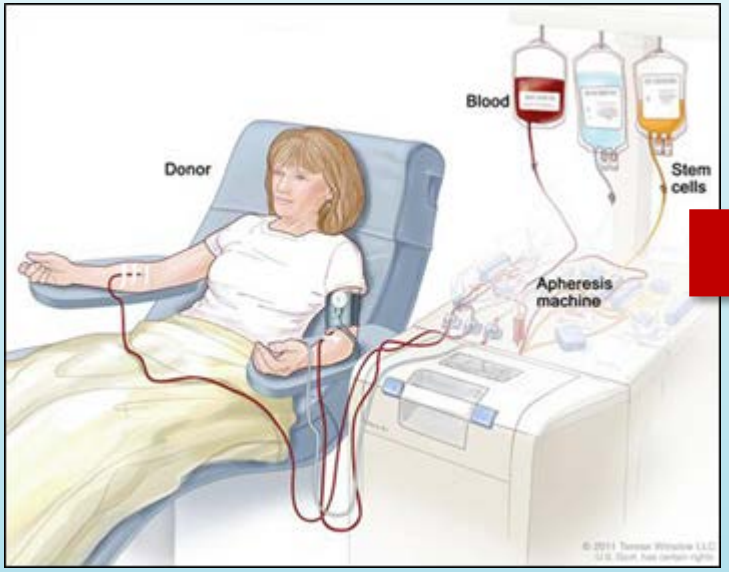


Decitabine

(Dacogen®)



Bone Marrow or Stem Cell Transplantation



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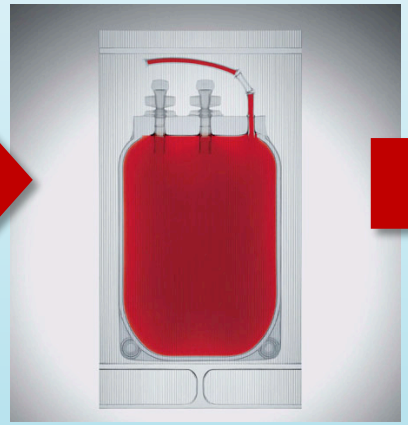
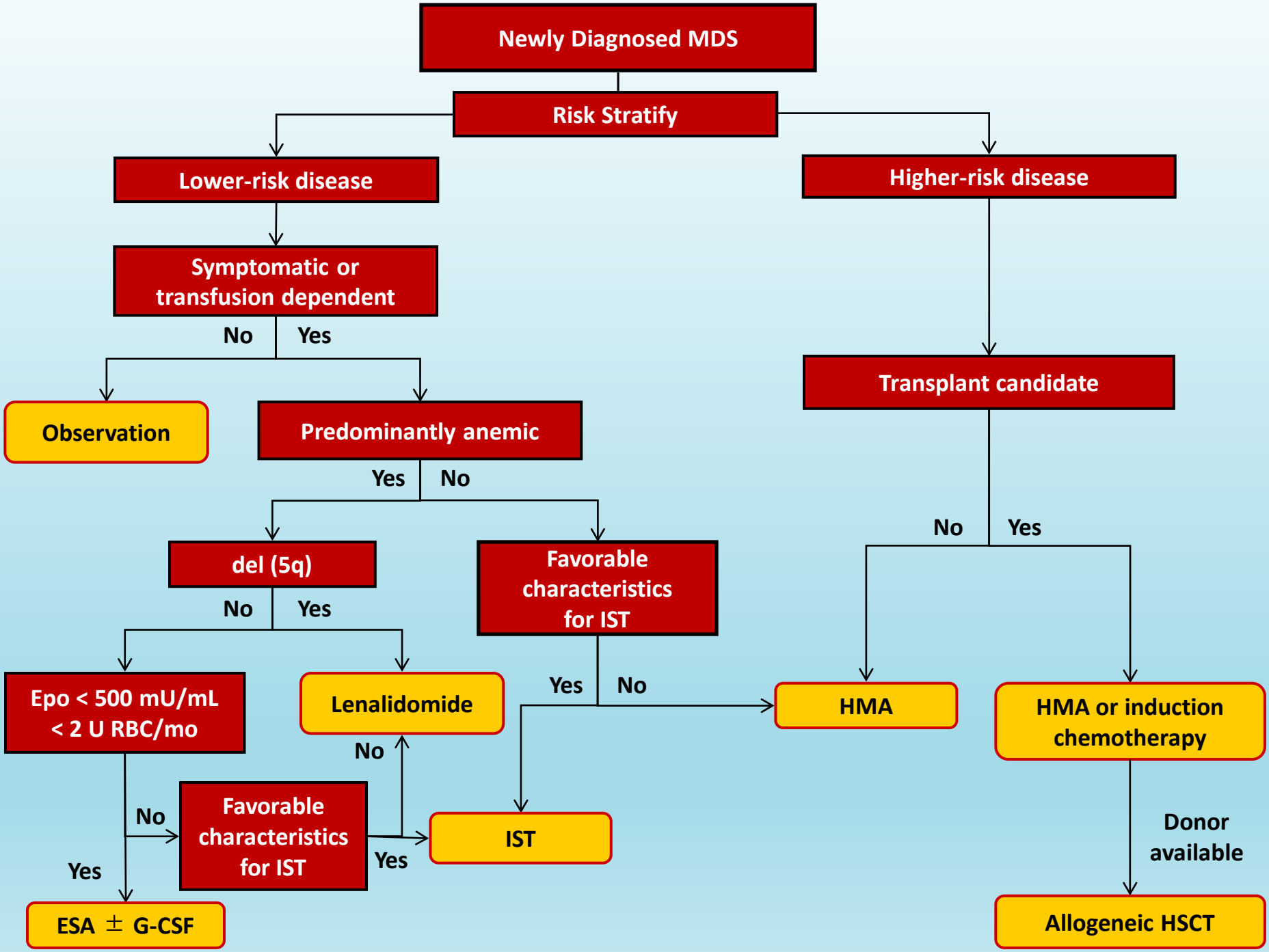


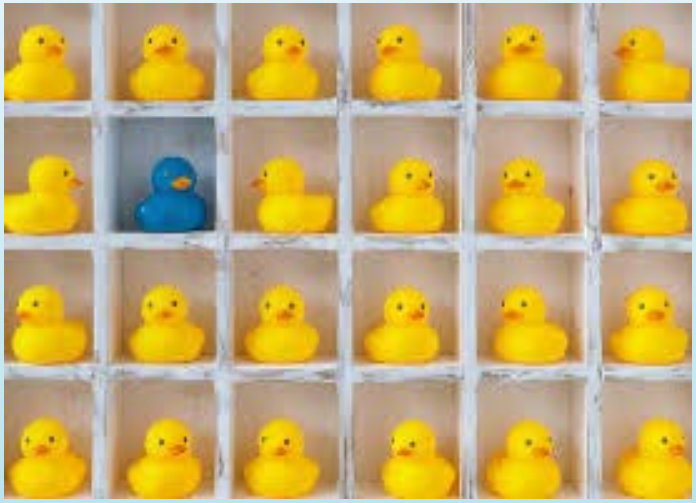
- The ONLY potential cure for MDS
- Very intensive, toxic therapy

https://www.cancer.gov/publications/dictionaries/


Newly Diagnosed MDS
Risk Stratify
Lower-risk disease
Higher-risk disease
Symptomatic or transfusion dependent
No
Yes
Observation
Predominantly anemic
Transplant candidate
Yes
No
del (5q)
Favorable characteristics for IST
No
Yes
Epo < 500 mU/mL < 2 U RBC/mo
Lenalidomide
Yes
No
HMA
HMA or induction chemotherapy
No
Favorable characteristics for IST
IST
Yes
Yes
ESA ± G-CSF
Donor available
Allogeneic HSCT

Prognosis Can Be Difficult to Make

- Each person is unique



- Each person's disease is unique and different
- How a disease progresses over time is unpredictable
- We have less information on rare diseases compared to more common cancers

https://lookeducation.com.au/marketing-your-unique-school/

Making Treatment Decisions

- This is a Team Sport. Treatment decisions are made with you, your family, and your physician all working together.
- Bring a Buddy to doctor visits
  - Consider designating a medical Power of Attorney before starting treatment

- ❖ Please ask questions!
- Compare benefits and downsides of each treatment option
- Do not be afraid to say “No” or “Stop”
- Do careful research: **www.aamds.org**
  NCCN Guidelines for patients at http://www.nccn.org and choose Patient Resources and then NCCN Guidelines for Patients

Image Courtesy
brucedwatson.wordpress.com

Please Ask Questions!

- Bring a Buddy to doctor visits
- Take Notes
- Ask for copies of labs and important test results including your bone marrow biopsy reports, cytogenetic results, and molecular results
- ***Ask questions…Always ask questions***
- Know what medications you are taking and will take in the future
  - **Bring a list**

Artist: Ron Morgan

Please Ask Questions!

- Ask your doctor to write out a treatment plan and make sure to update your other physicians and specialists from other medical fields
- Make sure you know what to do in case of emergencies!
- Always ask for a ***contact phone number*** in case of any problems, new symptoms, or if you have any questions

Artist: Ron Morgan

Summary/Conclusions

- Bone marrow failure diseases are a complex set of diseases that requires accurate diagnosis.
- Patient outcomes vary widely and treatment is tailored by risk scores.
- For patients with lower-risk disease, the goals of care are to improve number of times a patient needs a blood transfusion and improve quality of life/symptoms.
- The standard of care for higher-risk patients is therapy that can include chemotherapy with or without allogeneic stem cell transplantation.
- A variety of new agents are being evaluated in clinical trials for patients with bone marrow failure

Thank You! Any Questions?

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