Myelodysplastic Syndrome: Primary Care Perspective

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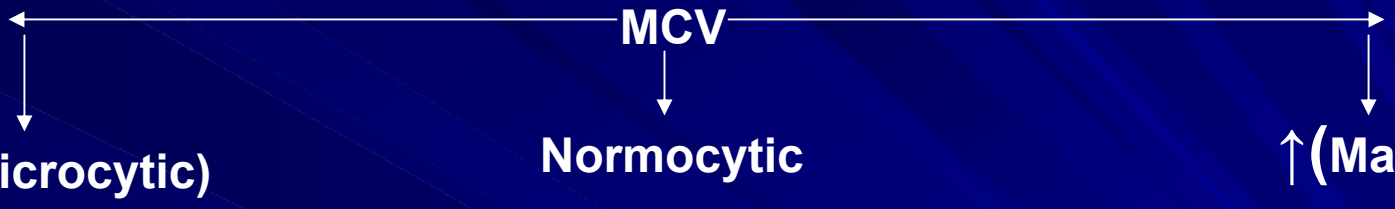
Conflicts of Interest

- Honoraria/Advisory Boards: Alexion, Novartis, Janssen & Celgene
- Research Funding: Celgene, Alexion

Investigation of Anemia



- **Iron deficiency**
- **Anemia of chronic disease**
- Sideroblastic anemia
- Hemoglobinopathy

- **Anemia of chronic disease**
- Aplastic anemia*
- **Marrow infiltration***
- **Increased destruction***

- **B12 deficiency**
- Folate deficiency
- **Thyroid disease**
- Drugs
- Liver disease
- All normocytic disorders* except ACD

INVESTIGATIONS:

- History/Physical
- CBC, diff & smear
- Renal/liver function & **LDH**
- Hematinics – Serum ferritin and B12
- **Reticulocyte count**
- DAT (Direct Coombs)
- **SPEP and serum free light chains**
- TSH

If no cause identified
- Bone marrow exam
- Hematology consult

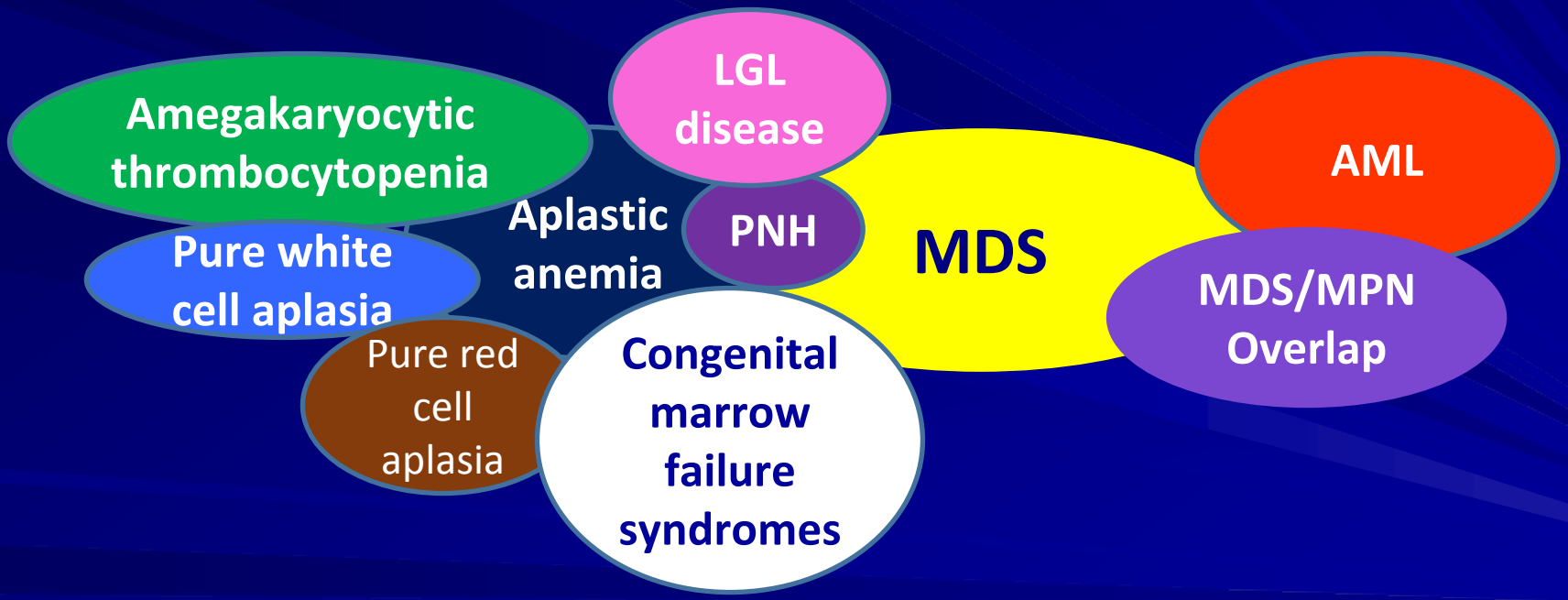
↓

Primary marrow disorder
#1= MDS

BACKGROUND: MDS

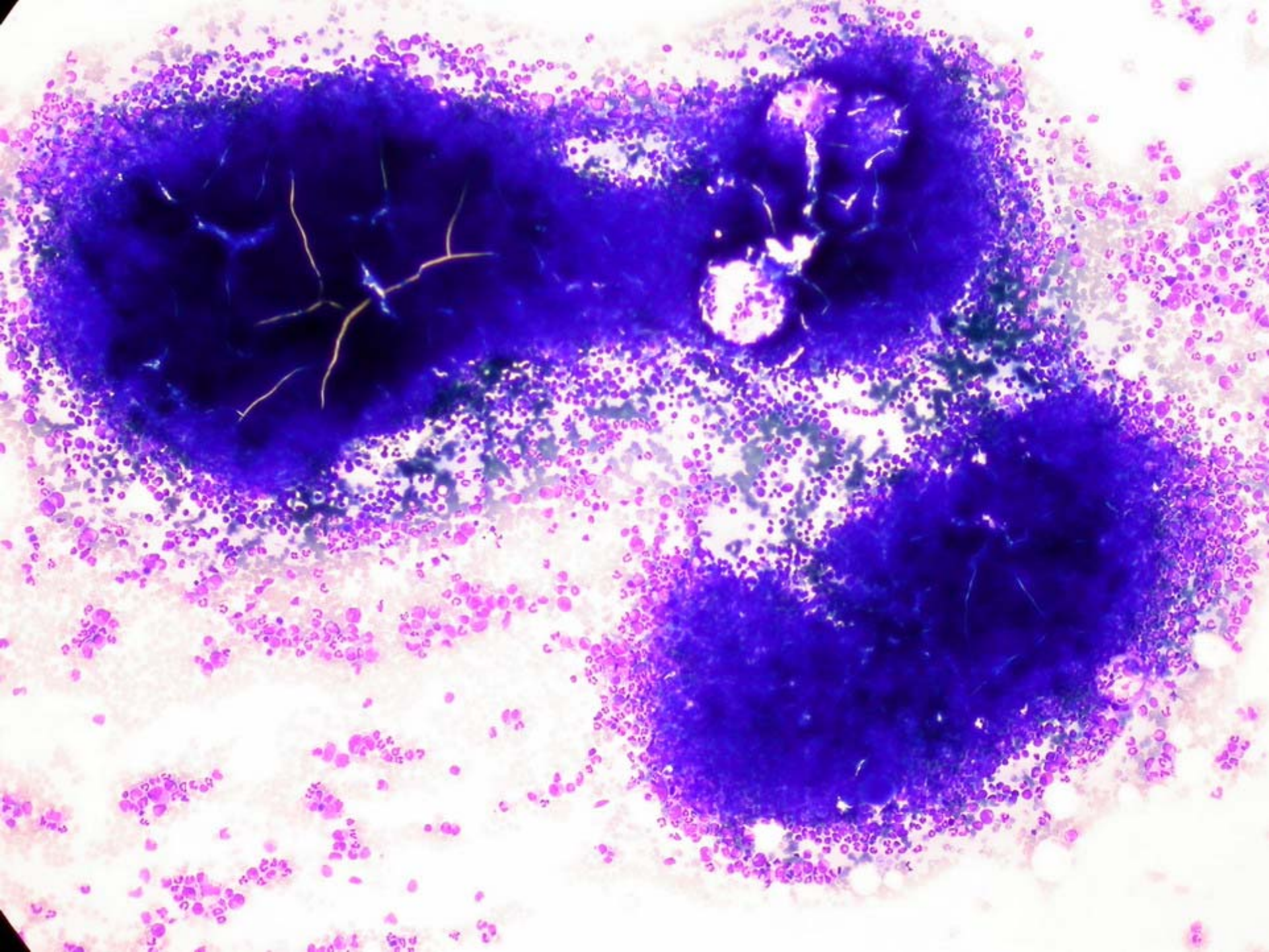
- Clonal stem cell disorder
- Propensity to transform to AML (~50%)
- Incidence uncertain (SEER: 36/million/y)
- Median age $\geq$ 65 yrs
- M = 1.4 x F
- Familial, de novo or treatment-related
- Overlap with other marrow failure syndromes

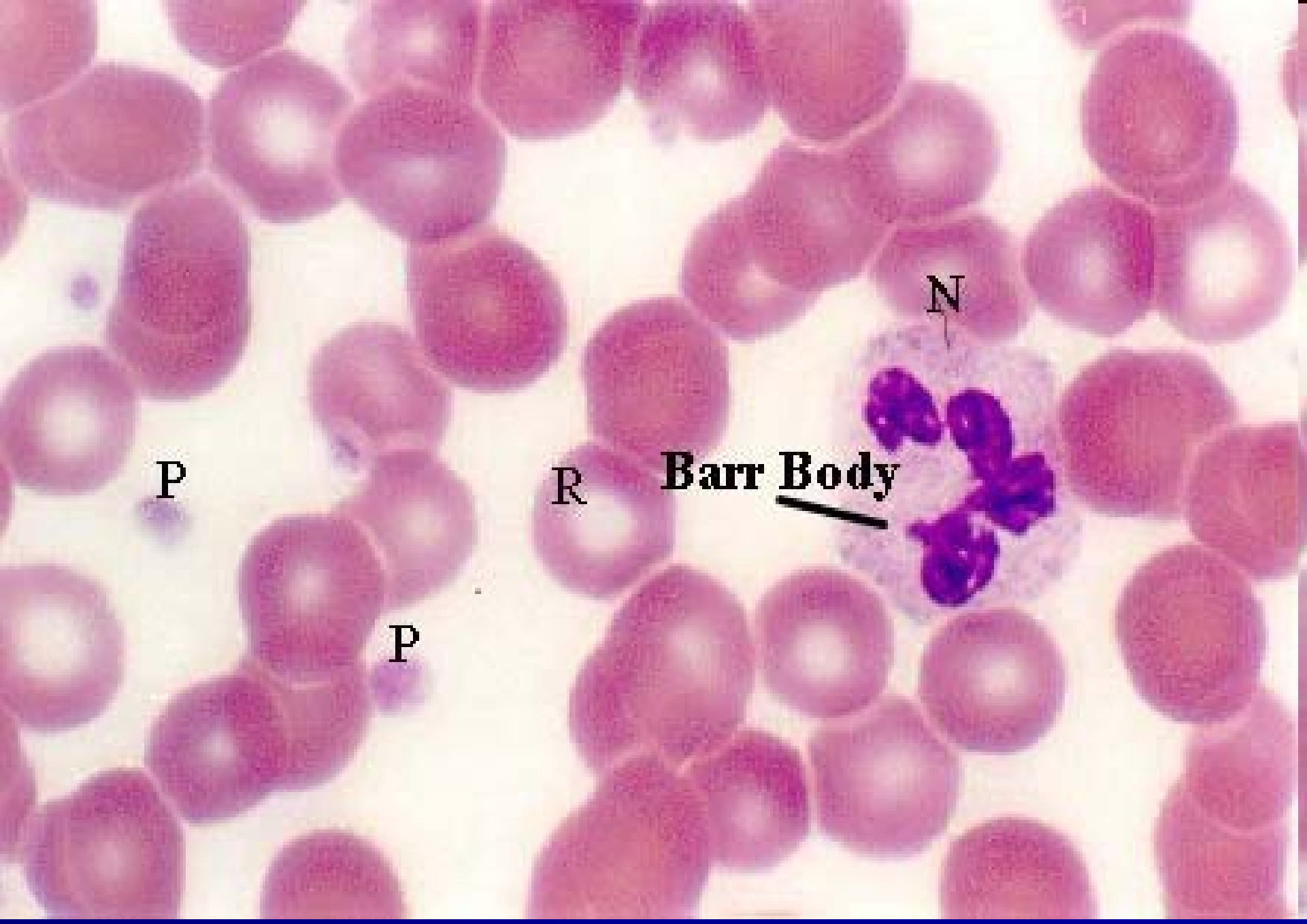
Marrow Failure Syndromes: 2015



BACKGROUND: MDS

- Presentation is (typically) pancytopenia
- 80% have hyperactive (but ineffective) marrow
- 20% have underactive marrow
- **Abnormal (dysplastic) red cells, WBCs & plts**
- **50% have abnormal marrow chromosomes**
- Extraordinarily heterogeneous disease
- Highly variable prognosis

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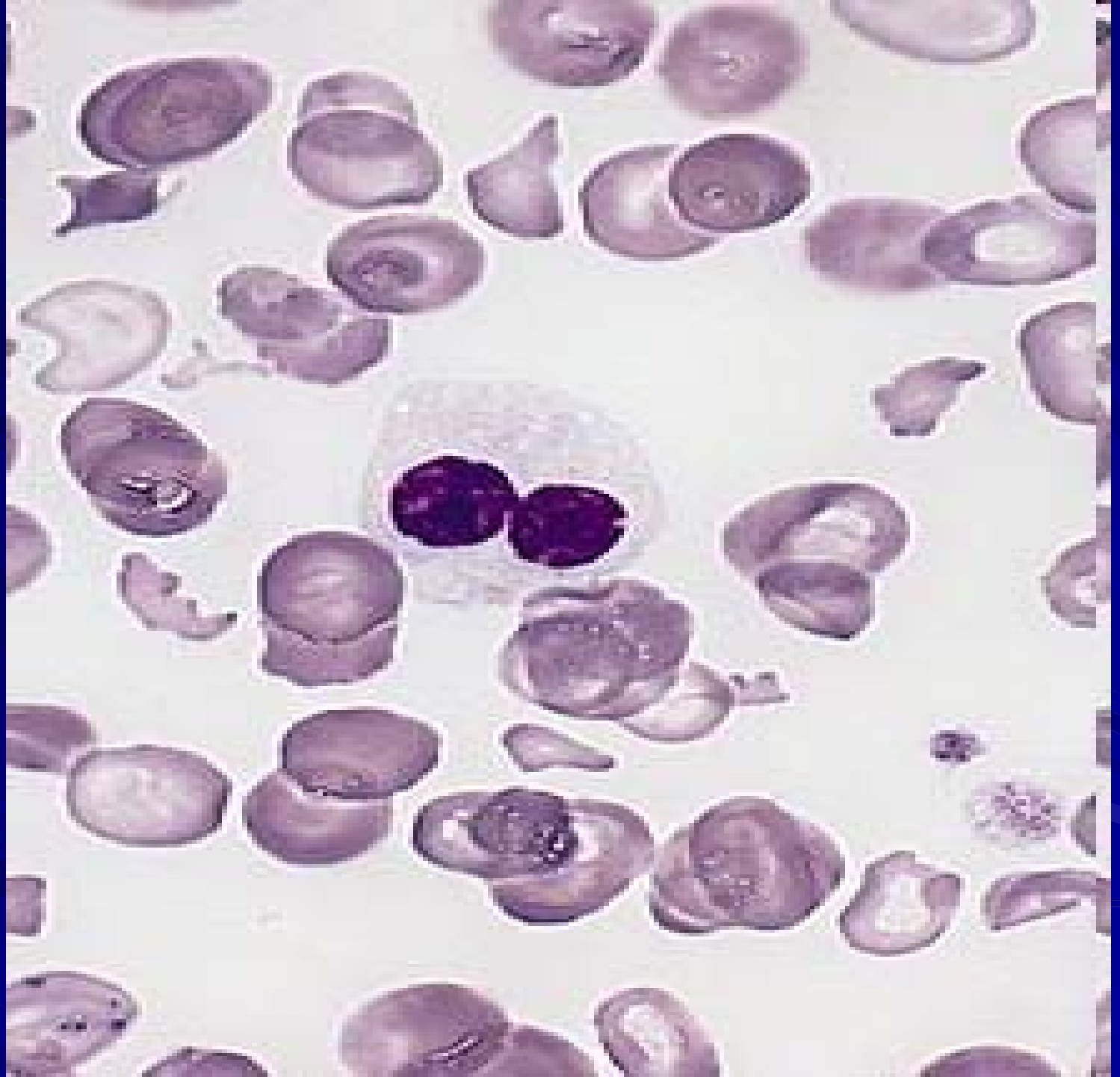

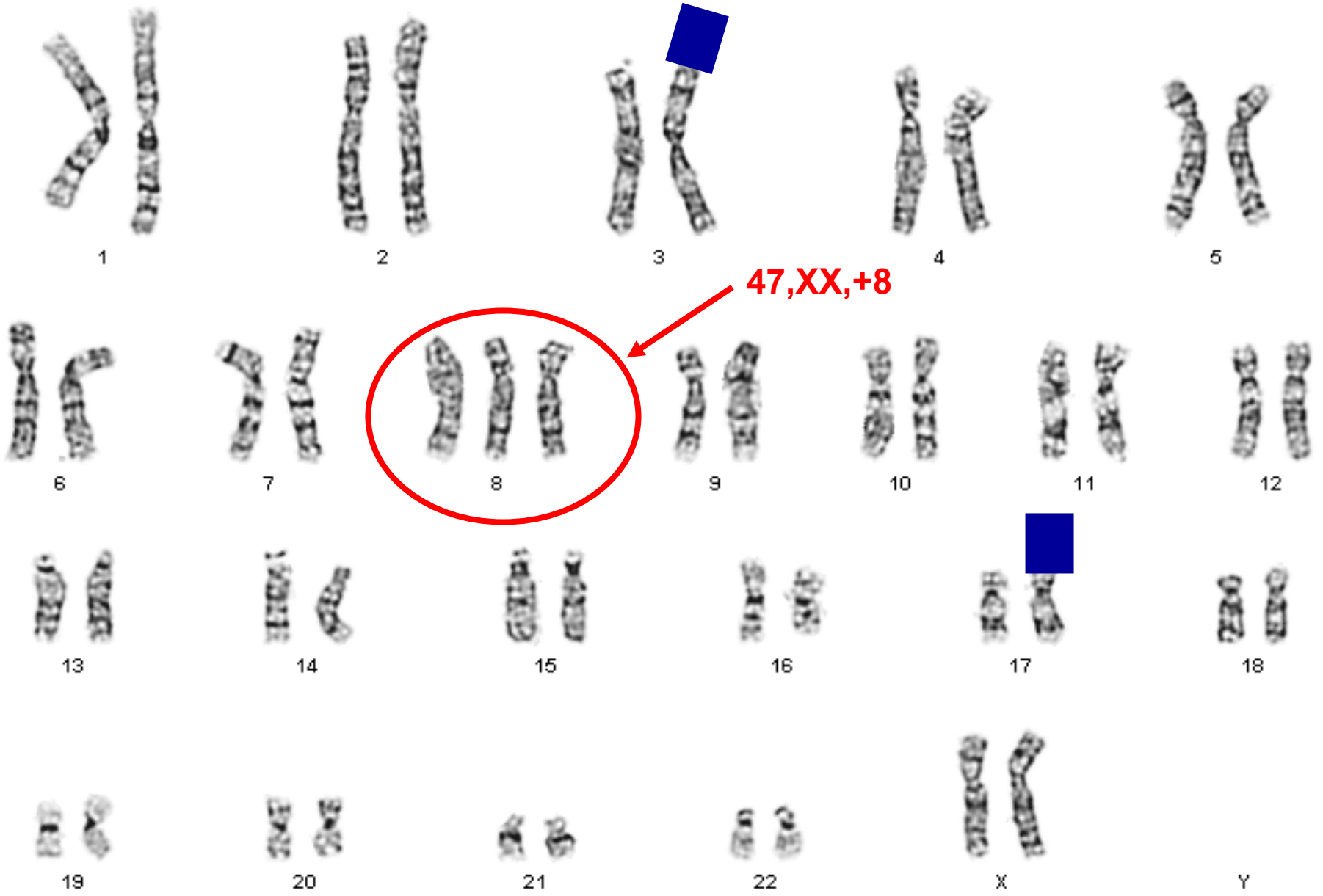
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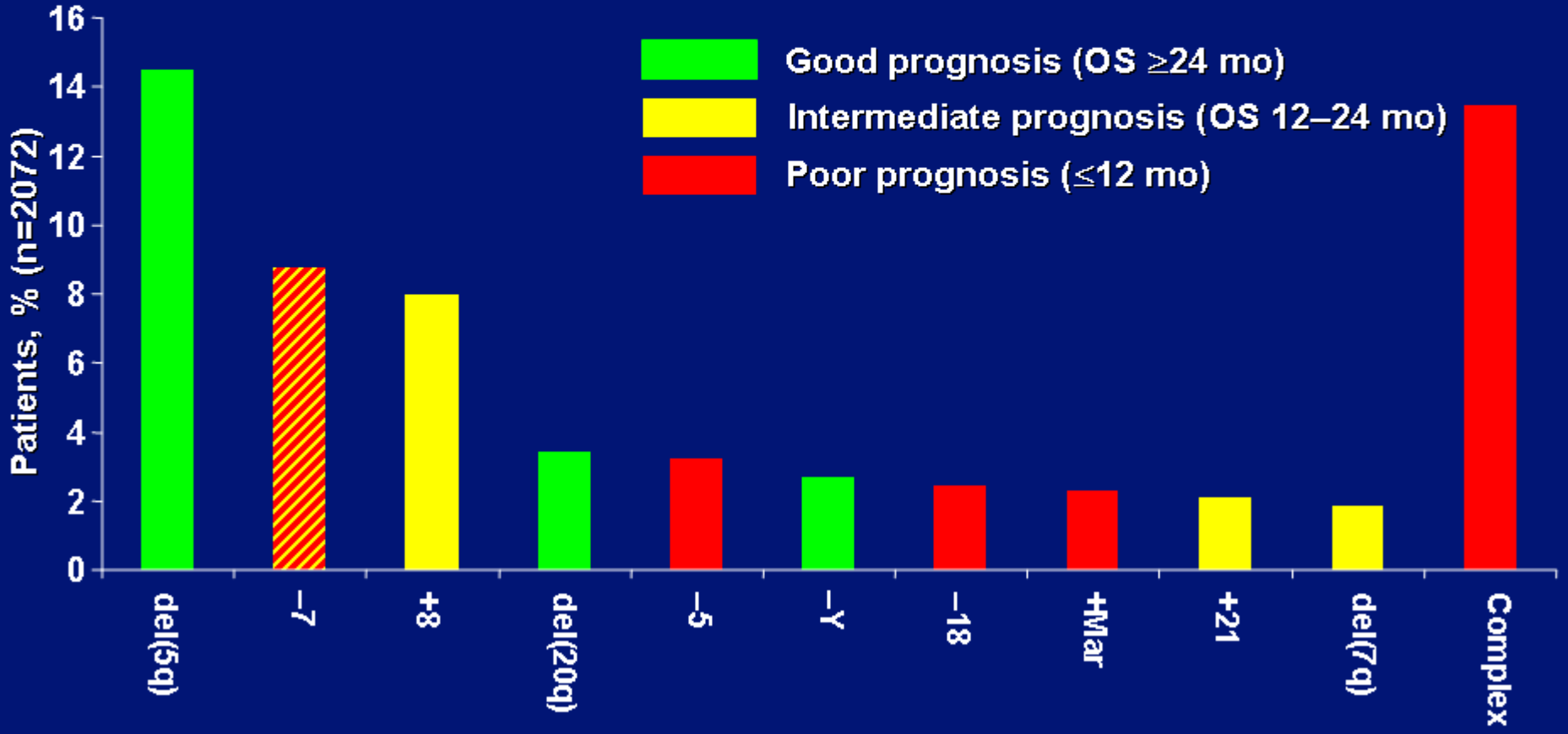
Frequency of Common Cytogenetic Abnormalities in 2124 MDS Patients

- 2124 MDS patients from 8 institutions in Austria and Germany
  - 2072 had successful cytogenetic analyses
  - 1080 (52.1%) had clonal cytogenetic abnormalities



Haase D et al. *Blood*. 2005;106:232a [abstract 787]

MDS Prognosis: The IPSS

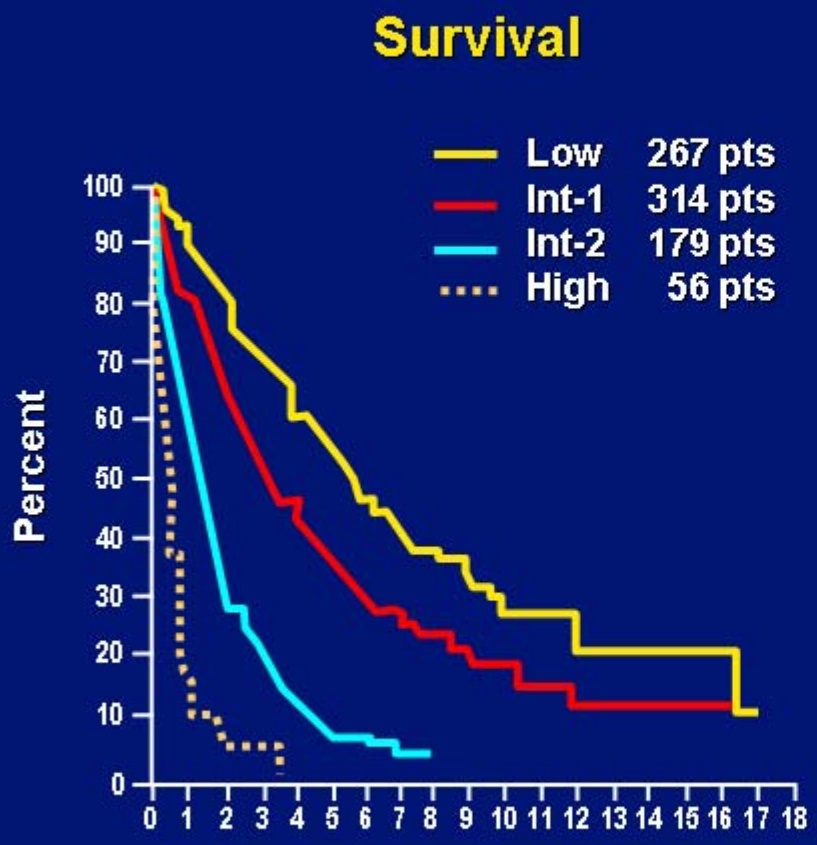
- Number of cytopenias (RBC,WBC,PLTS)
- Blast percentage in marrow
- Marrow chromosome analysis
  - Good
  - Intermediate
  - Poor

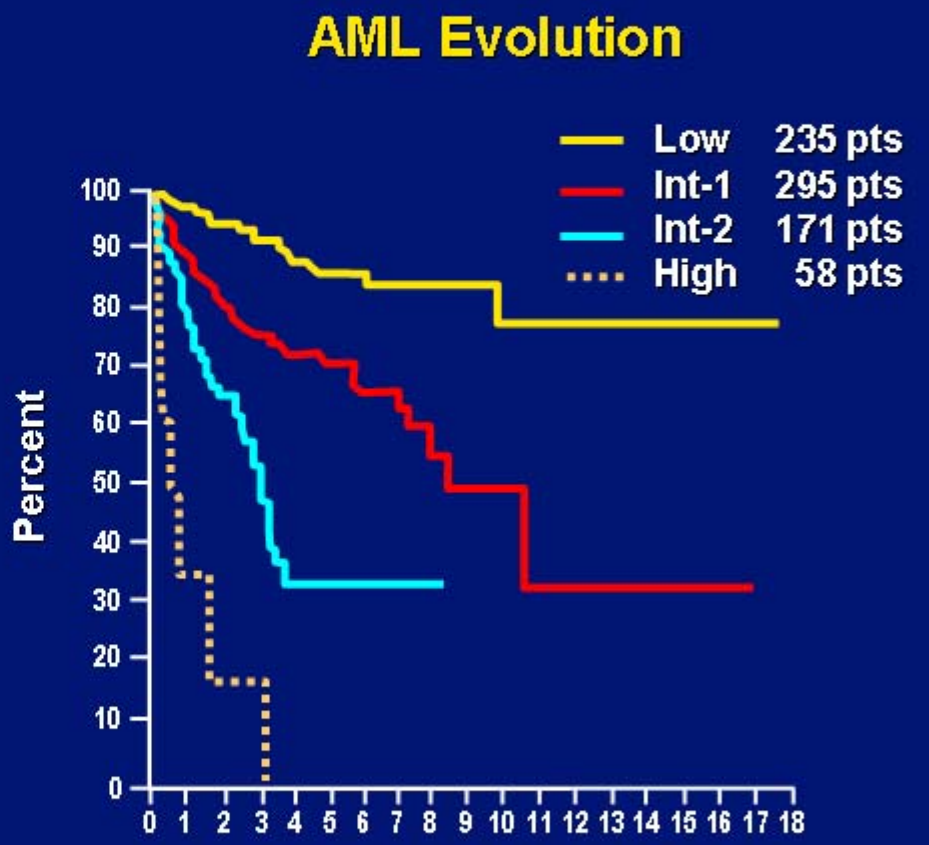
INTERNATIONAL PROGNOSTIC SCORING SYSTEM

		SCORE
Number of cytopenias		
Hb <100 ANC <1.5 Plt < 100	0-1	0
	2-3	0.5
Marrow blast count		
5-10%		0.5
11-20%		1.0
> 20 %		1.5
Cytogenetics		
Good		0
Intermediate		0.5
Poor		1.0

LOW=0 INT-1=0.5-1.0 INT-2=1.5-2.0 HIGH≥2.5

Survival and AML Evolution by IPSS Classification





MDS: PATHOGENESIS

INITIATING EVENT	→	SECONDARY EVENTS	→	PROMOTIONAL EVENTS

UNCOMMON

- **Inherited/acquired gene mutations**
  - -NF1
  - -AML-1
  - -DKC

Acquisition of typical cytogenetic abnormalities

(5, 7, 3q, +8, 11q)

*****CUMULATIVE ENVIRONMENTAL EXPOSURES*****

Microscopic DNA Changes

Involving one or more of:

- -Ras (link → chr 7)
- -p53 (link → 17p-)
- -gene methylation

COMMON

Complex genetic polymorphisms

- -DNA repair
- -Carcinogen metabolism
- -immune regulation

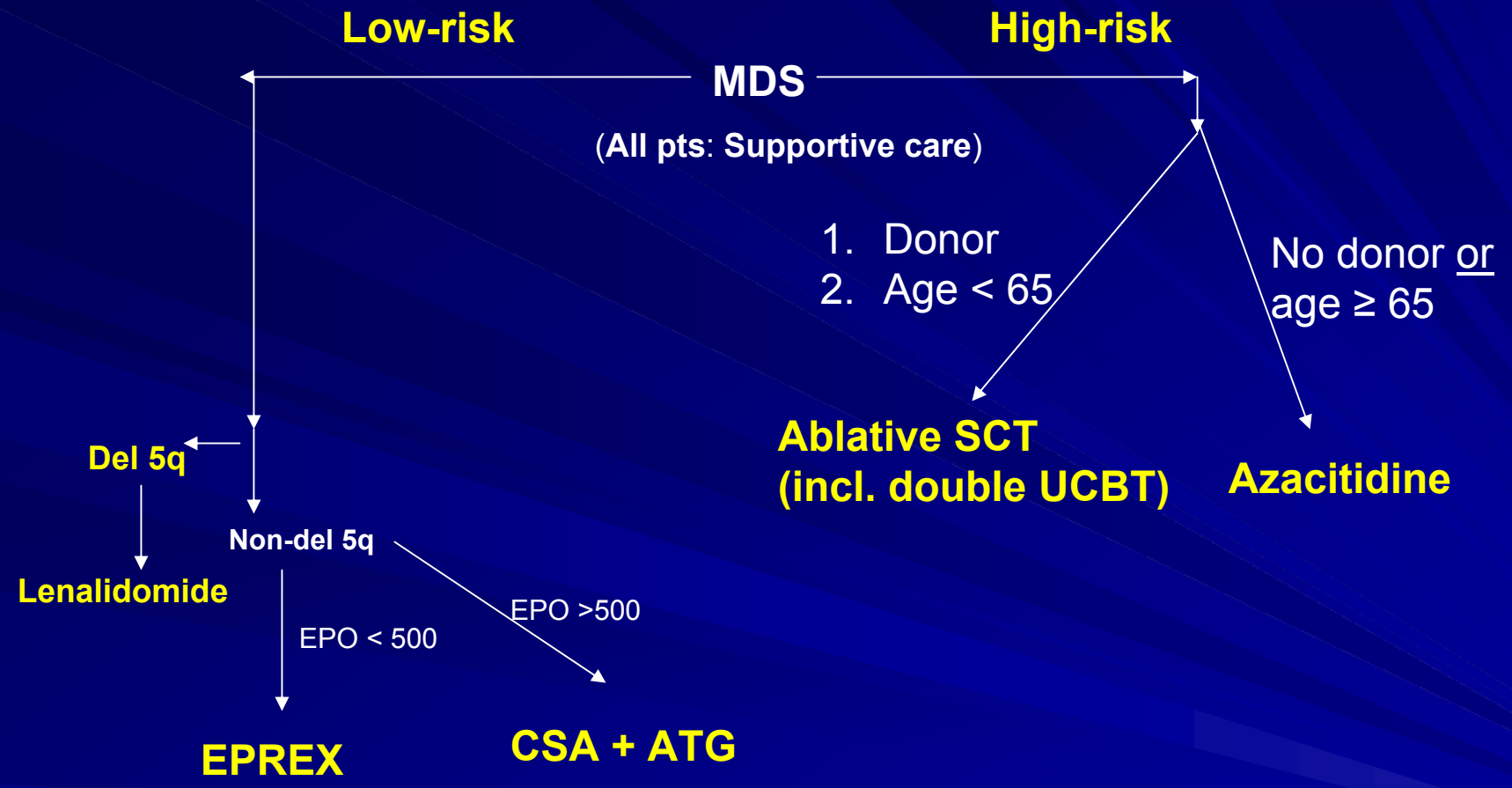
MDS:
Key Environmental Exposures

- Key modifiable risk → smoking (OR 2.4)
- Gasoline, oil & exhaust exposure (OR 11.4)
- Pesticides, herbicides & fertilizers (OR 2.1-5.3)
- Benzene exposure (OR 3.73)
- Hair dye use (OR 1.46)

MDS: High-risk professions/surroundings

- Health care professional (OR 10.0)
- Involvement with benzene
  - Painting (building & renovations)
  - Gas/oil refinery workers, machine oper'tors
  - Pulp and paper mills
  - Tire/rubber plants
  - Plastics/Detergents
  - Agricultural workers
  - Automotive, railway, dock, barge workers
  - Textile/stone/cereal dust

MDS Treatment Algorithm 2012



Case 1

71 y.o. ♀

- 1-year Hx of progressive macrocytic anemia
- Hb 66 (MCV 127), neutropenia (ANC 1.2)
- Hx of a sarcoma of left leg 10 yrs previously → surgery + RT
- BM: Dysplastic/hypolobated megakaryocytes
- Karyotype: del(5q) plus other abnormalities

Case 1

- Rx: Lenalidomide (Revlimid) 10 mg x 21/28d
- Moderate thrombocytpenia
- Dose-reduced to 5 mg/d x 21/28 d
- RBC-independent for the past 3 1/2 years

Lenalidomide for del(5q) MDS: Key Points

- Immunomodulatory agent
- Mechanism of action not well-understood
- Erythroid response in low-risk MDS ~25%
- Response rate much higher in del(5q) [75%]
- Median duration of response 2.2 yrs
- Adverse effect: ↓ANC/Plts (predicts response!)
- Thrombogenic →DVT/PE ± arterial events

Case 2

75 y.o. ♂

- Routine CBC: Hb 129, WBC 2.7, Plt 140
- BM: Hypocellular with 26% blast cells
- Normal karyotye → "MDS/AML"
- PMHx: 50-yr Hx of smoking; angioplasty of femoral artery 15 yrs previously; known asymptomatic aortic stenosis

Case 2

Date	Treatment	Hb	ANC	Plt
Jun-09	Azacitidine s.c. x 7/35d	116	0.8	119
Aug-09		123	1.5	269
Oct-09		125	2.3	156
Aug-10	BM: 6% blasts	134	1.7	253

* Completed 32 cycles of Azacitidine – first RBC/Plt transfusions Dec 2011

Azacitidine in High-risk MDS: Key Points

- ~50% of pts have hematologic improvement
- CR rate only 10-15%
- CBC may deteriorate for 1-3 cycles, even in responders→ supportive care
- Treatment should be continued until progression of MDS documented
- Survival is prolonged in ALL patients compared to supportive care [UNLESS PD]

Case 3

49♀

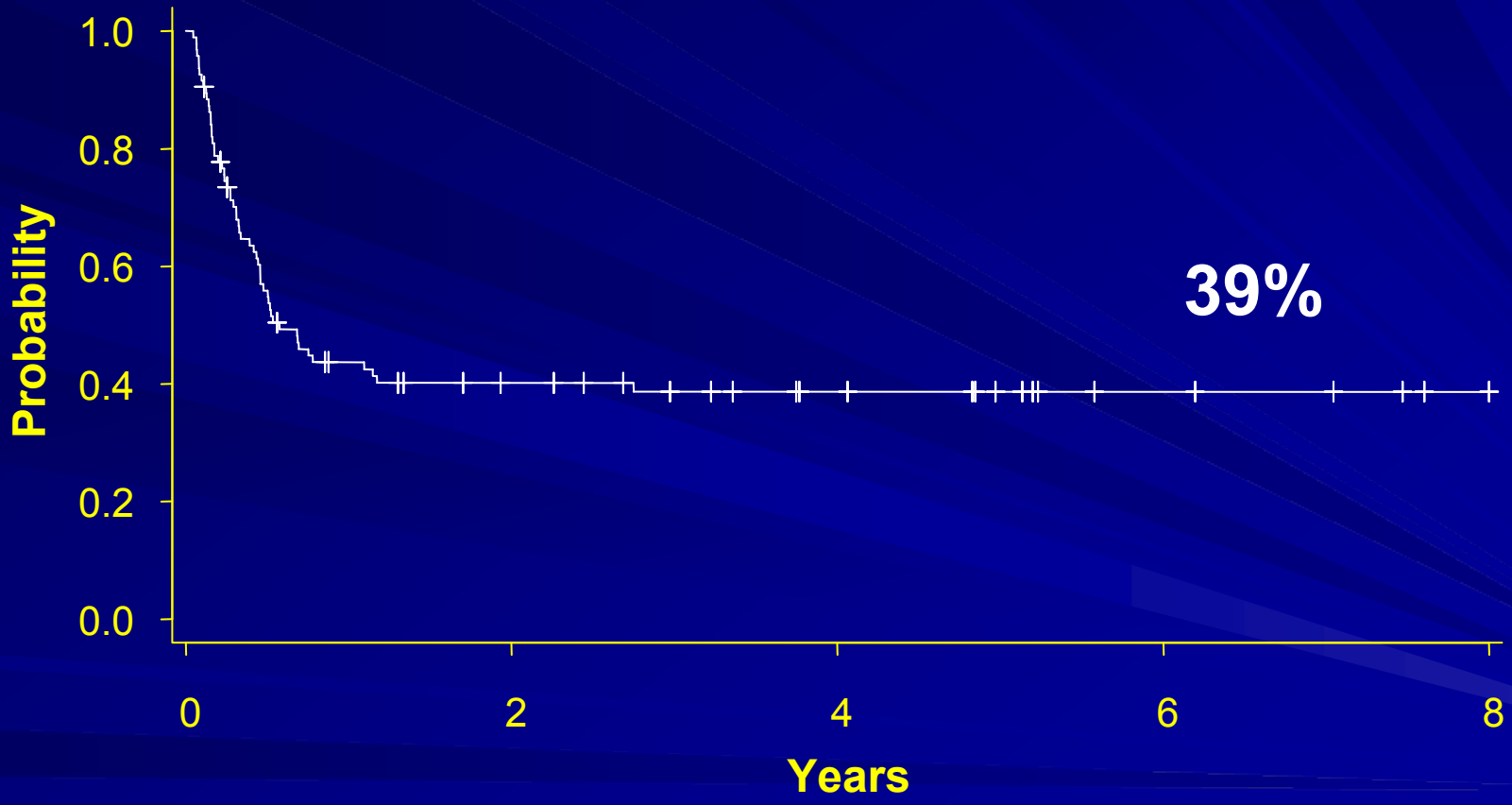
- Dental hygienist
- 2 month Hx of fatigue, SOBOE, oral ulcers
- CBC: Hb 78, ANC 0.9 and Plt 11
- BM: Hypocellular
  21% PNH clone
  Abnormality of chromosome 10q

- AA/PNH/MDS “Overlap syndrome”

Case 3

- No sibling or UD matches identified
- 2 partially matched cord blood units found
- Nov/2011: double cord blood transplant
- Mild acute GVHD
- **Follow-up:** Normal blood counts and no meds; approaching 4 years post-transplant

Allogeneic SCT for Primary MDS: Event-Free Survival (n=95)



Umbilical Cord Blood SCT for High-risk MDS: Key Points

- Transplantation is the ONLY curative treatment for MDS
- Cord SCT does not necessitate rigorous HLA-matching
- Option for ethnic minorities
- GVHD is common (?universal) but treatable
- Engraftment is slow, infections more common
- Double cords produce better survival despite more GVHD although only one cord survives

Case 4

51 y.o. ♂

- March 2011: ER → pleuritic chest pain
- CT scan: pulmonary emboli
- CBC: Hb 98, ANC 1.8 and Plt 53
- BM exam: erythroid dysplasia, ↓ megas and normal karyotype→ "MDS"
- Past Medical/Social Hx: no hospitalizations but worked as greenskeeper for municipality spraying trees with pesticides

Case 4

- Past 20 years employed as pipefitter working regularly on gas lines & in Victoria shipyards in fuel storage holds
- Younger brother was found to have incidental pancytopenia at age 35
- BM exam: hypocellular MDS
- Observed for two years with no hematologic Δ
- Died after developing rapidly progressive respiratory failure due to pulmonary fibrosis

REPEAT DIAGNOSTICS

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North Vancouver, BC V7M 1A5
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info@repeatdiagnostics.com

FAX: 778-340-1144
www.repeatdiagnostics.com

TELOMERE LENGTH MEASUREMENT — PATIENT REPORT

CLIENT INFORMATION

Ordering Dr:	Dr. T. Nevill				
Institution:	Vancouver General Hospital	City:	Vancouver	State/Province:	BC

SAMPLE INFORMATION

Name:		MR# / ID#:	03843483	Acct:		Spec:		Sex:	M	Age:	51

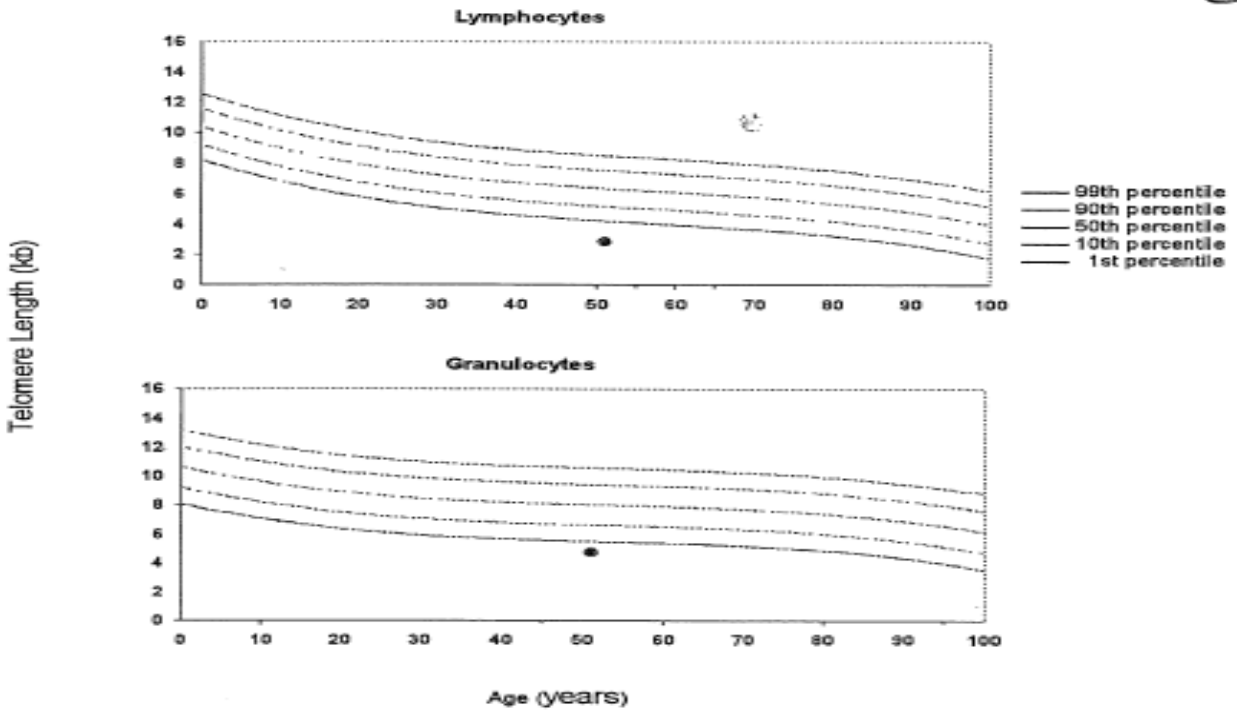
Sample Dates (mm/dd/yy):

Draw:	07/04/11	Received:	07/04/11	Processed:	07/11/11	Resulted:	07/14/11

Lymphocytes			Granulocytes		
MTL (kb)	MTLN (kb)	INT	MTL (kb)	MTLN (kb)	INT
2.9	6.4	VL	4.8	8.0	VL

MTL = Patient Median Telomere Length
MTLN = Normal MTL at age (50th percentile)
INT = Telomere length interpretation

VH = Very High (≥ 99th percentile)
H = High (≥ 90th and < 99th percentile)
N = Normal (≥ 10th and < 90th percentile)
L = Low (≥ 1st and < 10th percentile)
VL = Very Low (<1st percentile)



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Case 4

- MARKED telomere shortening (<1st perc'tile)
- Genetic testing: Dyskeratosis congenita
- DC is inherited disorder (X-linked/Auto. Dom)
- Often (but NOT invariably) characterized by oral leukoplakia, skin rash, nail Δ's, bone marrow failure, pulmonary fibrosis, liver dysfunction & predisposition to malignancies (esp. sq. cell)
- Environmental exposures may affect phenotype
- **In patients with MDS/Marrow failure, pay attention to a family history of low counts!**

QUESTIONS?