What is MDS? How Do We Determine Prognosis?

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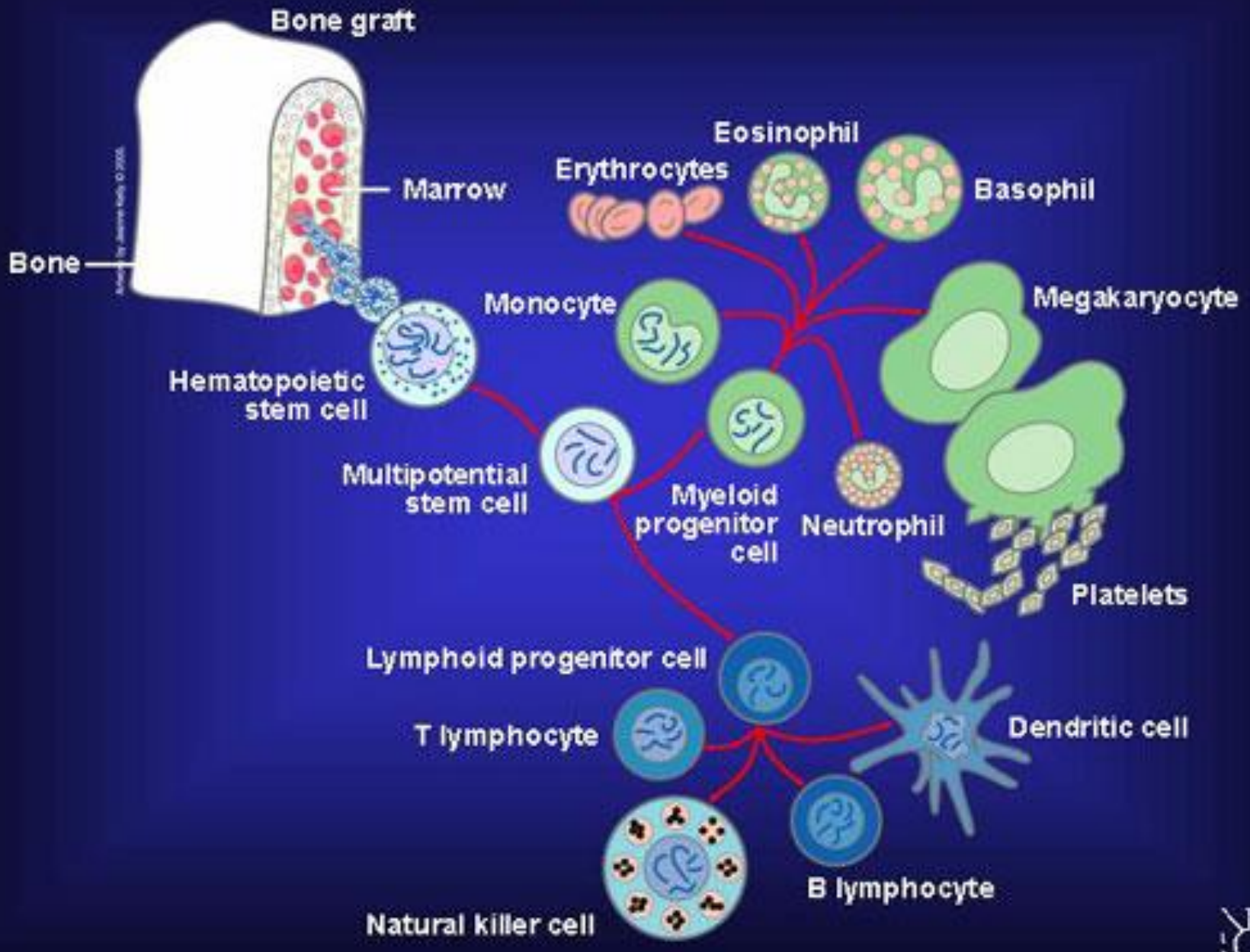
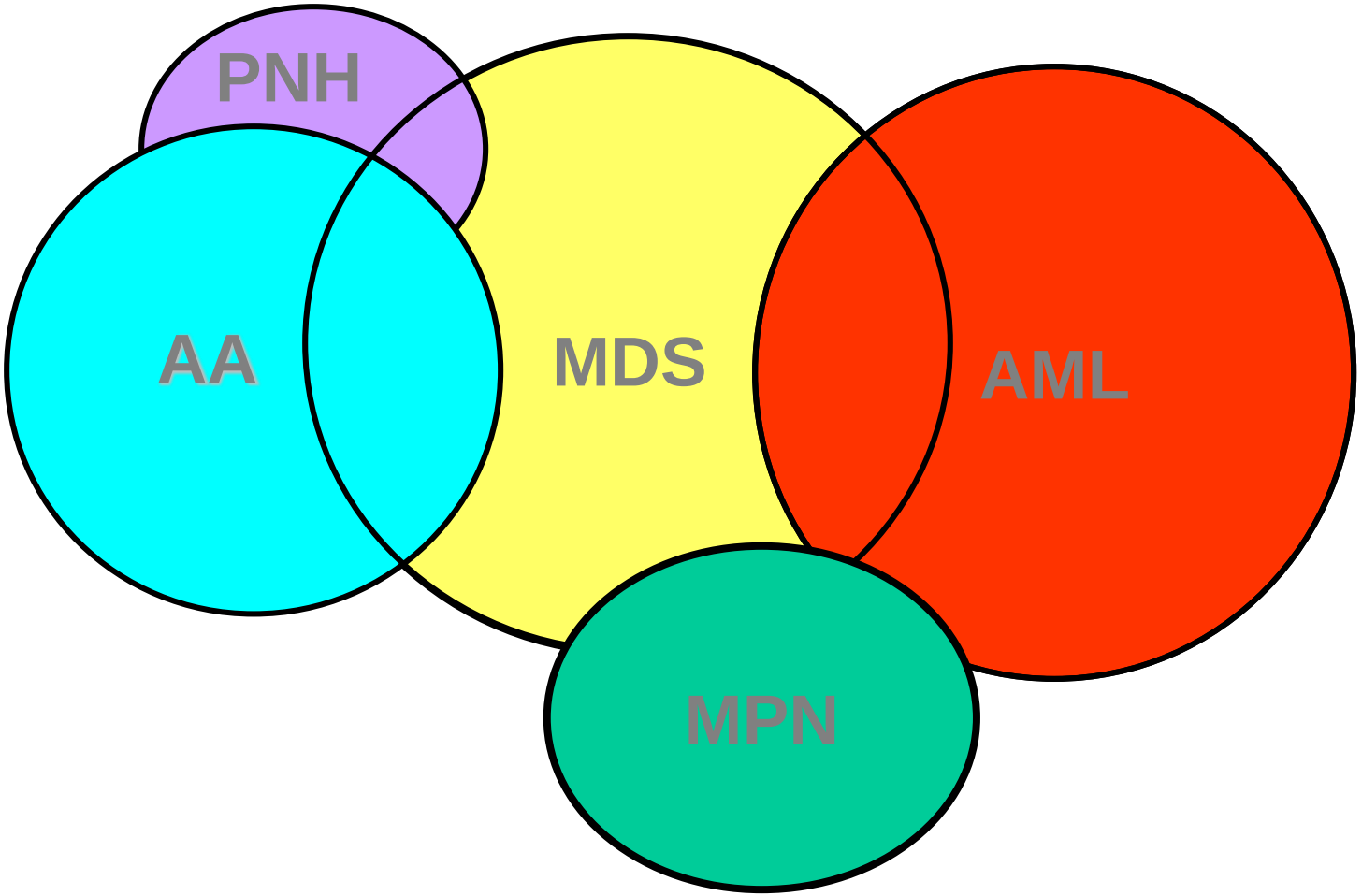
Blood Stem Cells



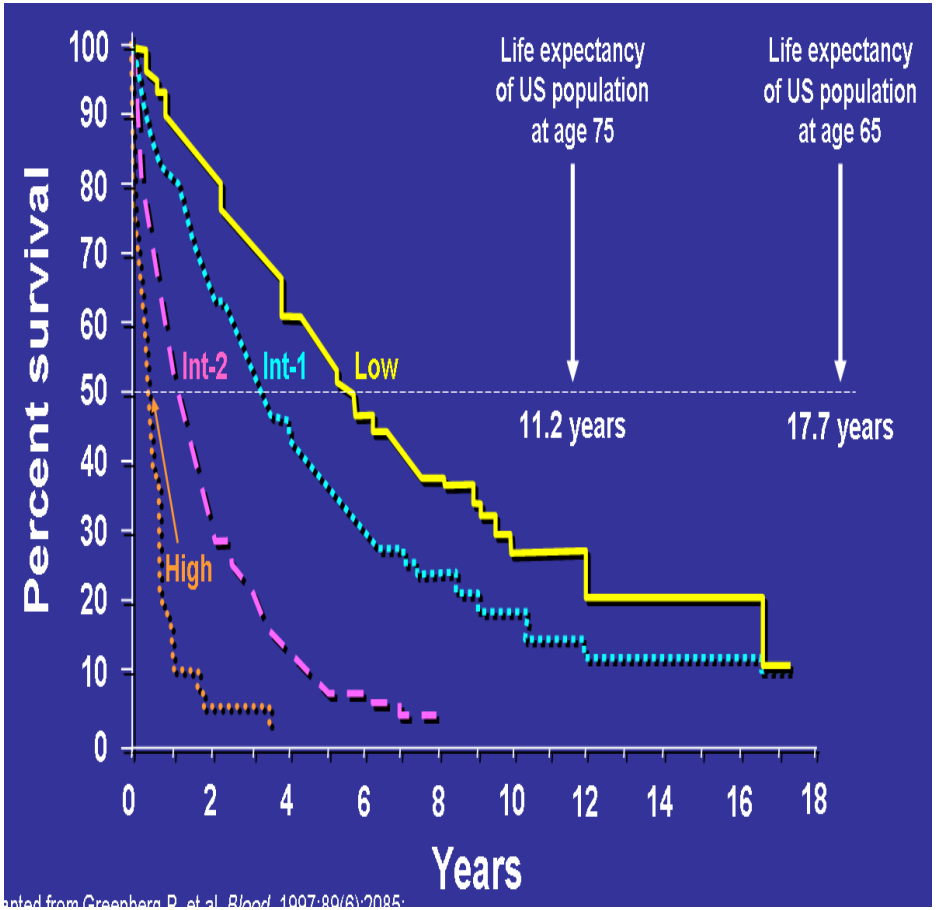
Bone Marrow Failure Syndromes



Young NS. *Ann Intern Med.* 2002 Apr 2;136(7):534-46

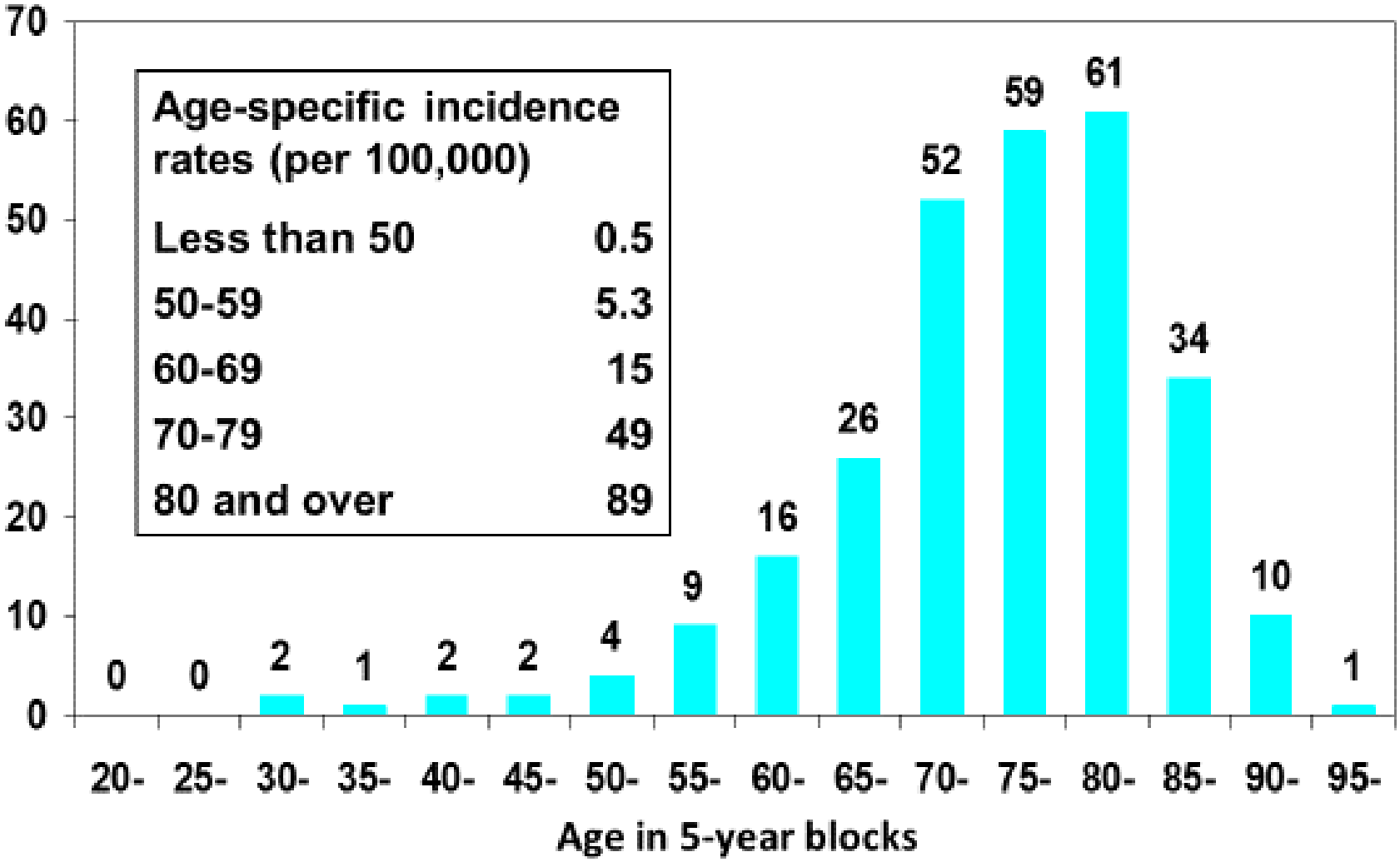
MDS: Epidemiology

- 9,700 new cases/year in US (Adults)
- More common than AML
- Median survival 2-3 years
- Disease burden likely underestimated
- Predominantly a disease of the elderly
  - Median age > 70
  - Incidence males > females
  - Incidence ↑ with age



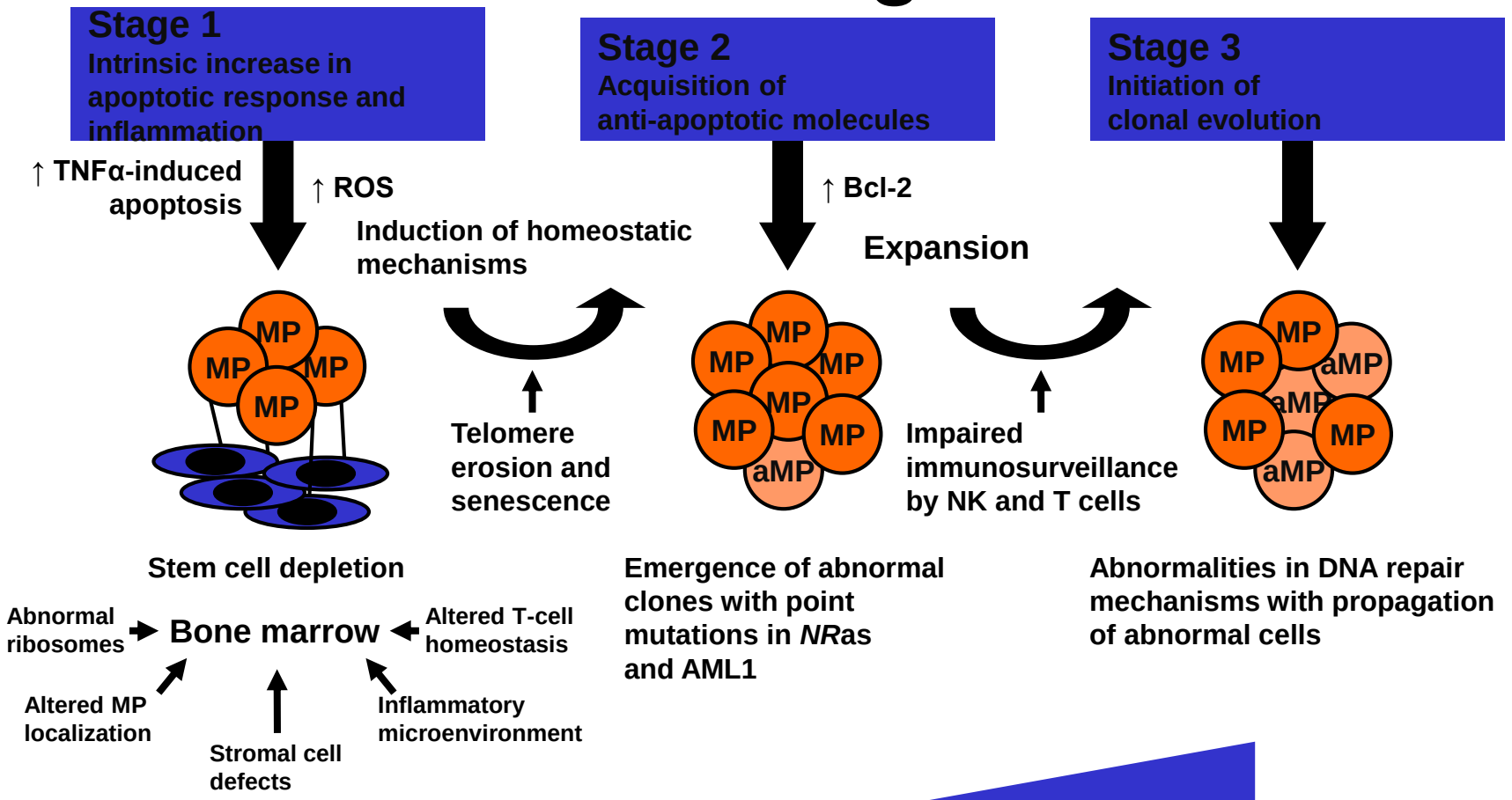
Rollison et al. Blood. 2008;112:45-52
Greenberg et al. Blood 1997; 89:2085-

Age-Related Incidence of MDS



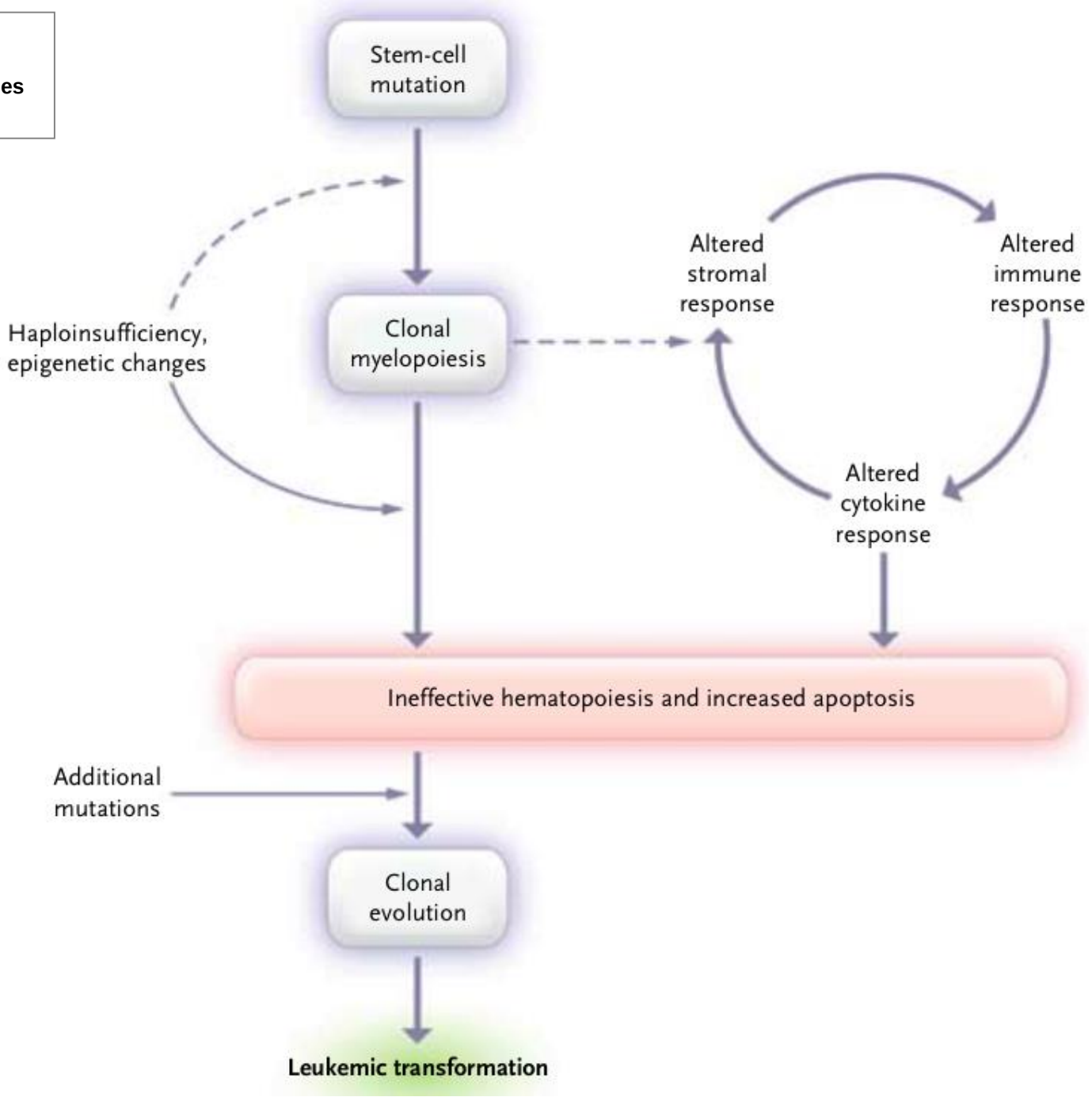
Williamson PJ, et al. *Br J Haematol.* 1994 Aug;87(4):743-5.

MDS Pathogenesis

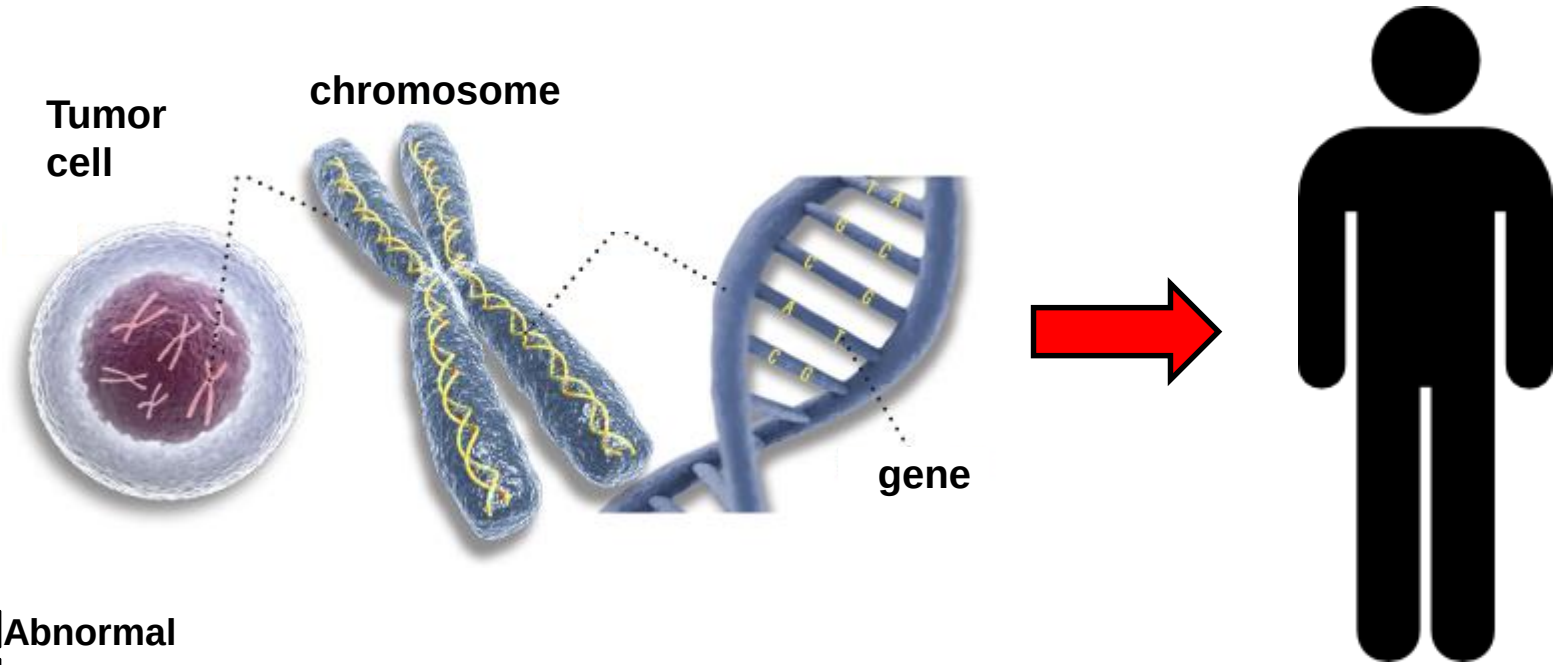


Epling-Burnette PK, et al. Curr Opin Hematol. 2009;16:70-76.

Tefferi A & Vardiman JW
Mechanisms of disease: Myelodysplastic syndromes
NEJM 2009; 361:1872-85



Cancer Genomics



Mutation discovery/Clonality

- •Cytogenetics
- •Candidate gene sequencing
- •Whole Genome Sequencing (unbiased comprehensive platform)

Patient care

- diagnosis
- risk stratification
- therapy

MDS Diagnostic Criteria

WHO Criteria: MDS

Minimal Morphologic Criteria

- ≥10% of the cells in at least one lineage must show dysplasia
- Dysplasia not required if defining cytogenetic abnml present, BM blasts ≥ 5%, PB blasts ≥ 2%, or Auer rods
- At least one cytopenia* present
- Causes of secondary dysplasia^ must be excluded

Presumptive Diagnosis

Unbalanced	Balanced	Other
-7 or del(7q)	t(11;16)(q23;p13.3)	Complex karyotype (≥ 3 abnormalities)
-5 or del(5q)	t(3;21)(q26.2;q22.1)	
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)	
-13 or del(13q)	t(2;11)(p21;q23)	
del(11q)	inv(3)(q21q26.2)	
del(12p) or t(12p)	t(6;9)(p23;q34)	
del(9q)		
idic(X)(q13)		

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

^Hypothyroidism, Vit B 12 deficiency, Cu level, ETOH use

Vardiman et al. Blood. 2009;114:937-951
Arber et al. Blood. 2016;127:2391-2405

WHO 2016 Classification of MDS

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
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 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 ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-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-RS with multilineage dysplasia (MDS-RS-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 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 excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	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
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Arber et al. Blood. 2016;127:2391-2405

IPSS and Comprehensive Cytogenetic Scoring System

Classification / Prognostic Group	Abnormalities		
	Single	**Double**	**Complex**
IPSS			
Good	Normal; -Y; del(5q); del(20q)	—	—
Intermediate	Other	Any	—
Poor	7*	—	≥ 3†
5-Group			
Very good	-Y; del(11q)	—	—
Good	Normal; del(5q); del(20q); del(12p)	Incl. del(5q)	—
Intermediate	del(7q); +8; i(17q); +19; any other	Any other	—
Poor	-7; Inv(3)/t(3q)/del(3q)	Incl. -7/ del(7q)	3†
Very poor	—	—	>3†

*** Any chromosome 7 abnml**
† number of clonal abnml

Greenberg P, et al. *Blood*. 1997;*89*:2079-2088
Schanz J. et al. *J Clin Oncol*. 2012;30:820-829

Revised IPSS (IPSS-R)

points	0	0.5	1	1.5	2	3	4
blasts (%)	<2%	-	2-4%	-	5-10%	>10%	
Hemoglobin	>10 g/dl		8-10 g/dl	<8 g/dl			
ANC	>0.8 G/l	<0.8 G/l					
Platelet	>100	50-100	<50				
Cytogenetics	**Very Good** -Y del(11q)		**Good** Normal der(1;7) del(5q) del(20q) del(12p) Double incl del(5q)		**Intermed** -7/7q +8 Iso(17q) +19 +21 other double inclusions	**Poor**: der3q(21) der3q(26) Complex Double inclusion 7q/7	**Very Poor** Complex >3

4 categories

3 categories

2 categories

3 categories

5 categories
16 subgroups

Greenberg PL, et al. Blood. 2012;120:2454-2465

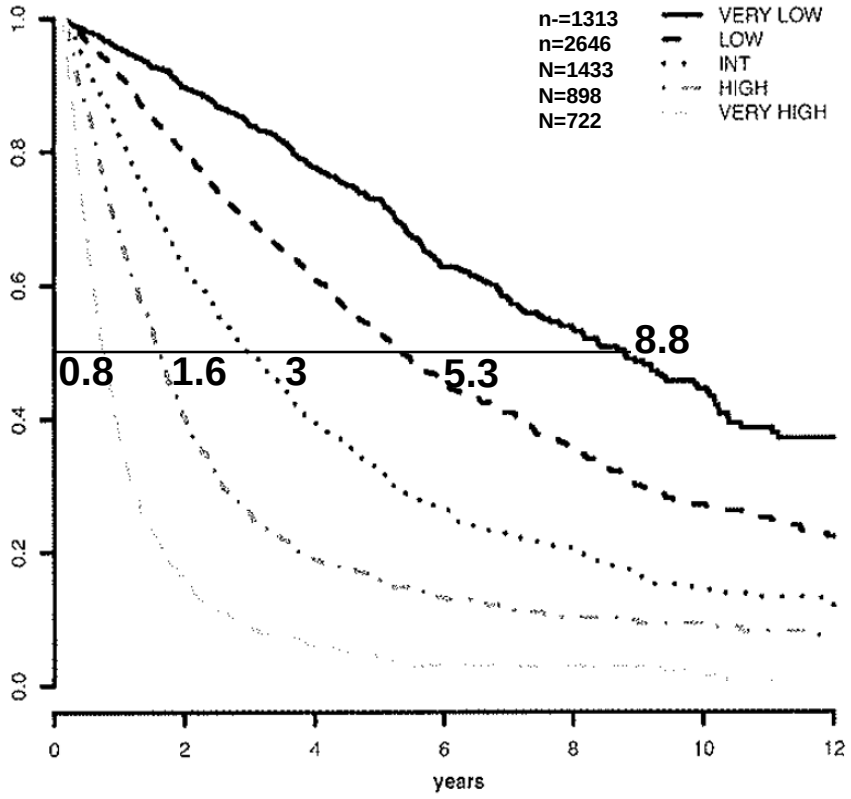
IPSS-R

Table 3. IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Inter-mediate	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					

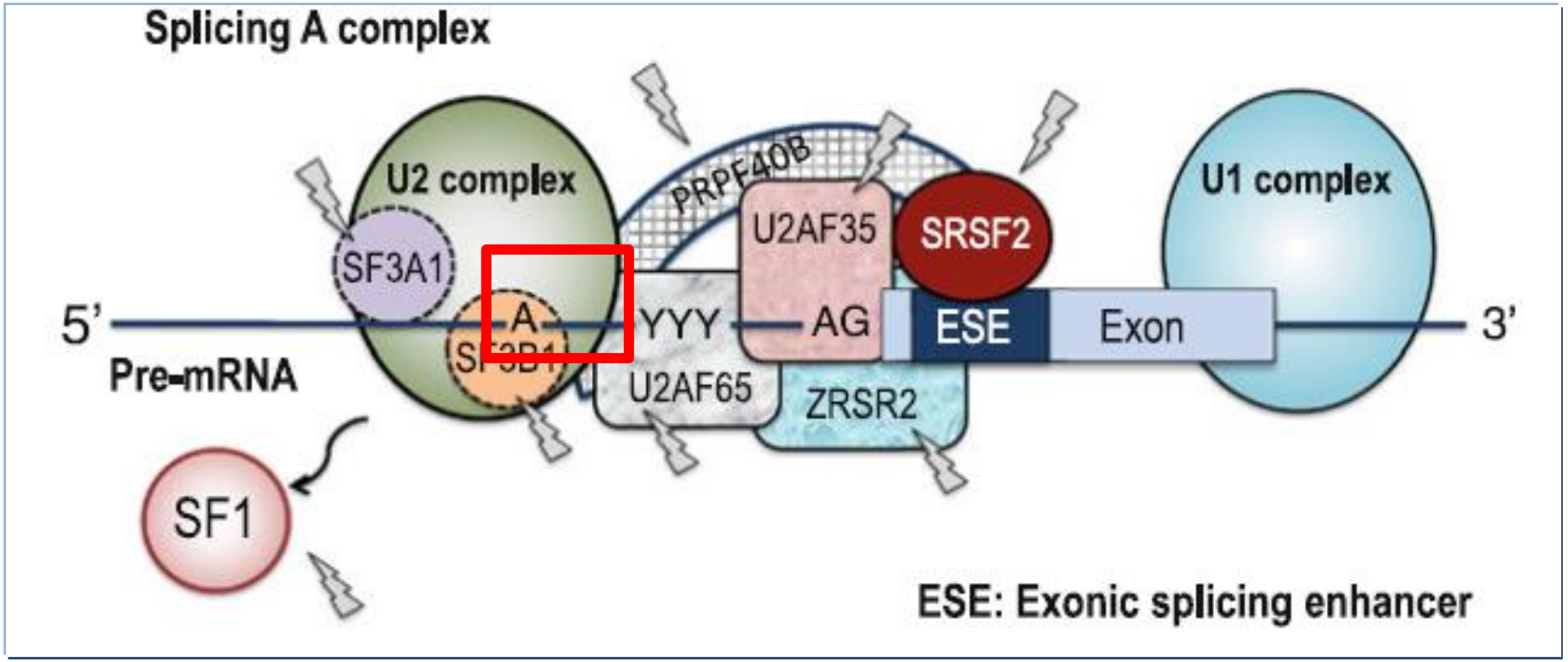
Table 4. IPSS-R Prognostic Risk Categories/Scores

RISK GROUP	RISK SCORE
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6



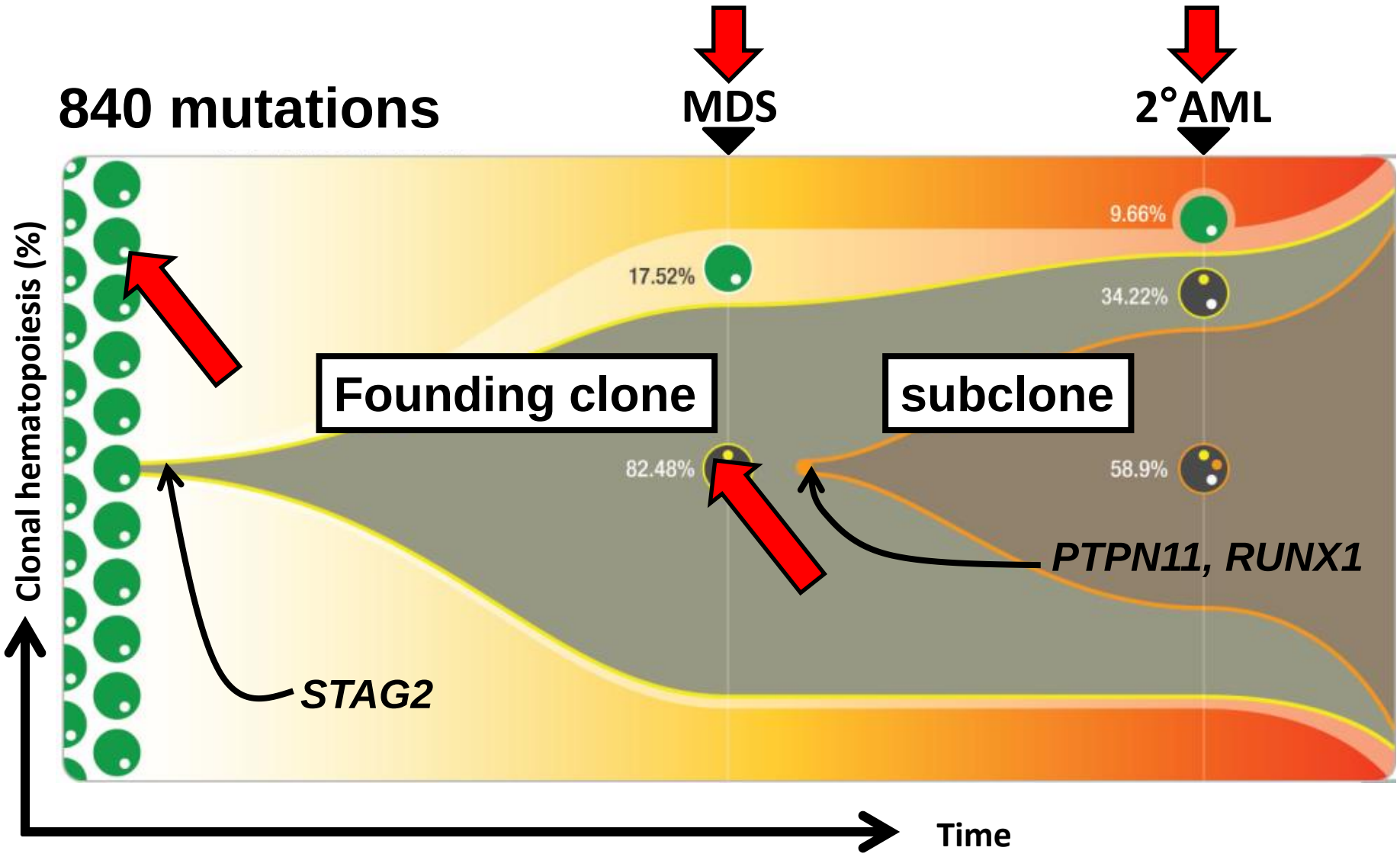
Greenberg PL, et al. Blood. 2012;120:2454-2465

Spliceosome mutations in 85% of MDS



Haferlach T et al. *Leukemia* 2014;28:241-247

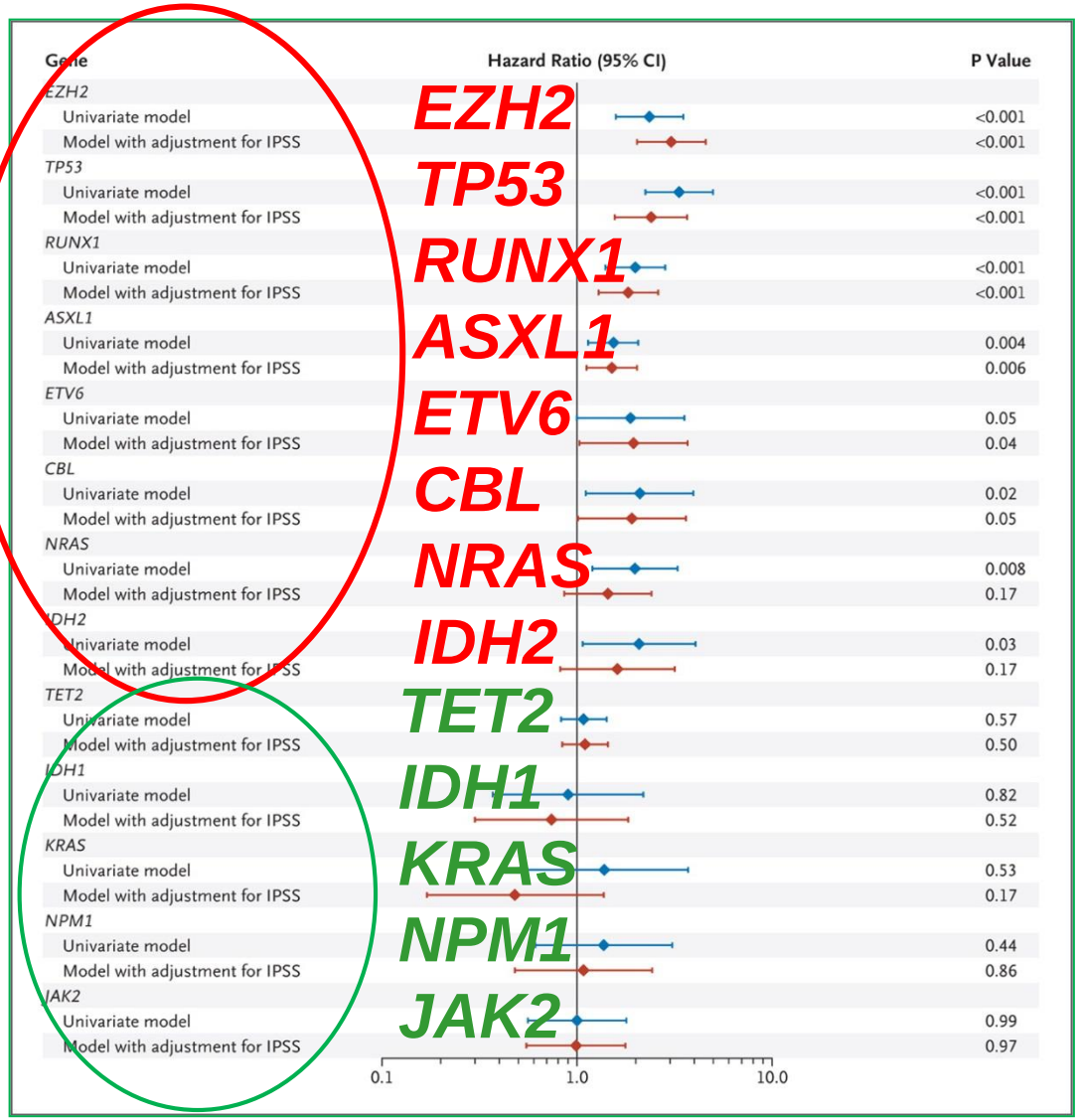
Clonal evolution model

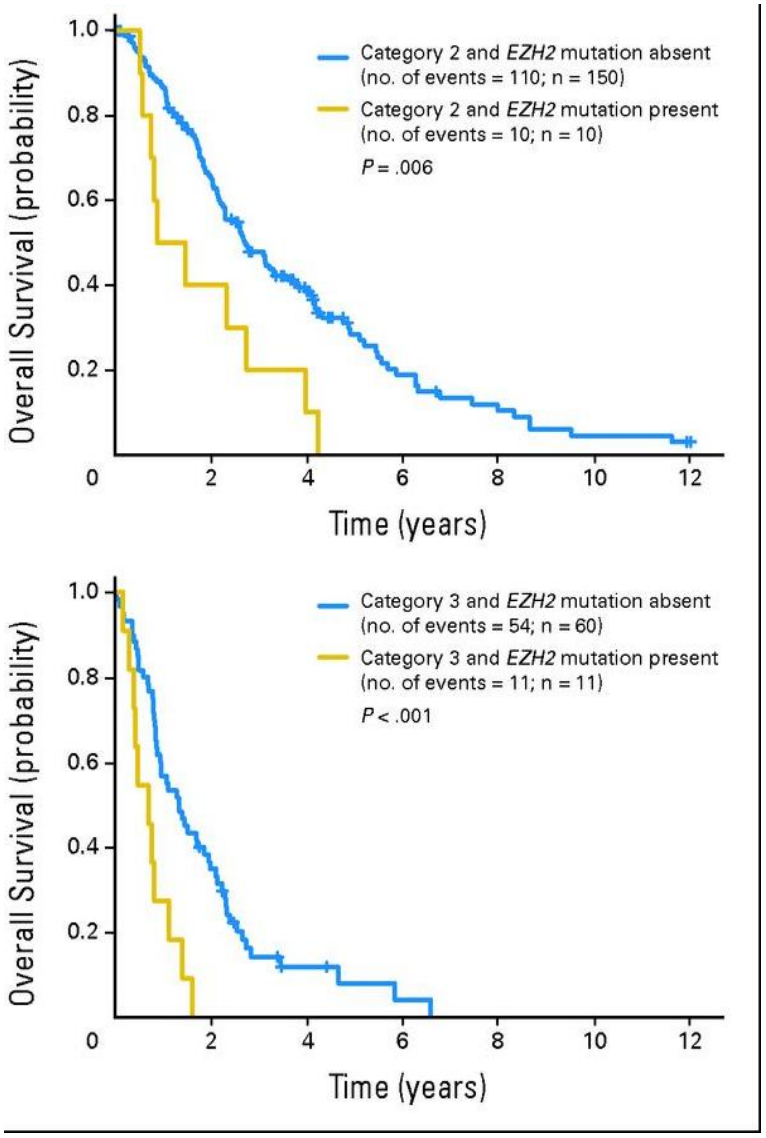


Walter et al, *NEJM* 2012

Survival by Mutational Abnormalities in MDS

439 MDS Patients





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

Bejar R et al. *J Clin Oncol* 2012;30:3376-3382

Development of a novel prognostic risk classification

$$AIC = 2k - 2\ln(L)$$

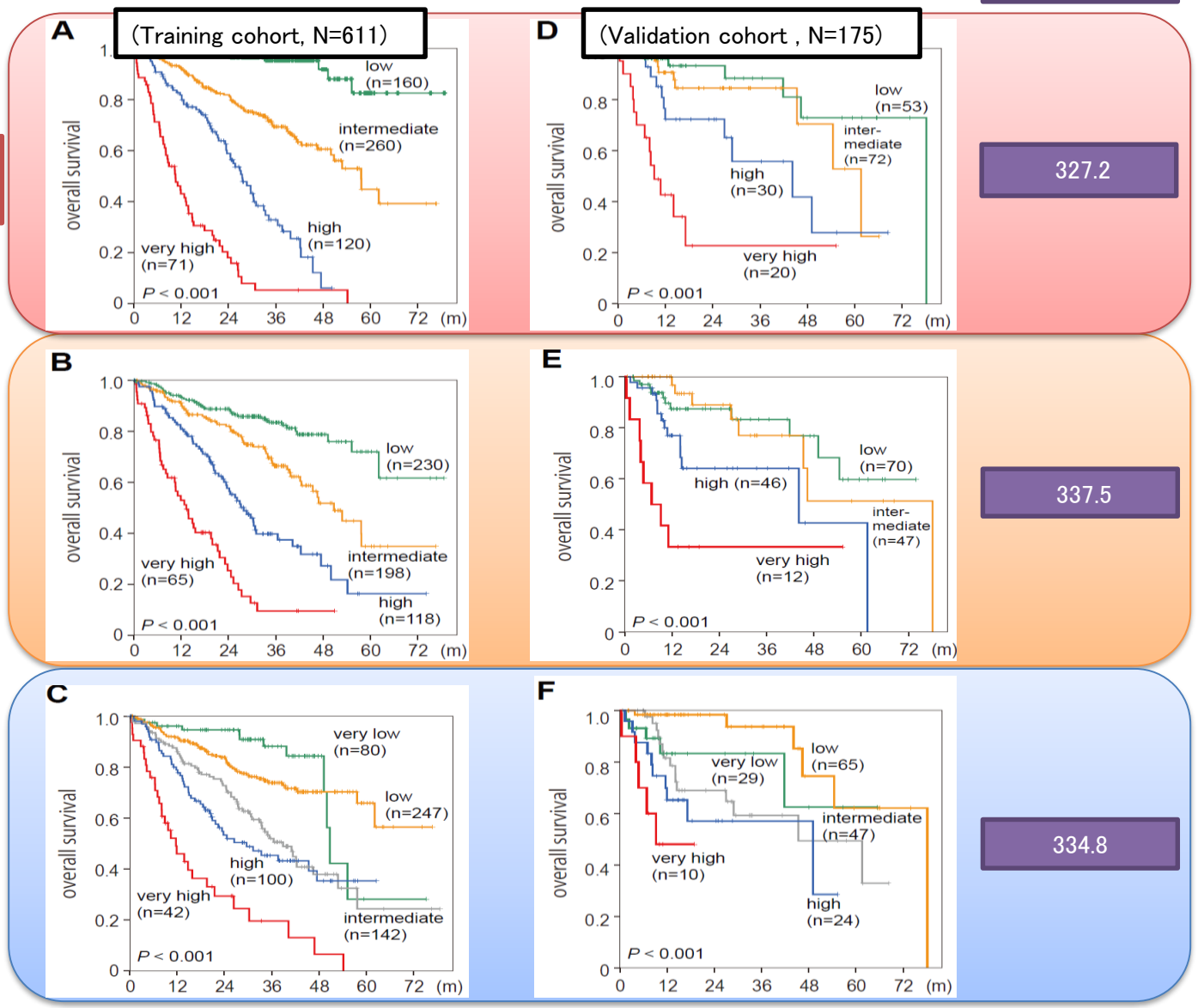
The mutation/deletion status of multiple genes independently correlated with OS and combined with conventional prognostic factors was successfully used to construct a statistically relevant prognostic model.

AIC
(Akaike's Information Criterion)

Clinical and genetic parameters (Model-1)

Only genetic parameters (Model-2)

Conventional model (IPSS-R)



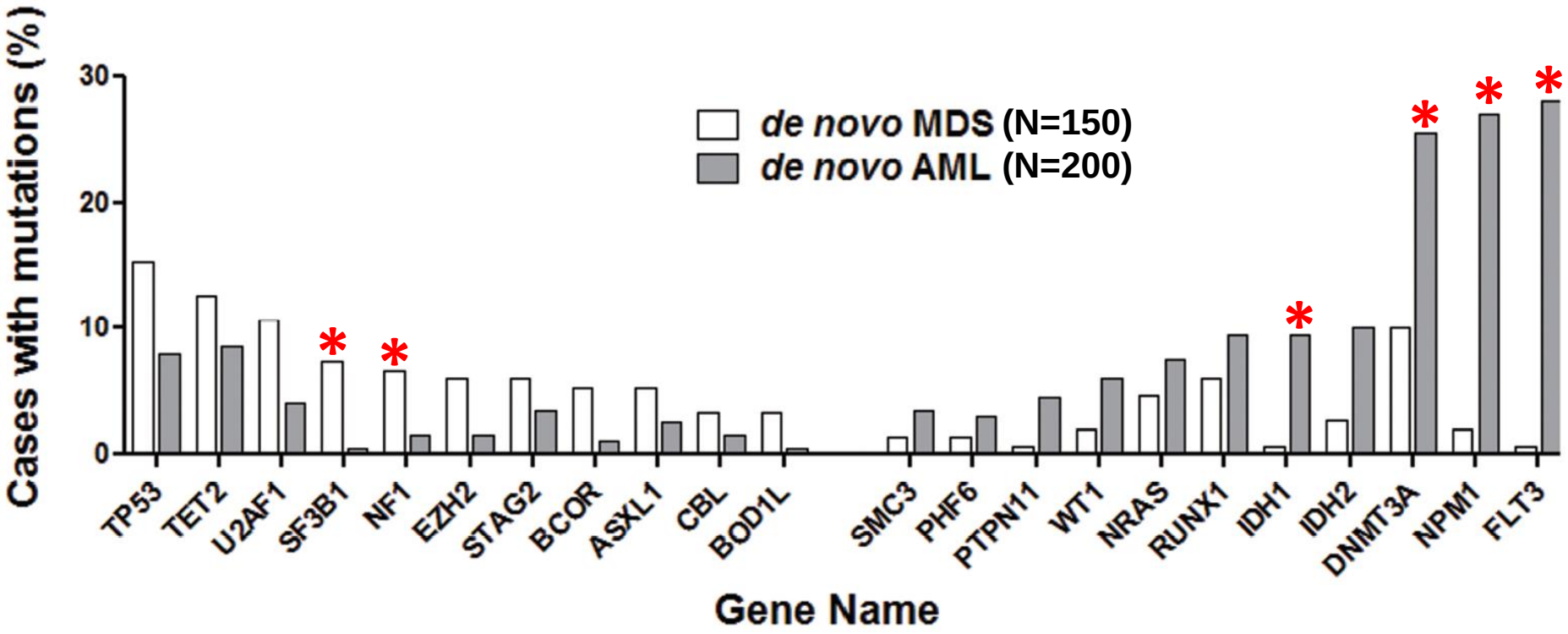
327.2

337.5

334.8

Haferlach T et al. *Leukemia* 2014;28:241-247

Frequency of gene mutations differ in MDS vs. AML



* FDR<0.05

Clinical Presentation

- Asymptomatic

- Symptoms related to low blood counts
  - Anemia (fatigue, SOB, DOE, angina, CHF)
  - Infection (principal cause of death)
  - Bleeding (petechiae, ecchymosis, epistaxis, hemorrhage)

Diagnostic Evaluation: Peripheral Blood

Diagnostic Study	Clinical Significance
CBC with Differential & Platelet Count, Reticulocyte Count	Evaluate for cytopenias, peripheral blasts
Serum Fe, TIBC, Ferritin, Folic Acid, B12	Evaluate for other possible causes of anemia
LDH, Haptoglobin, Reticulocyte Count, Coombs	Evaluate for possible underlying hemolysis
Serum Erythropoietin	Baseline to determine role for growth factor

NCCN *Clinical Practice Guidelines in Oncology.™ Myelodysplastic Syndromes.*V. 5, 2007.

Diagnostic Evaluation: Bone Marrow

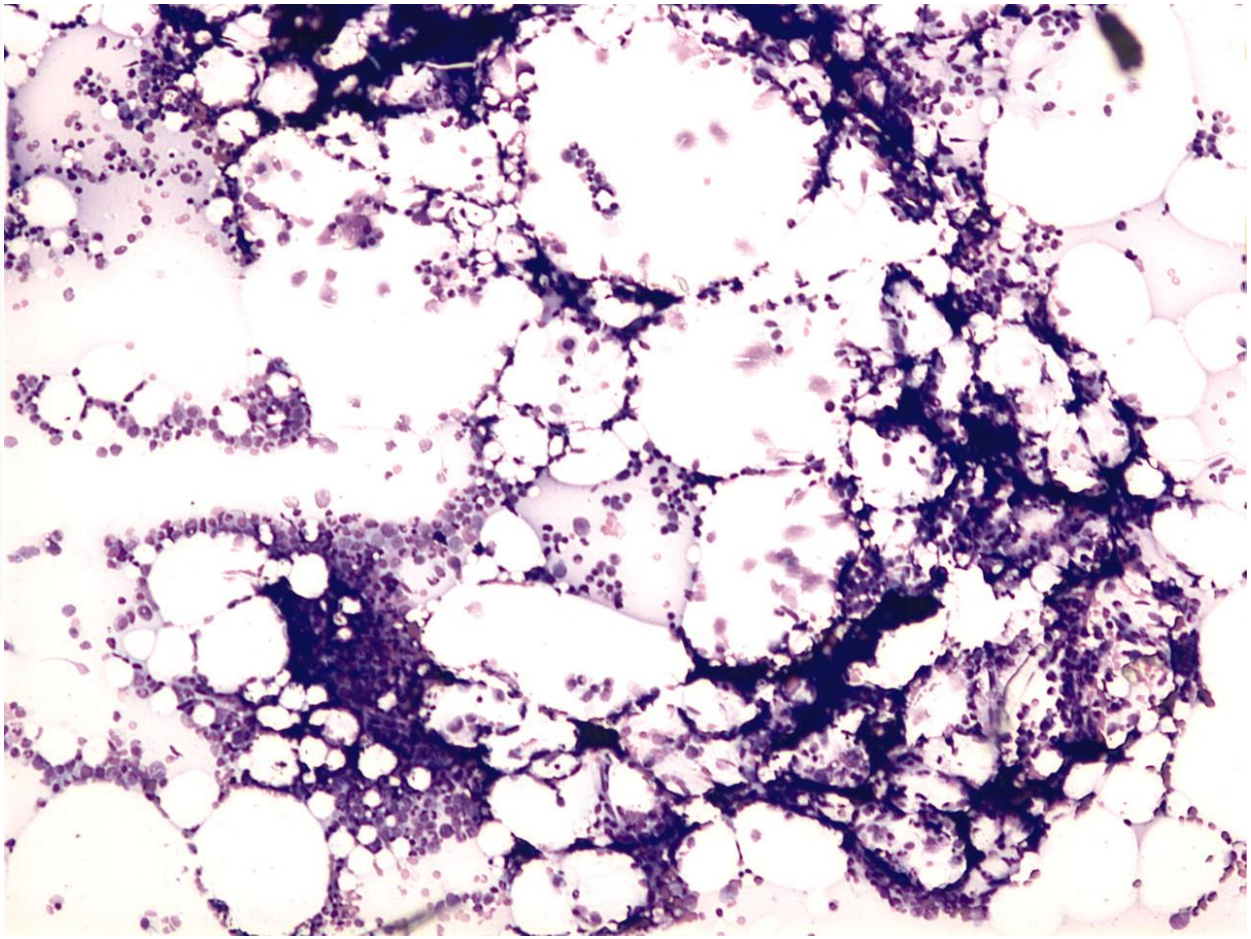
Diagnostic Study	Clinical Significance
Aspirate	Evaluate for morphologic abnormalities. Used for flow, cytogenetics, FISH
Biopsy	Evaluate cellularity & presence of fibrosis
Cytogenetics	Evaluate for ***non-random*** chromosomal abnormalities. Examine 20 metaphases. > 2 = non-random event

NCCN *Clinical Practice Guidelines in Oncology.™ Myelodysplastic Syndromes.*V. 5, 2007.

Bone Marrow Findings

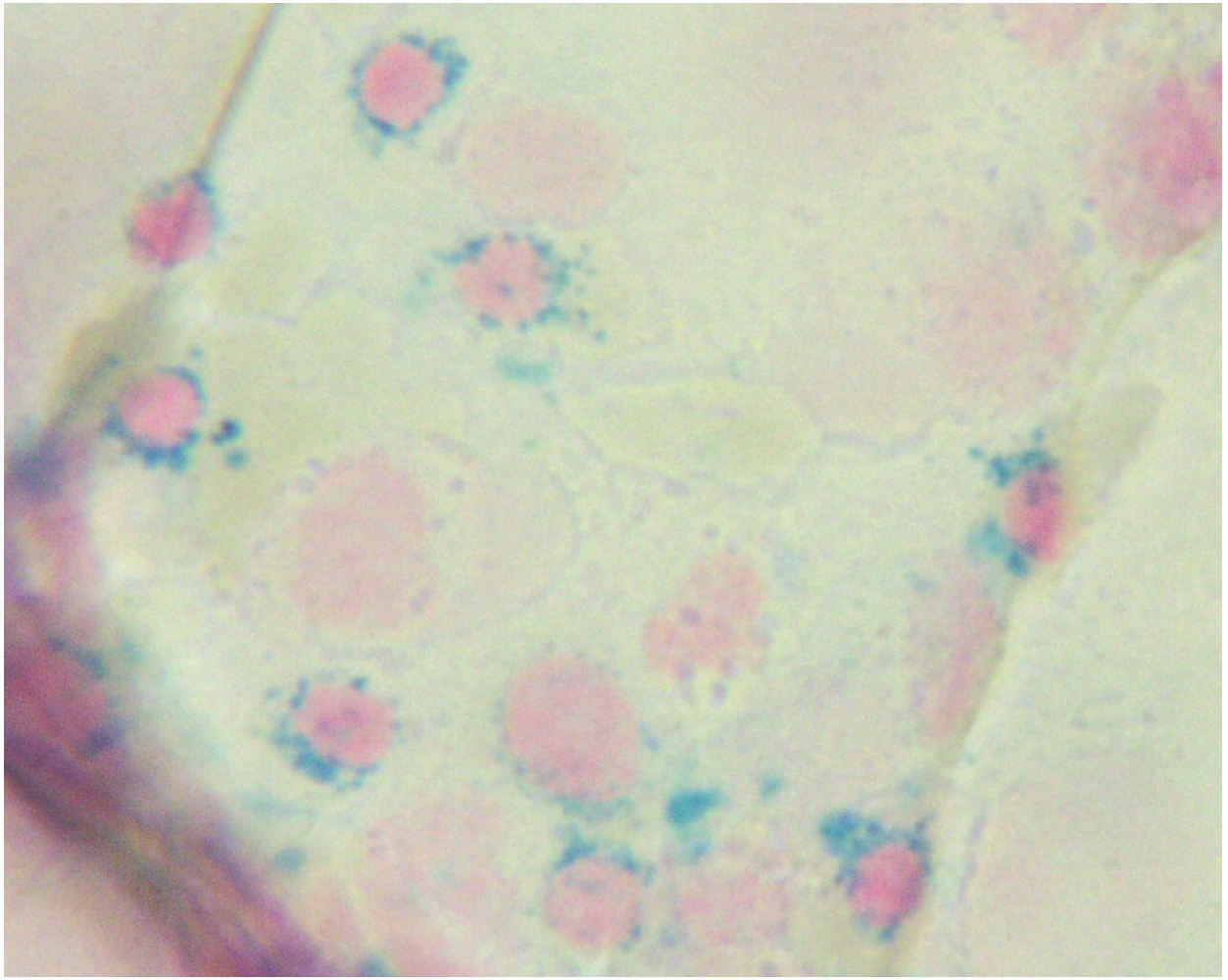
- Myelodysplastic Syndromes (MDS)
  - Usually hypercellular, although can be hypocellular
  - Dysplasia involving at least 10% of any single cell line
  - Characteristic cytogenetic findings
  - Excess Blasts (≥5%)
  - Ringed sideroblasts (RARS)
  - CD 34 + cells >0.5%

Figure 2. Hypocellular MDS may be confused with Aplastic Anemia



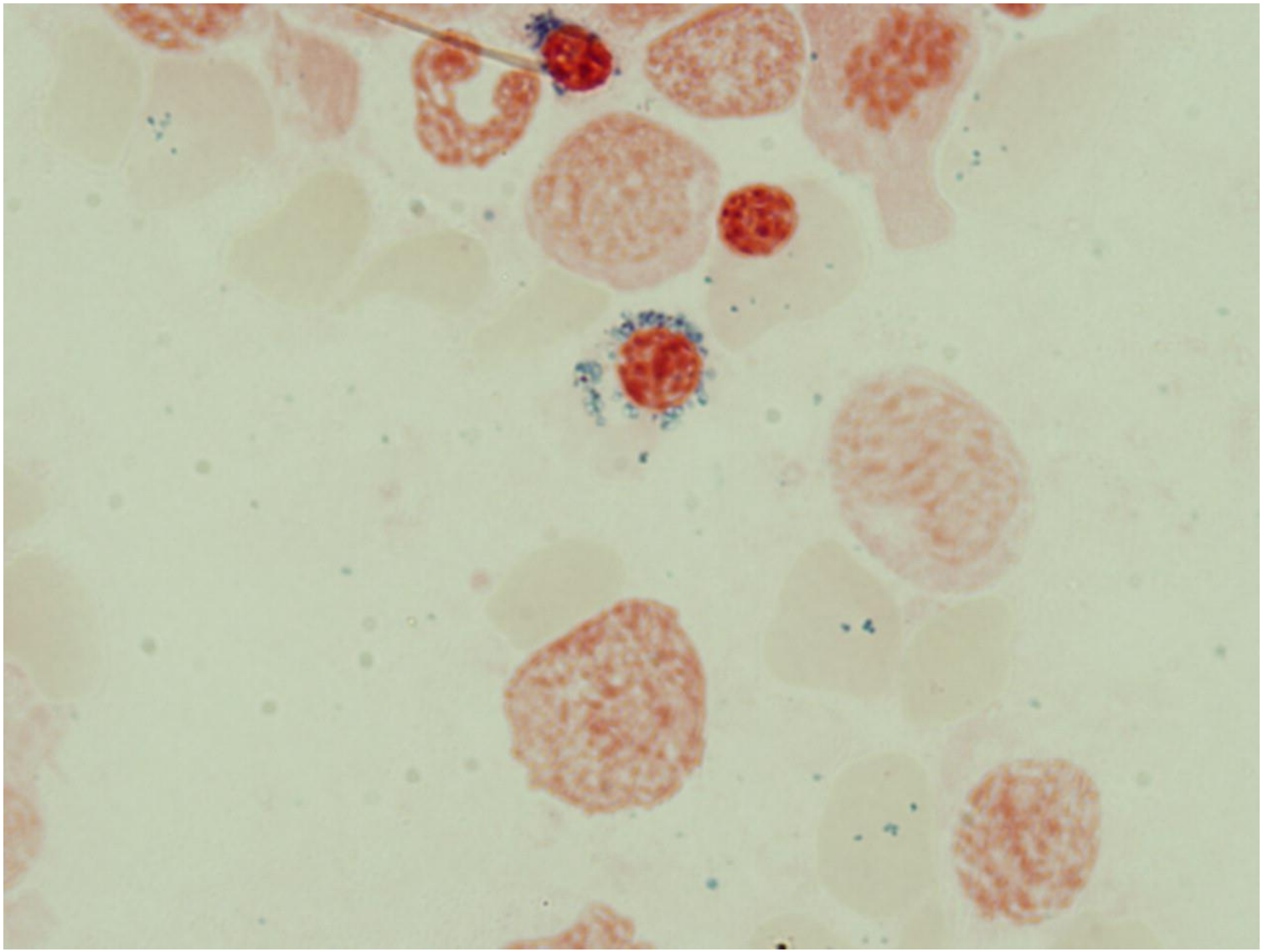
Maslak, P. ASH Image Bank 2004;2004:101115

Figure 1. A Prussian Blue histochemical stain of a bone marrow aspirate of a patient with myelodysplastic disorder, refractory anemia with ringed sideroblasts, is shown



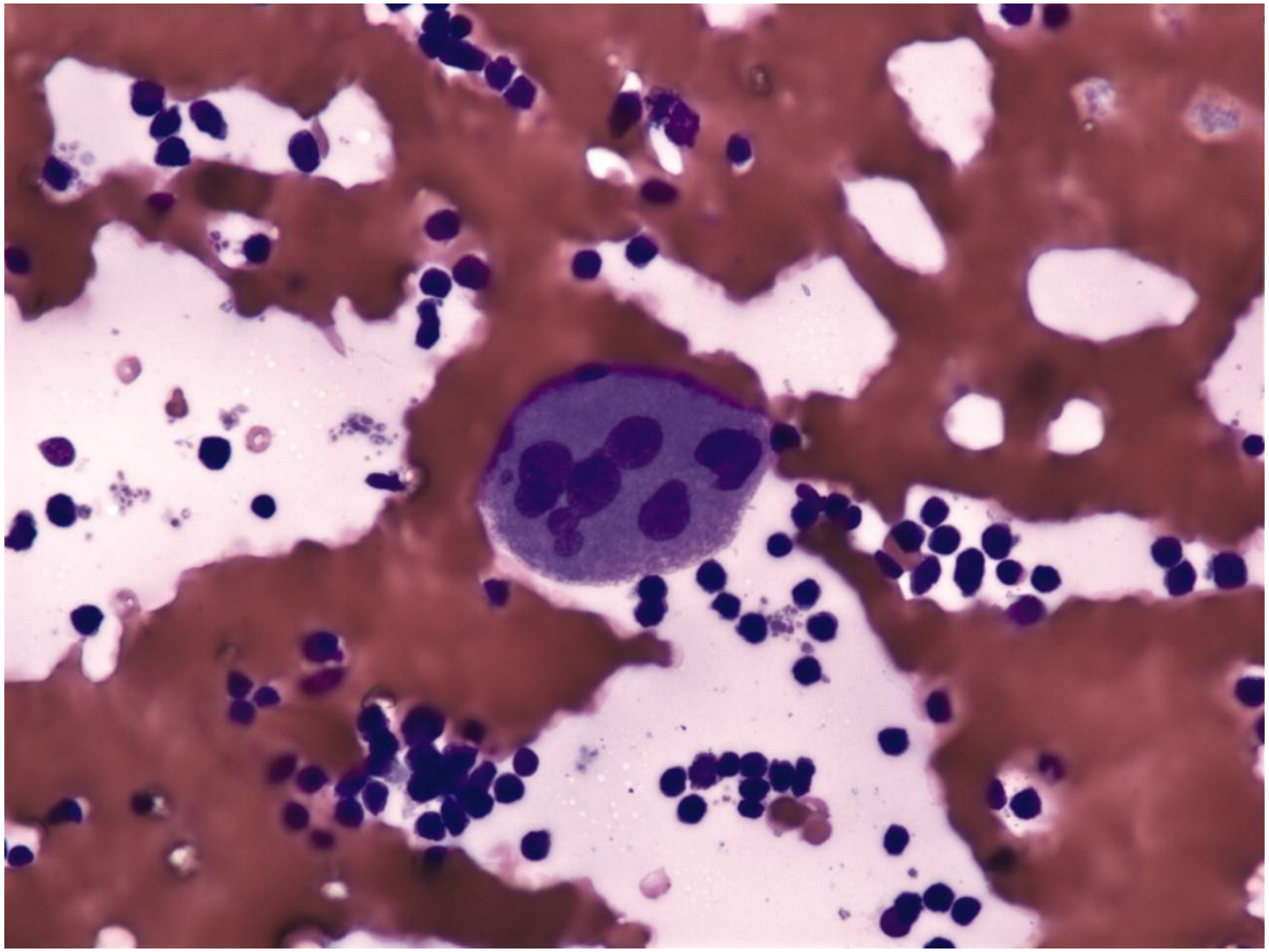
Lazarchick, J. ASH Image Bank 2008;2008:8-00114

Figure 3. Ringed sideroblast, myelodysplastic syndromes (MDS), shown with a Prussian blue stain at low power



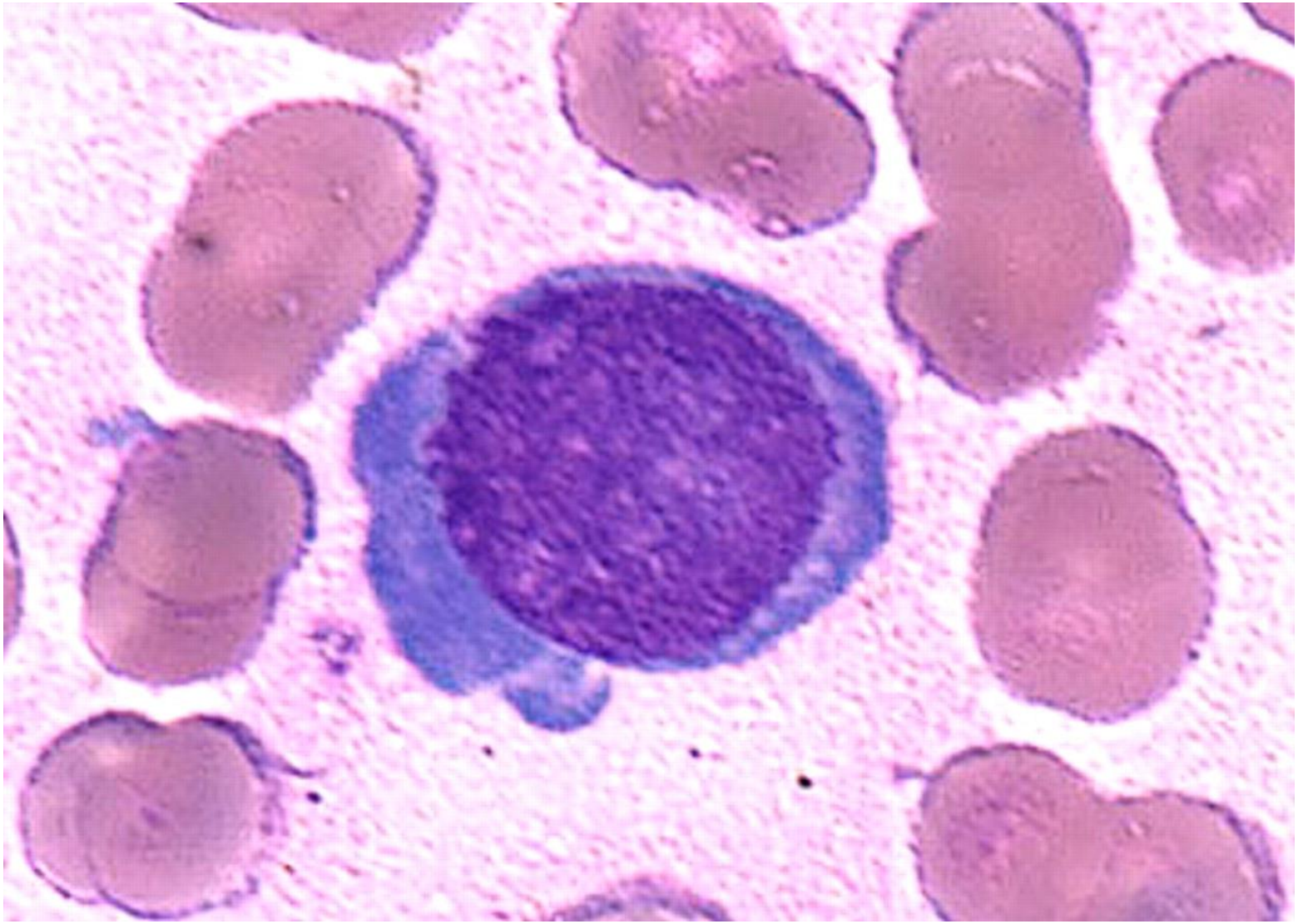
Fukumoto, J. et al. ASH Image Bank 2006;2006:6-00022

Figure 1. Dysplastic megakaryocytes



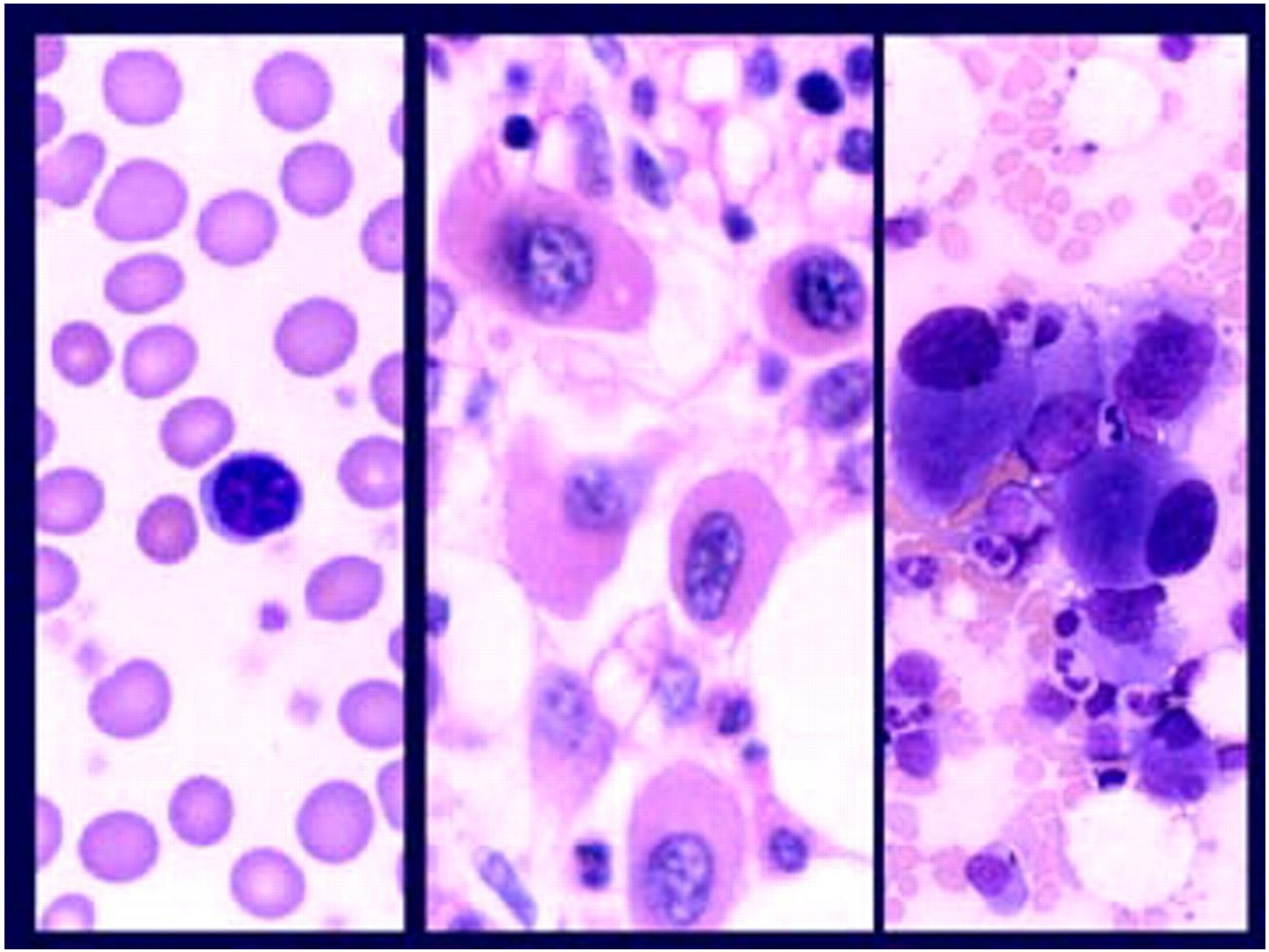
Maslak, P. ASH Image Bank 2004;2004:100973

Figure 1. Dysplastic erythroid precursor has open chromatin and basophilic cytoplasm

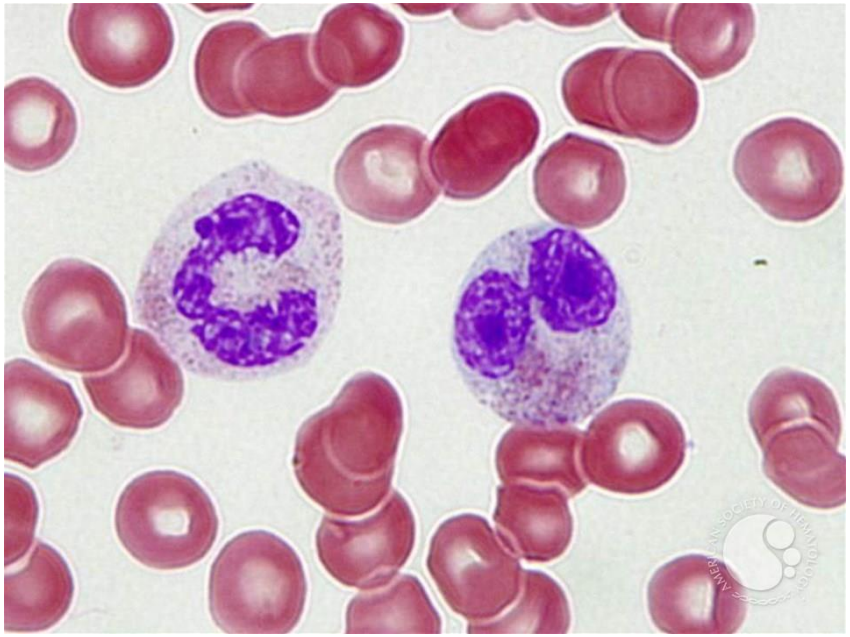


Maslak, P. ASH Image Bank 2004;2004:101102

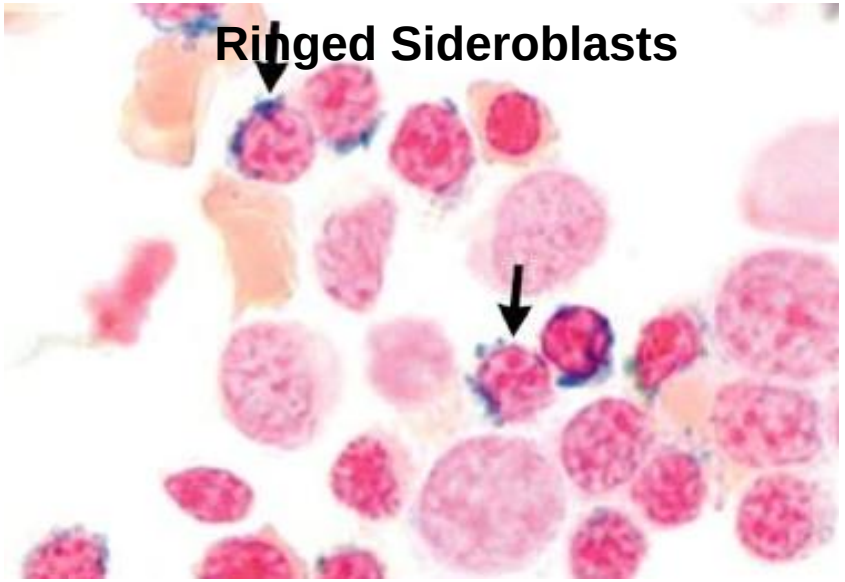
Figure 8. This figure summarizes the characteristic findings associated with MDS with an isolated del(5q) syndrome



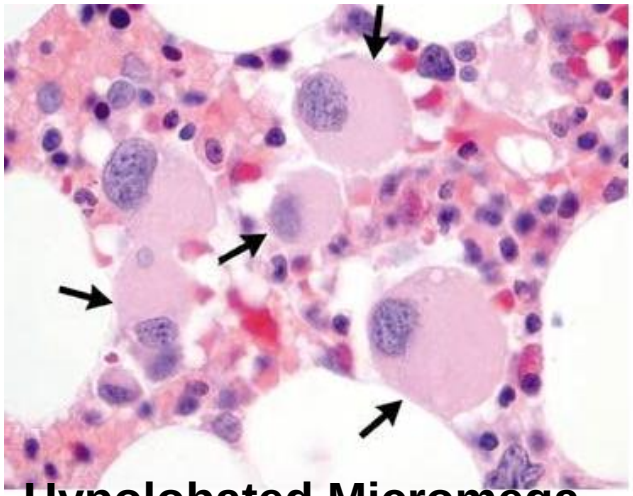
Vardiman, J. W ASH Image Bank 2001;2001:100197



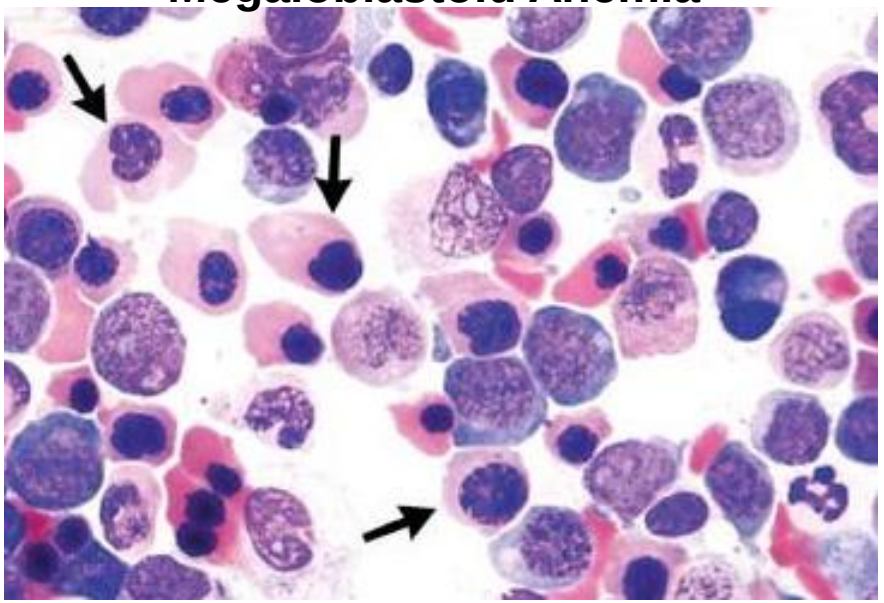
Pseudo Pelger-Huet cell



Ringed Sideroblasts



Hypolobated Micromega



Megaloblastoid Anemia

Conclusions

- Myelodysplastic syndromes are difficult to diagnose
- Clinical and diagnostic studies are imprecise
- Many of bone marrow failure entities overlap
- Cytogenetic and molecular testing is increasingly important