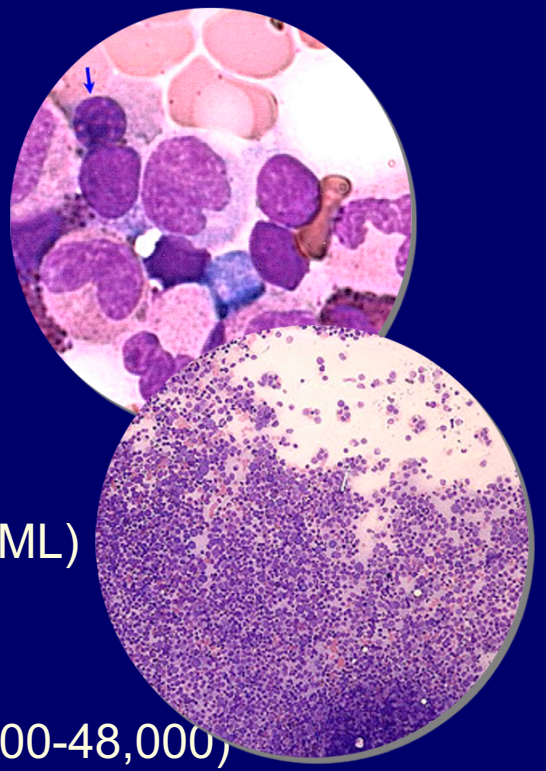
WHAT IS MDS?

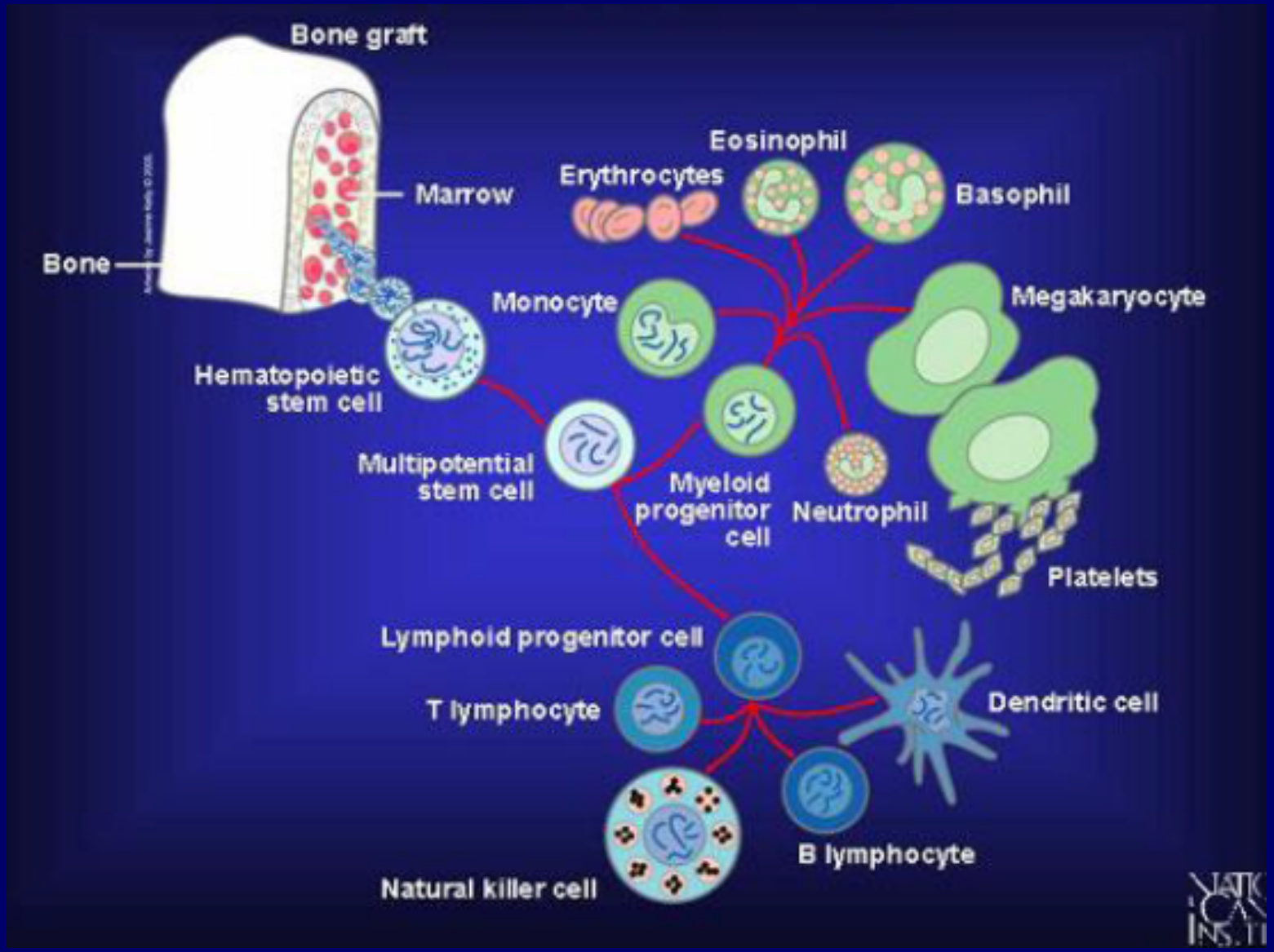
Myelodysplastic Syndromes

- A group of blood disorders characterized by[1]
  - Bone marrow malfunction related to decreased production of red cells, white cells and platelets
  - The bone marrow cells don't look normal under a microscope. They look "Dysplastic"
  - Tendency to progress to acute myelid leukemia (AML)
- Overall incidence 3.7-4.8/100,000[2]
  - ≈ 10,000/yr in United States (true estimates ≈ 37,000-48,000)
  - Median age: 70 yrs; incidence: 34-47/100,000 > 75 yrs[3]



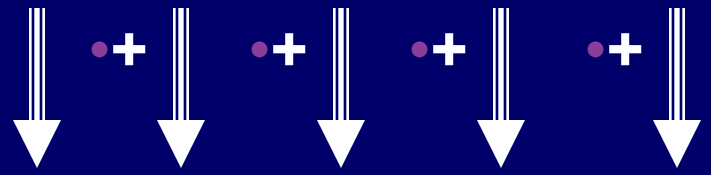
1. Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, editors. Clinical oncology. New York NY: Churchill Livingstone; 2004. pp. 2849-2881. 2. SEER data 2000-2009. 3. SEER 18 Data. 2000-2009.

Bone marrow stem cells give rise to various blood cells

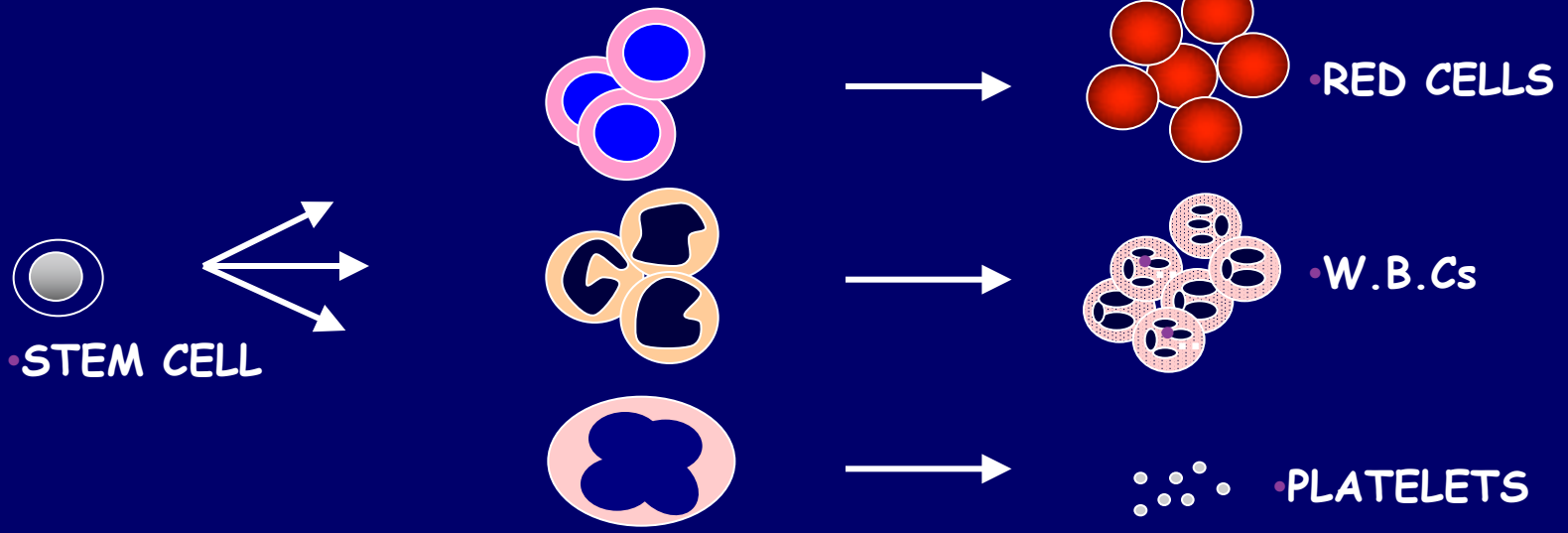


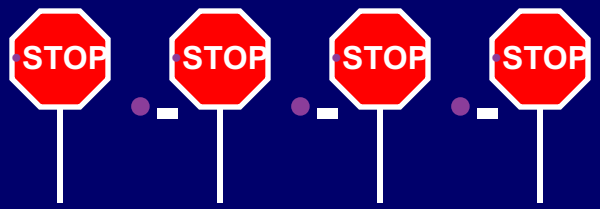
•STIMULATORY GROWTH FACTORS

•Erythropoietin (EPO), GCSF, GMCSF, TPO, IL-3, SCF



•*HEMATOPOIESIS*

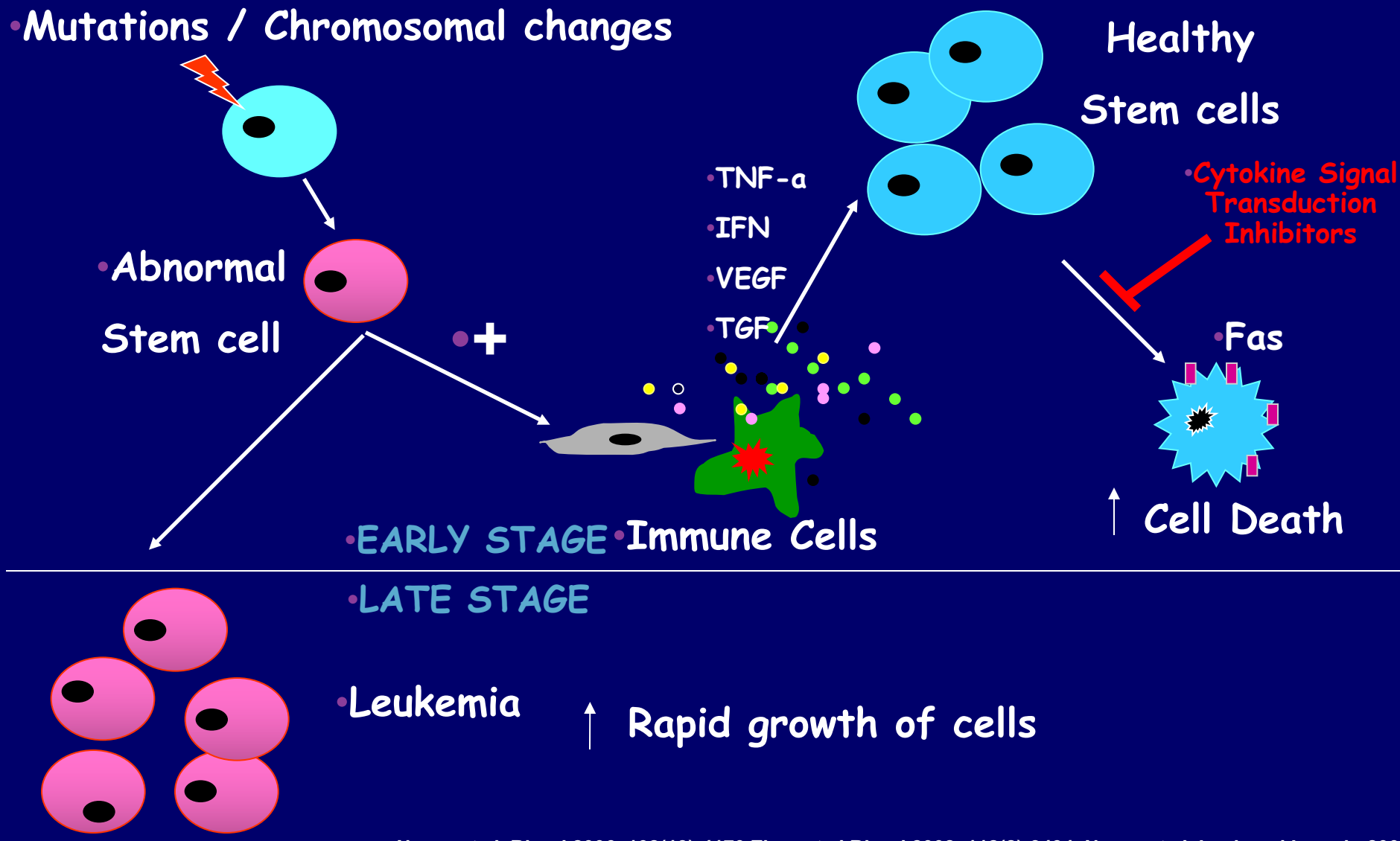




•INHIBITORY CYTOKINES

•TNF, TGF, IL-6, IL-1, Interferons

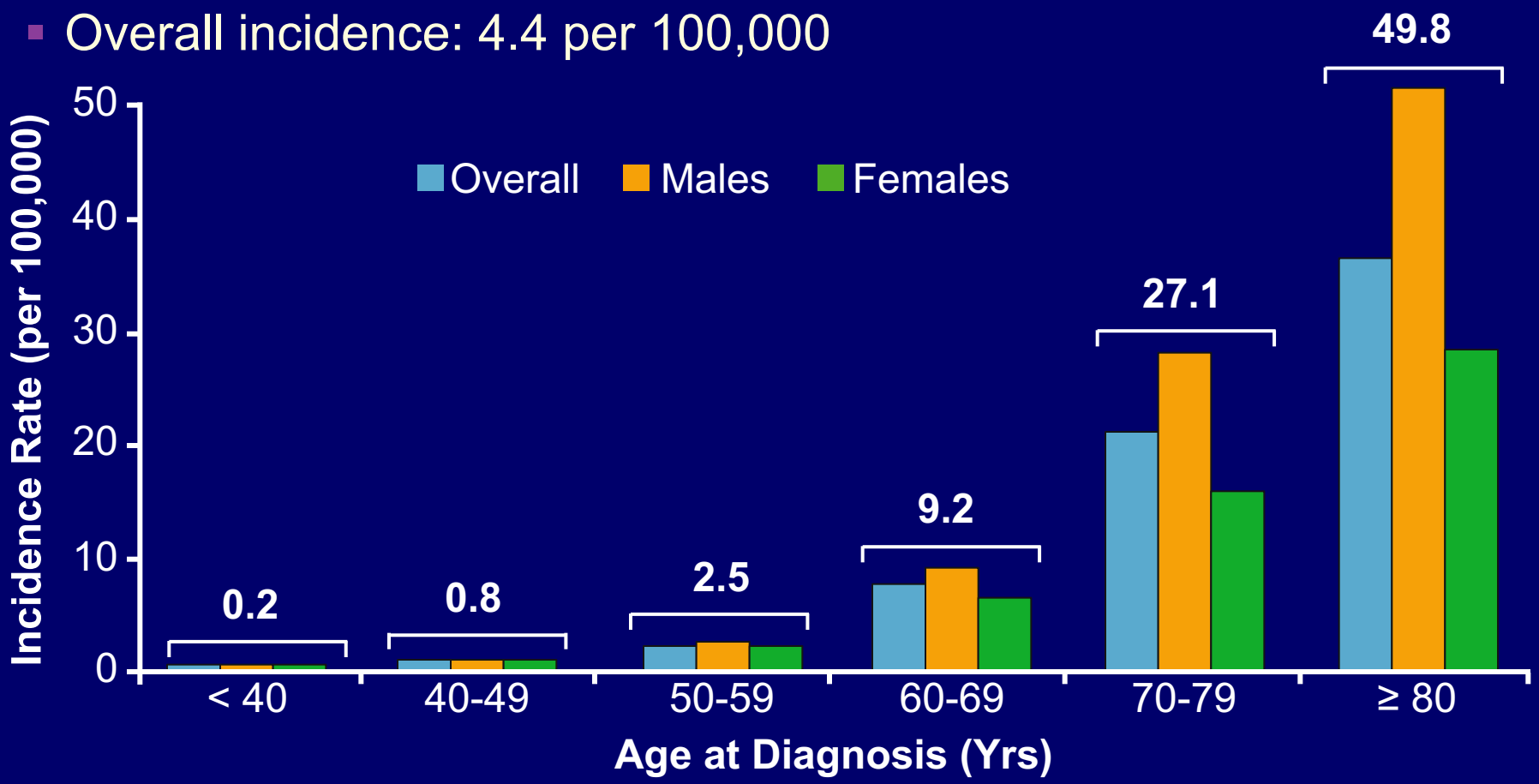
How does MDS happen?



•Navas et al, Blood 2006, 108(13):4170 Zhou et al Blood 2008, 112(8):3434, Navas et al, Leuk and Lymph, 200

MDS occurs with increasing age

- Overall incidence: 4.4 per 100,000



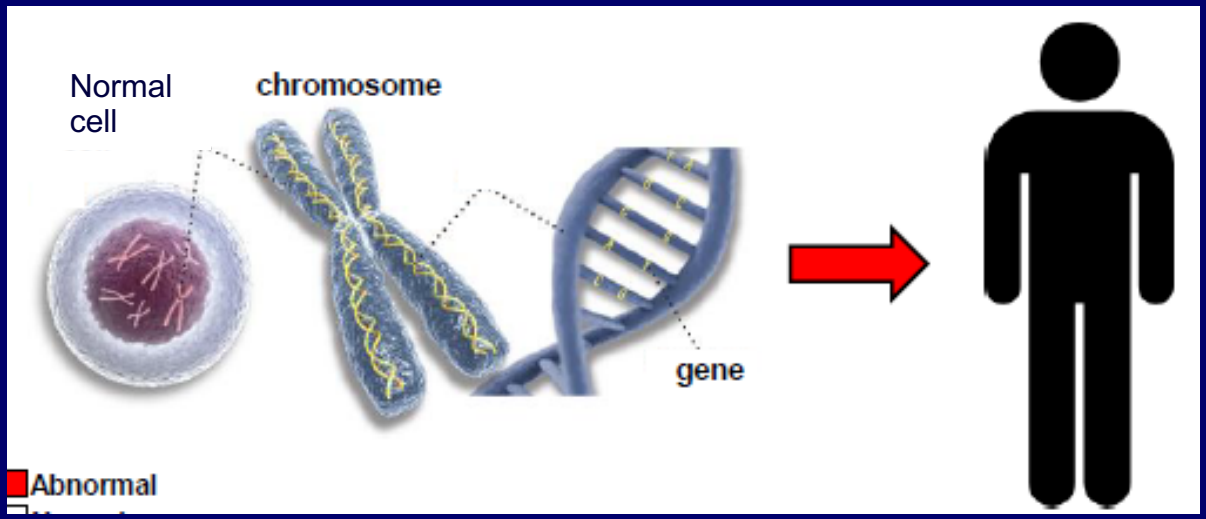
SEER Cancer Statistics Review 1975-2008. Section 30, myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMD), and chronic myelomonocytic leukemia (CMML).

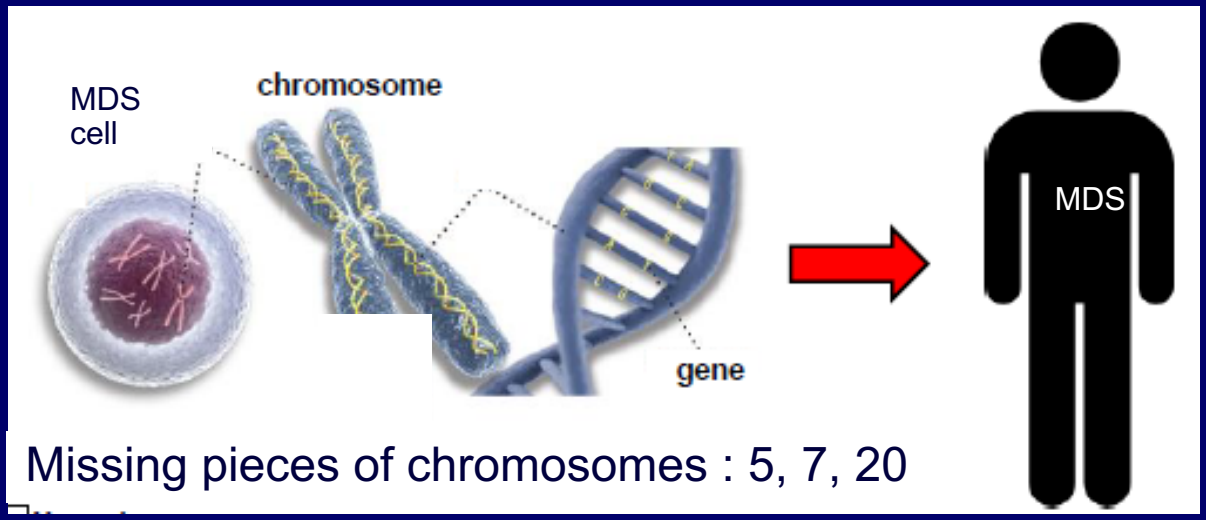
How is MDS Diagnosed?

- Most patients have low blood counts
- Low red blood cells-Anemia- Fatigue
- Low white cells- infections
- Low Platelets- Bleeding, Bruising
- Diagnosis requires
  - Peripheral blood examination
  - Bone marrow aspirate and biopsy
  - Genetic and Cytogenetic studies

Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, editors. Clinical oncology. New York, NY: Churchill Livingstone; 2004. pp. 2849-2881.

Chromosomal changes are seen in MDS





Missing pieces of chromosomes : 5, 7, 20

Mutations in genes are found in MDS

Gene mutations : p53, IDH, TET, ASXL, RAS and others

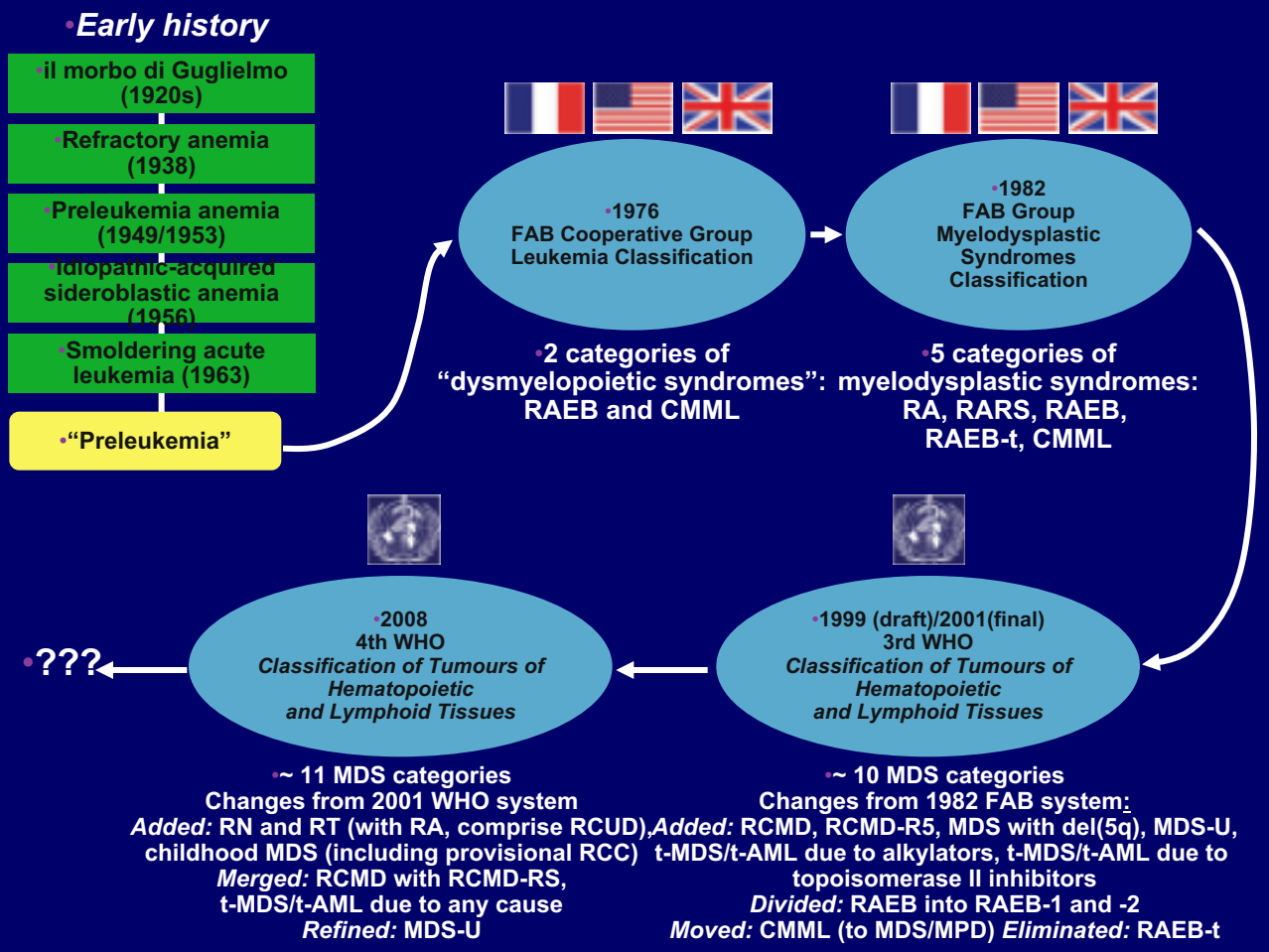
Tested from blood samples

Paid by insurance

Can predict risk

Mutations can be targeted by drugs: IDH and Flt3

Evolution of Classification of MDS



•Steensma DP. Hematology AM Soc Hematol Educ Program. 2009;645-655.

French American British (FAB) Classification

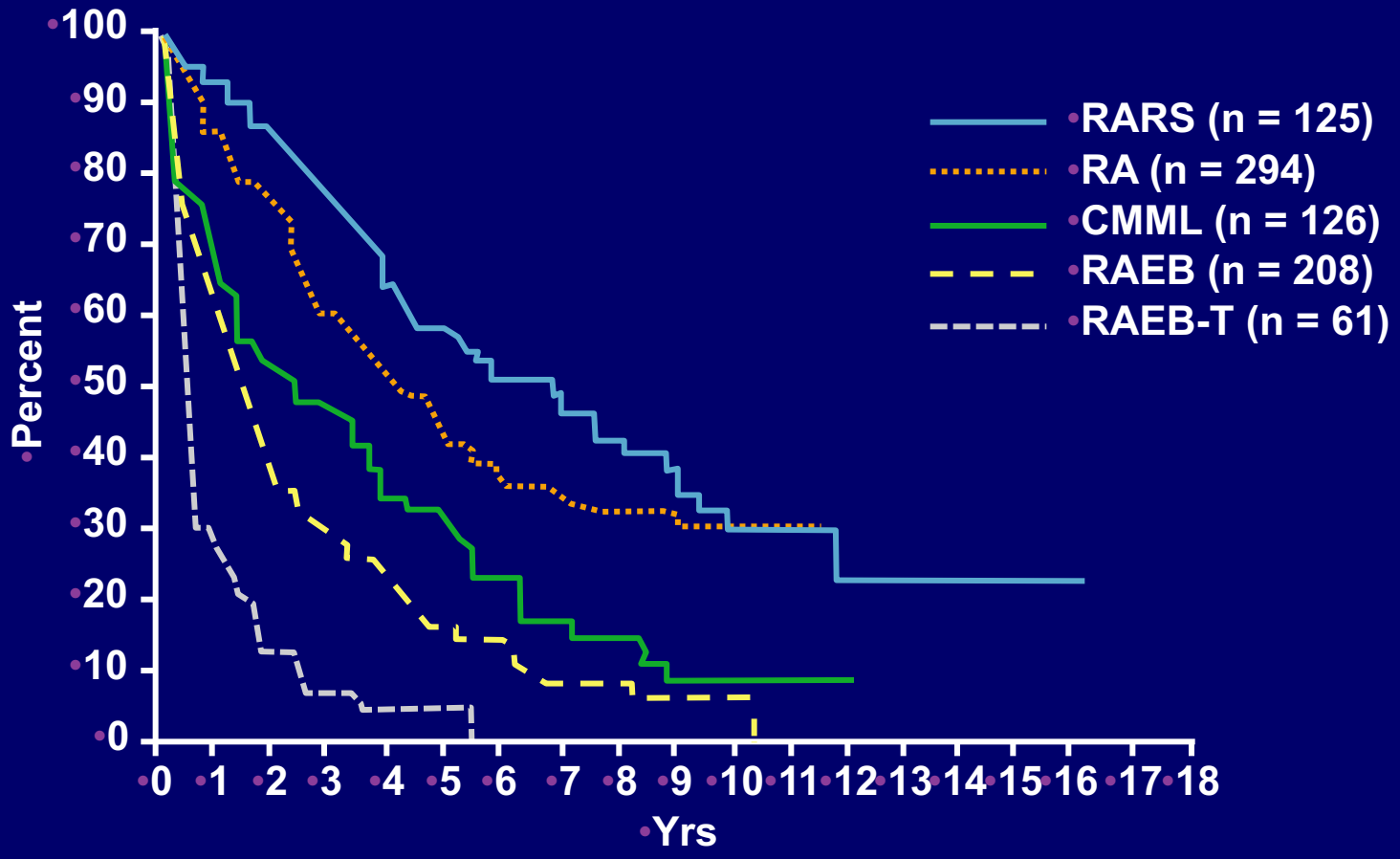
Type	Blasts in BM	Blasts in Blood	Sideroblasts in BM	Monocytes in Blood
RA	< 5%	< 1%	- (< 15%)	< 1 x 10^9/L
RARS	< 5%	< 1%	+ (> 15%)	< 1 x 10^9/L
RAEB	5% to 20%	< 5%	+/-	< 1 x 10^9/L
CMML	5% to 20%	< 5%	-	> 1 x 10^9/L
RAEB-t	21% to 29%	< 5%	+/-	< 1 x 10^9/L
AML	≥ 30%	> 5%	+/-	

Blast Cells are leukemia cells. The percentage of blast cells is higher in higher risk forms of MDS

More than 20% Blasts = Leukemia

•Bennett J, et al. Br J Haematol. 1982;51:189-199.

MDS: Survival Based on FAB Classification



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

Prognosis by WHO Classification

Category	Patients, n (%)	Transformation to AML, %	Median Survival, Mos
RA	107 (8.5)	7.5	69
RARS	138 (11.0)	1.4	69
RCMD	306 (24.0)	10.0	33
RCMD-RS	183 (15.0)	13.0	32
RAEB-I	256 (21.0)	21.0	18
RAEB-II	235 (18.5)	34.5	10
MDS 5q-	28 (2.2)	8.0	116

- Germing U, et al. Leuk Res. 2000;24:983-992.

IPSS Is Most Common Tool for Risk Assessment of MDS

	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%
Chromosomes*	Good	Intermediate	Poor	--	--
No. of Cytopenias†	0/1	2/3	--	--	--

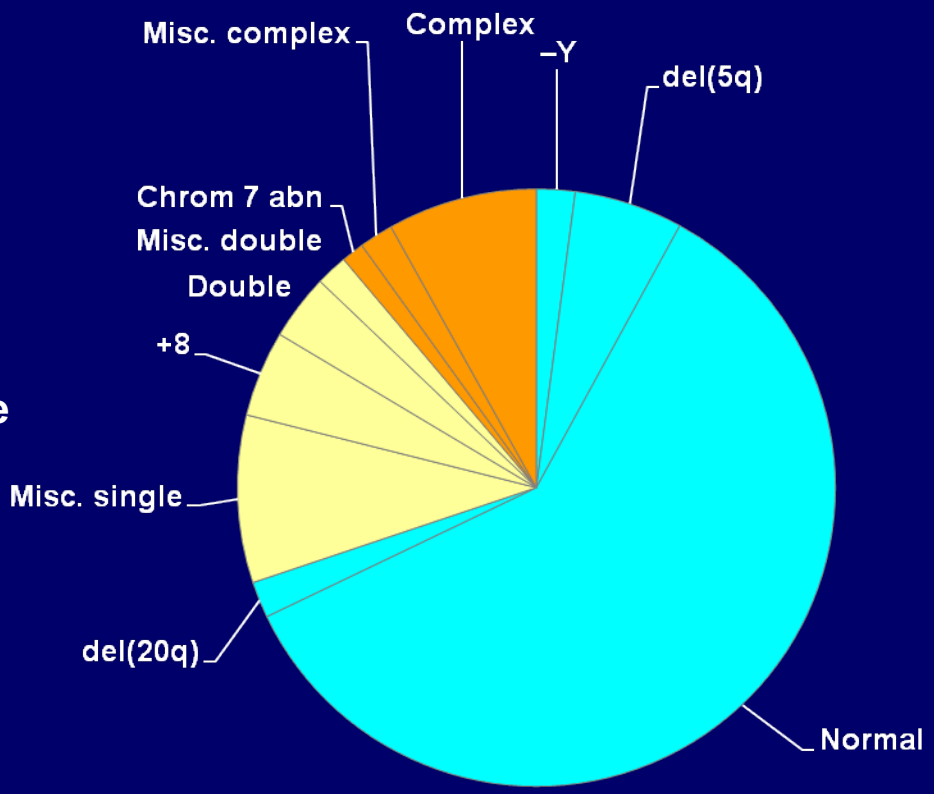
	Total Score					
	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥ 2.5**
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yrs	5.7	3.5		1.2		0.4

*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.

Greenberg P, et al. Blood. 1997;89:2079-2088.

Cytogenetic Abnormalities: IPSS Prognosis

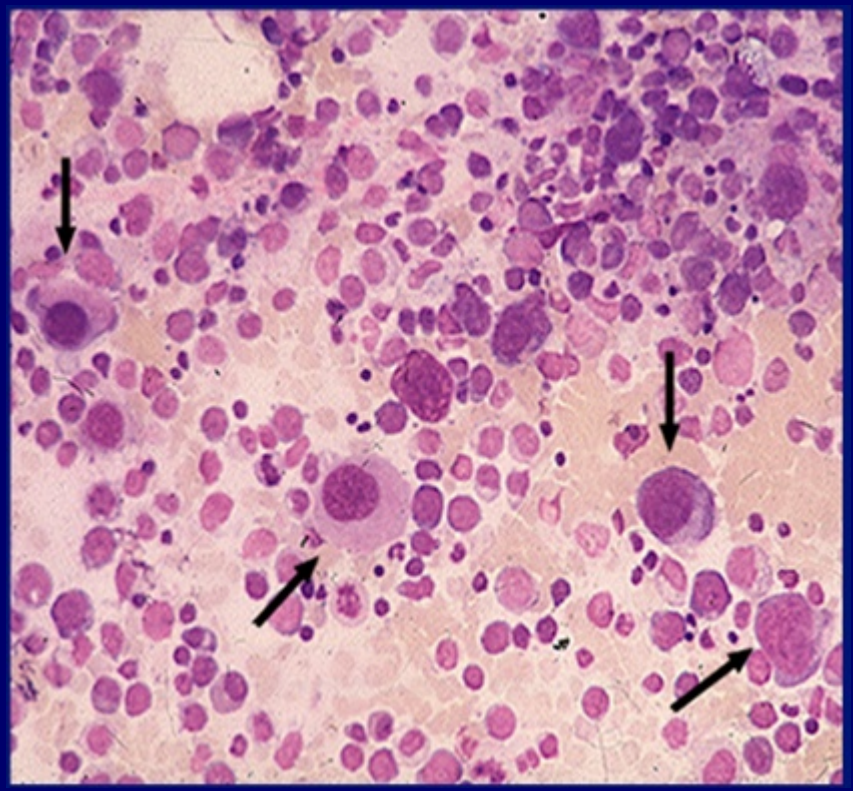
	Patients, n (%)	
-Y	17 (2)	Favorable
Iso del(5q)	48 (6)	
Normal	489 (60)	
Del(20q)	16 (2)	
Misc single	74 (9)	Intermediate
+8	38 (5)	
Double	29 (3)	
Misc double	14 (2)	
Chrom 7 abn	10 (1)	Unfavorable
Misc complex	15 (2)	
Complex	66 (8)	



- Greenberg P, et al. Blood. 1997;89:2079-2088.

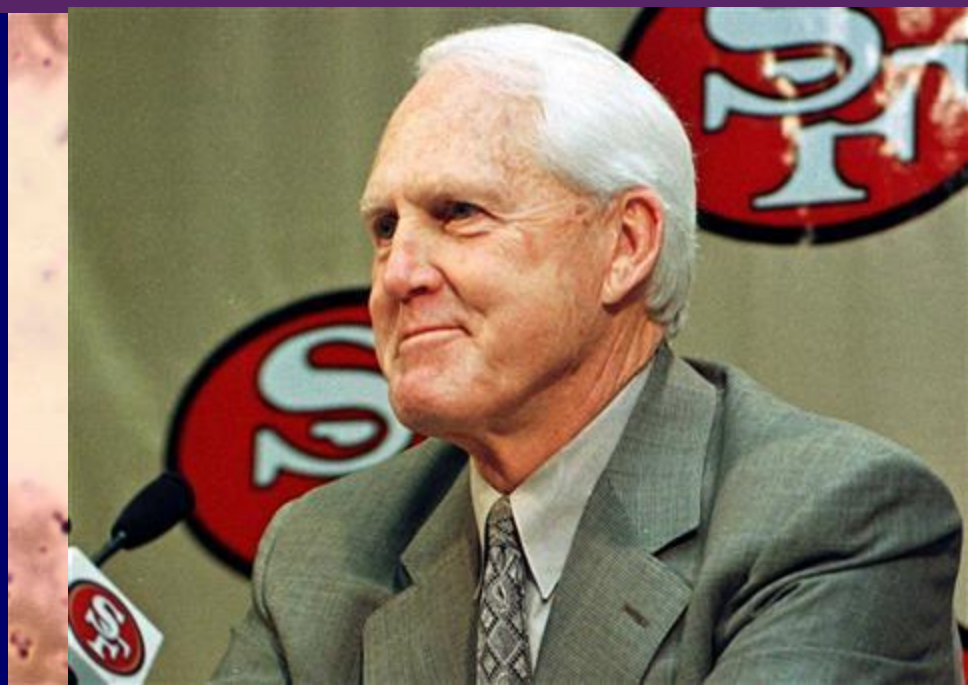
5q- Syndrome: A special type of MDS

- Deletion of chromosome 5
- More Females Affected
- Median age at diagnosis: 68 yrs
- Macrocytic anemia, mild leukopenia, normal or increased platelet count
- Responds to Revlimid
- Indolent course, favorable prognosis
  - AML transformation: 12% to 16%
  - Median survival: > 5 yrs



•Boultwood J, et al. Blood. 1994;84:3253-3260. Mathew P, et al 1993:81:1040-1045.

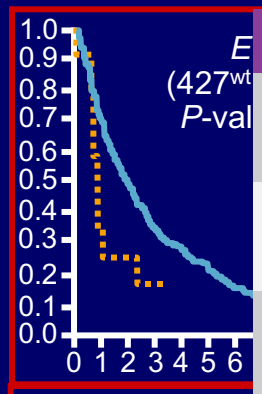
Faces of MDS



Questions?

Thank You!

Gene Point Mutations - Independent Predictors of OS



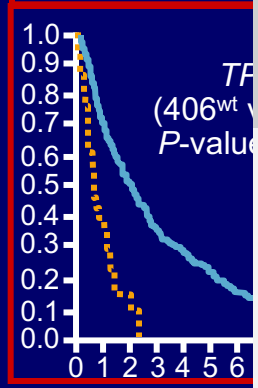
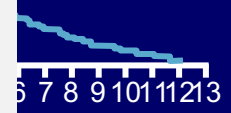


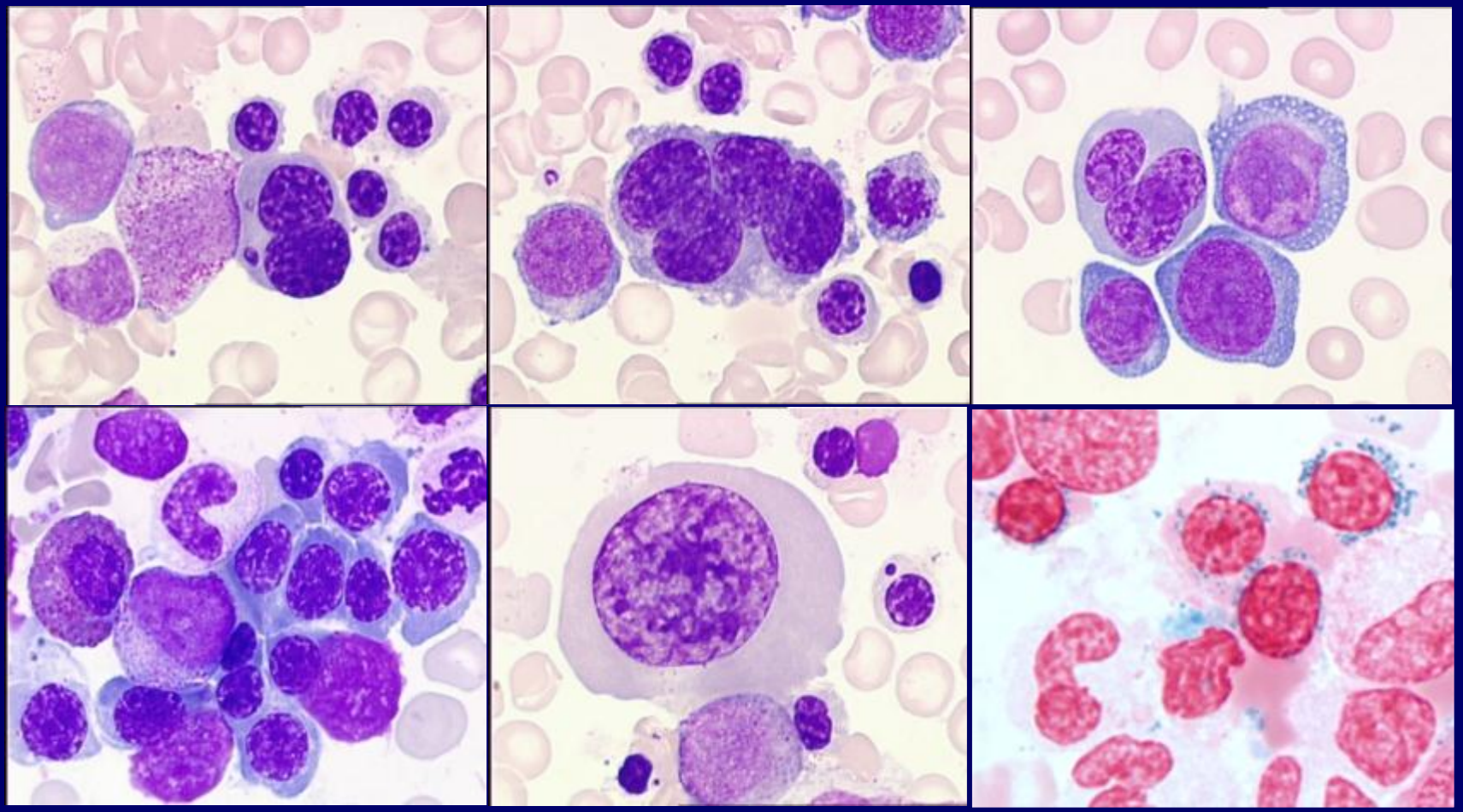
Table 2. Hazard Ratios for Death in a Multivariable Model

Risk Factor	Hazard Ratio (95% CI)	*P* Value
Age 55 yrs or older vs younger than 55 yrs	1.81 (1.20-2.73)	.004
IPSS risk group		
Intermediate 1 vs low	2.29 (1.69-3.11)	< .001
Intermediate 2 vs low	3.45 (2.42-4.91)	< .001
High vs. low	5.85 (3.63-9.40)	< .001
Mutational status		
TP53 mutation present vs absent	2.48 (1.60-3.84)	< .001
EZH2 mutation present vs absent	2.13 (1.36-3.33)	< .001
ETV6 mutation present vs absent	2.04 (1.08-3.86)	.03
RUNX1 mutation present vs absent	1.47 (1.01-2.15)	.047
ASXL1 mutation present vs absent	1.38 (1.00-1.89)	.049



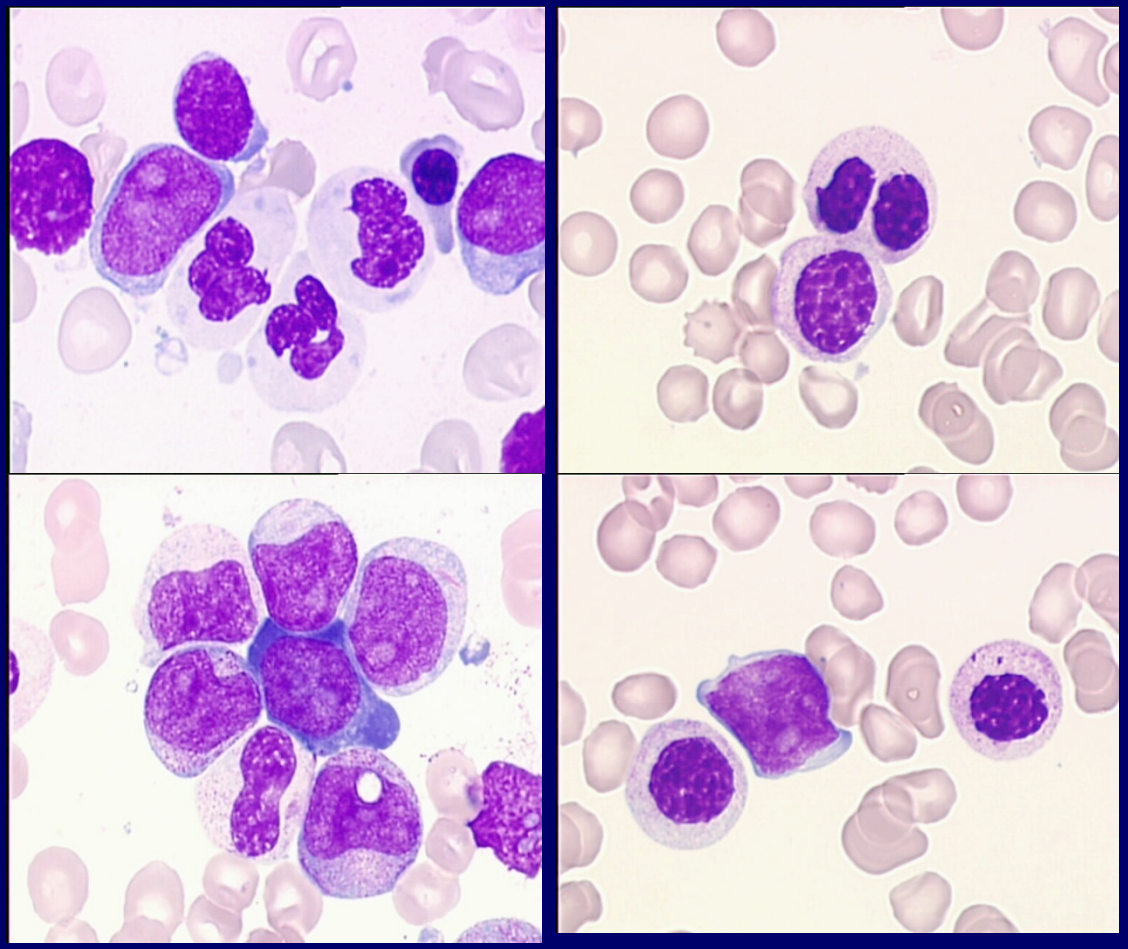
Bejar R, et al. N Engl J Med. 2011;364:2496-2506.

Cytologic Dysplasia: Bone Marrow DysErythropoiesis



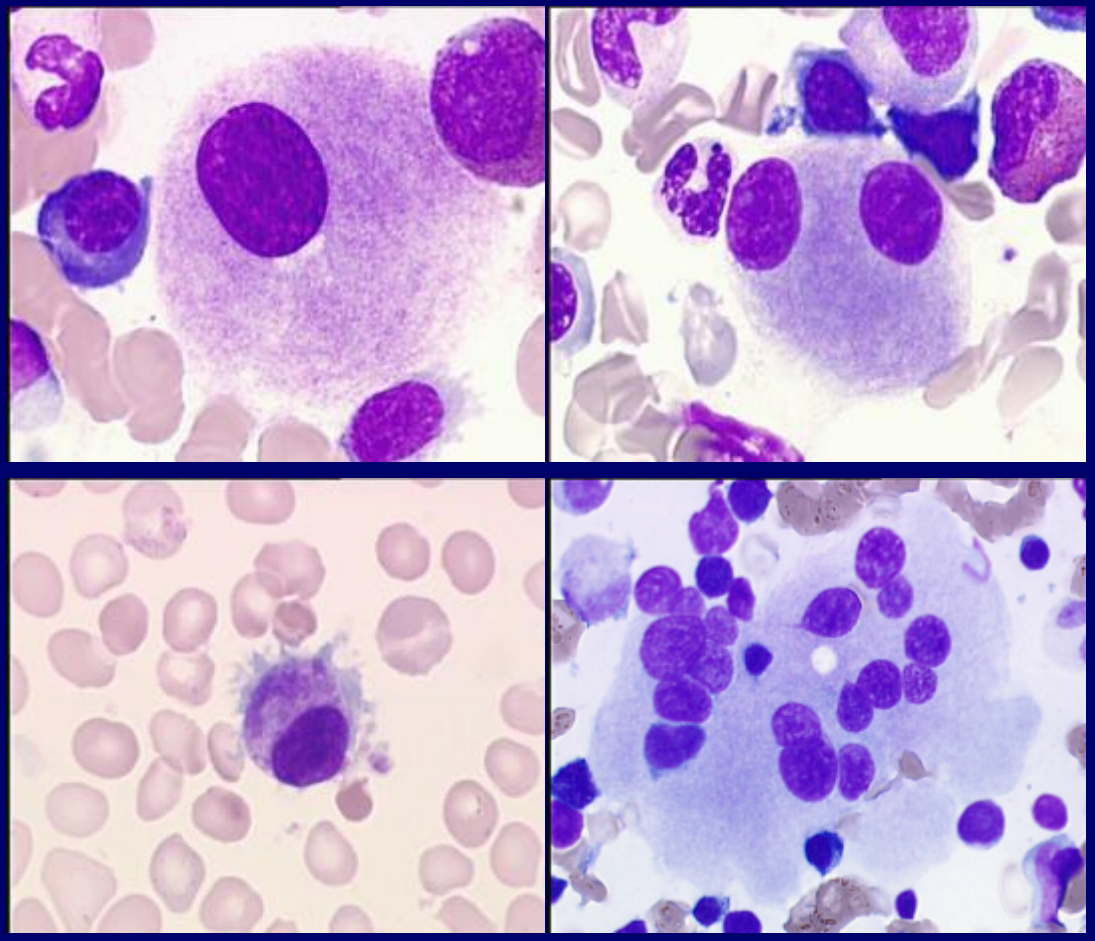
Courtesy of Dr. Bennett and Dr List.

Cytologic Dysplasia: Marrow and Blood DysGranulopoiesis



Courtesy of Dr. Bennett and Dr List.

Cytologic Dysplasia: Marrow and Blood DysMegakaryopoiesis



Courtesy of Dr. Bennett and Dr List.