Myelodysplastic Syndromes

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Outline

- Introduction and classifications
  - Epidemiology
  - Presentation
  - Workup
- Diagnosis
- Prognosis

Your Speaker

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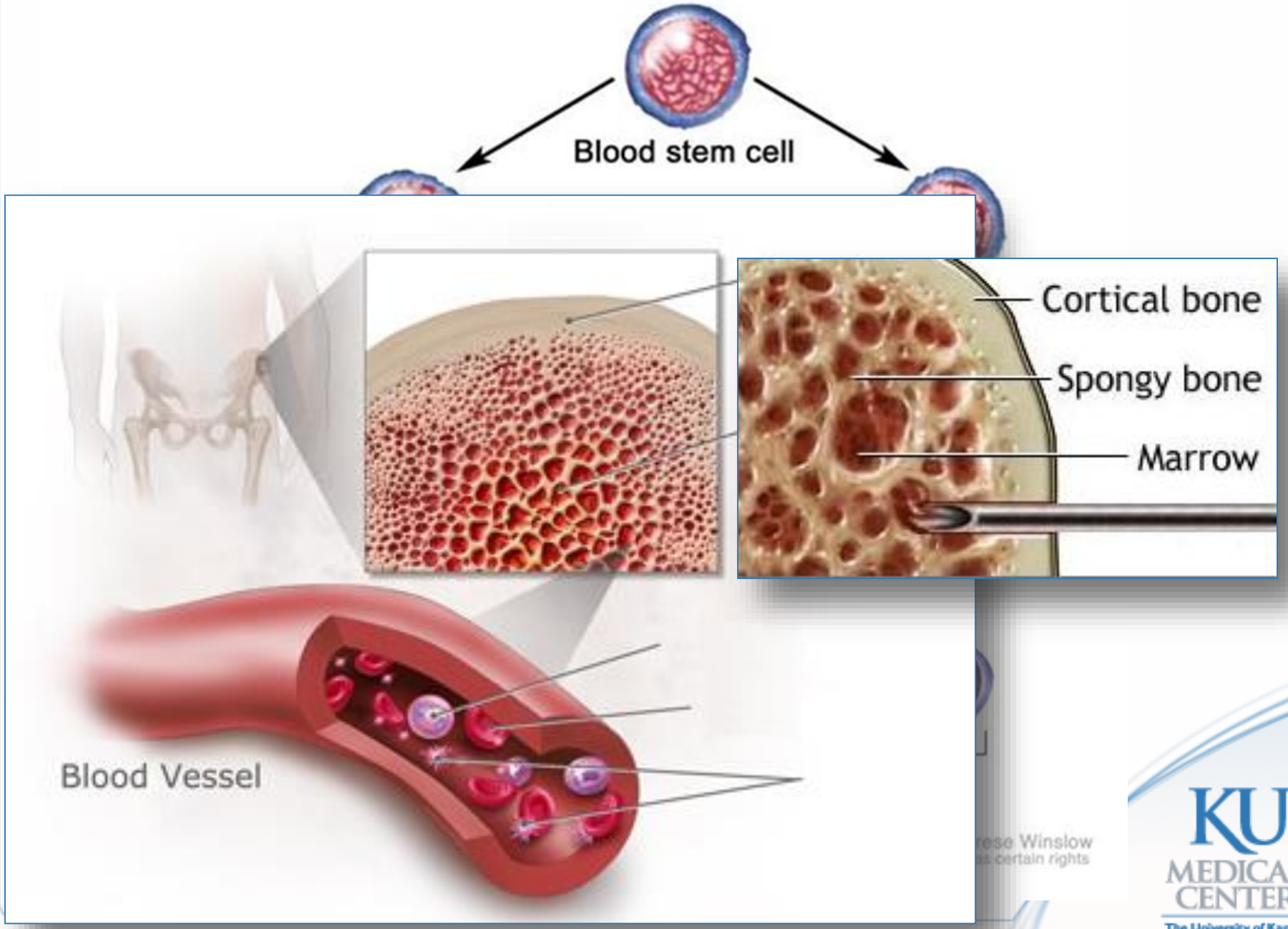

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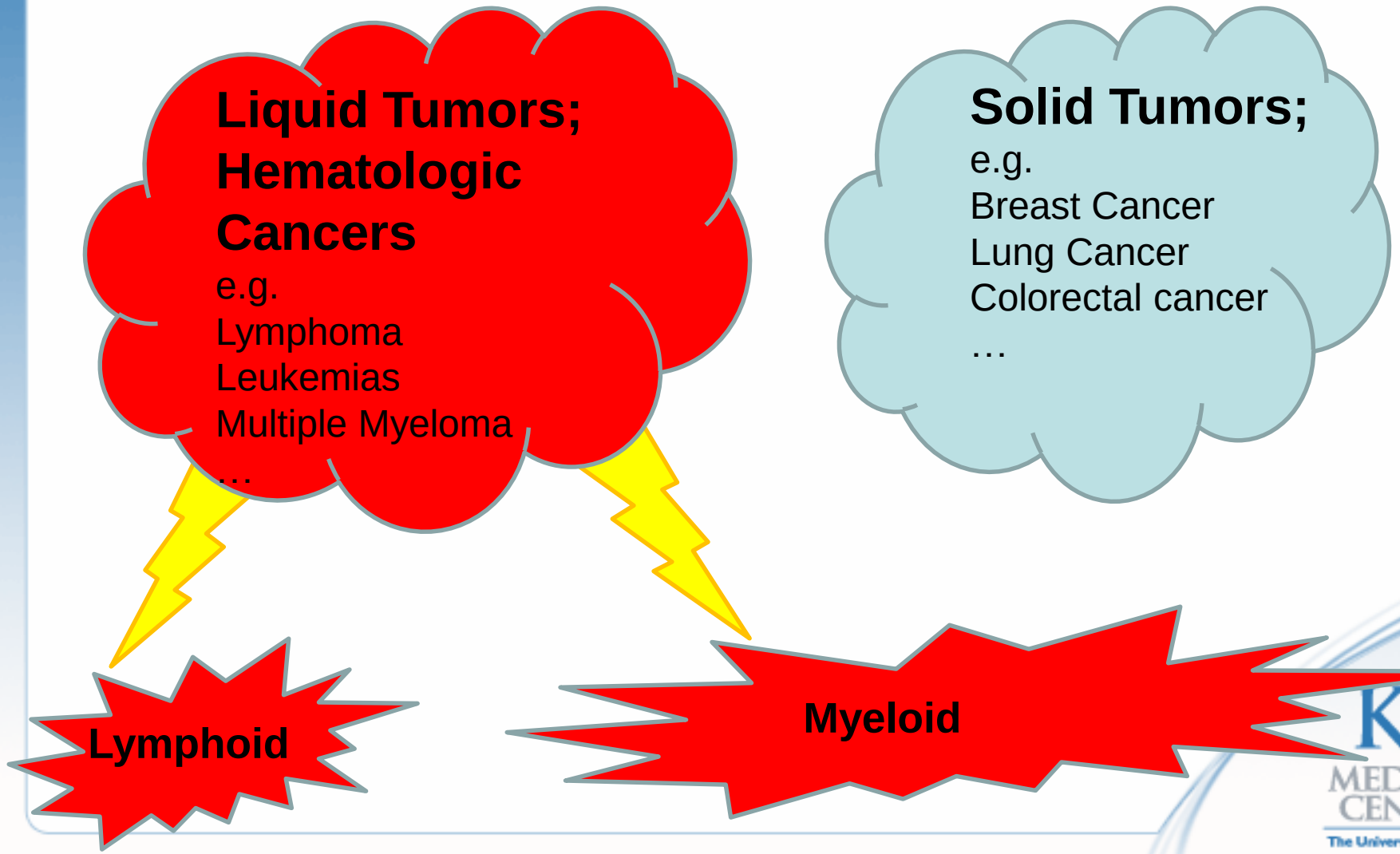
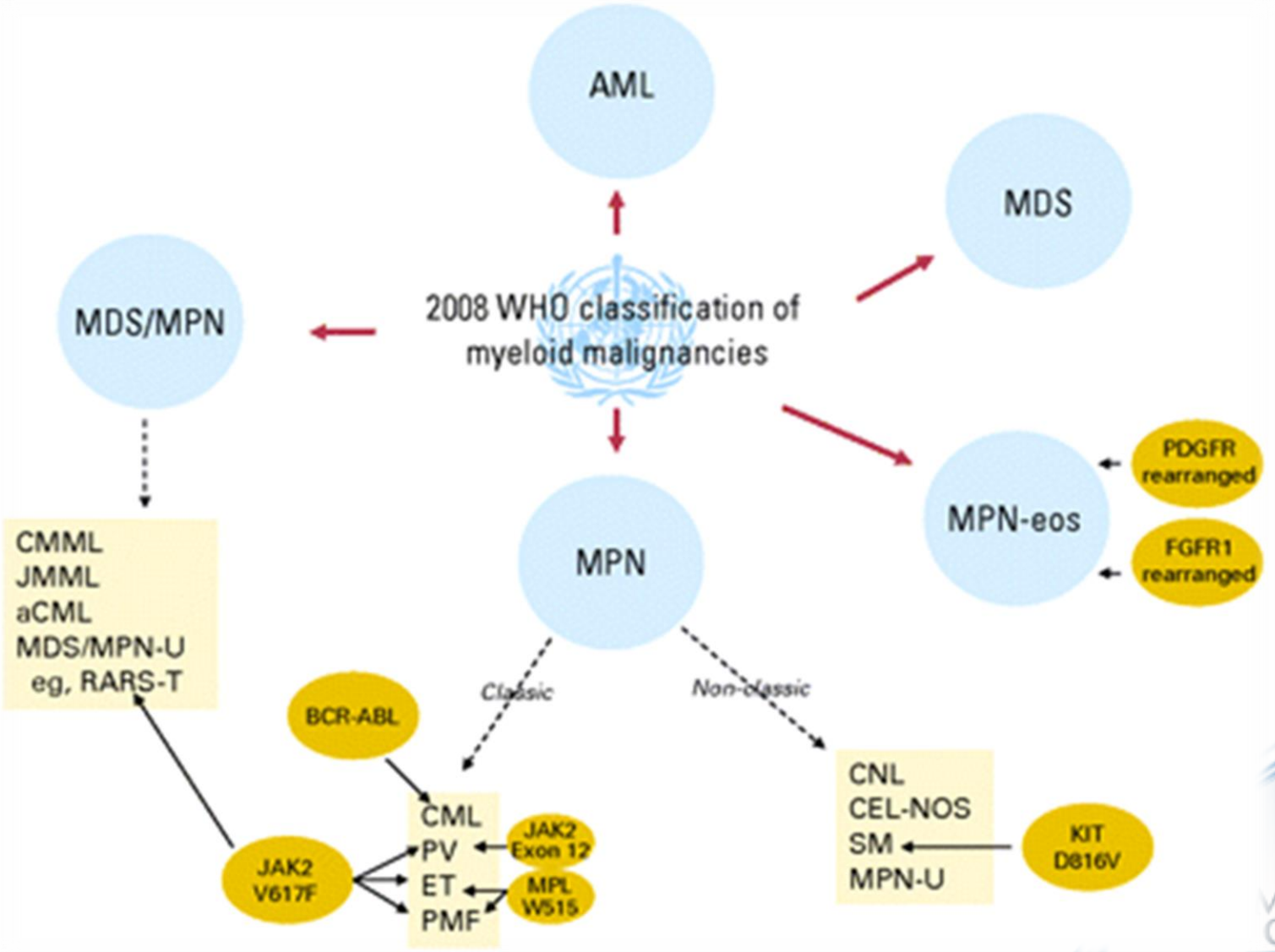
Classification of Human Cancers



Classification of Myeloid Cancers



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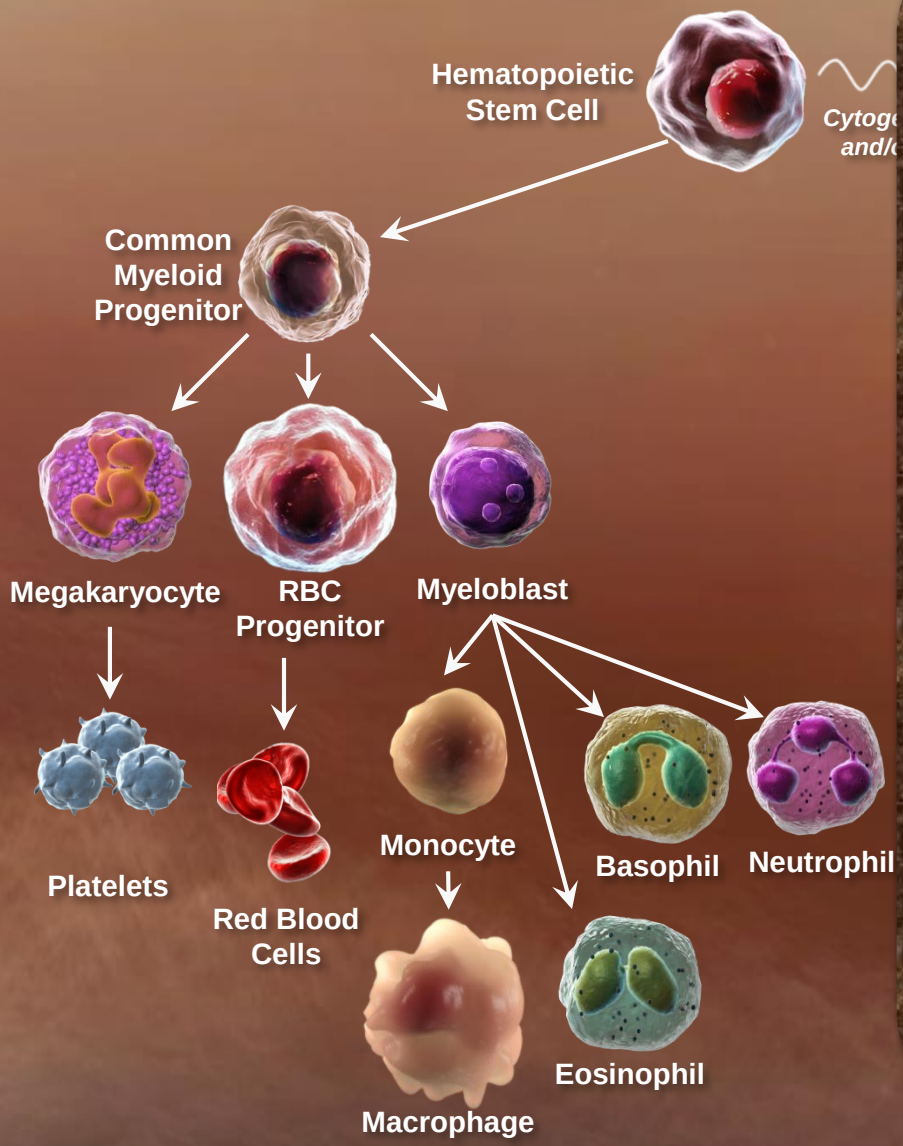
MDS Progression to Acute Myeloid Leukemia



1. Lichtman MA, et al. Williams Hematology. New York, NY: McGraw-Hill; 2006. 2. http://daley.med.harvard.edu/assets/Willy/haematopoiesis.jpg.
3. Blood. 2013;121(19):3811-3817 Chan SM, Majeti R. *Int J Hematol.* 2013;98:648-657.

MDS is Cancer

A Syndrome…

A heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective hematopoiesis.

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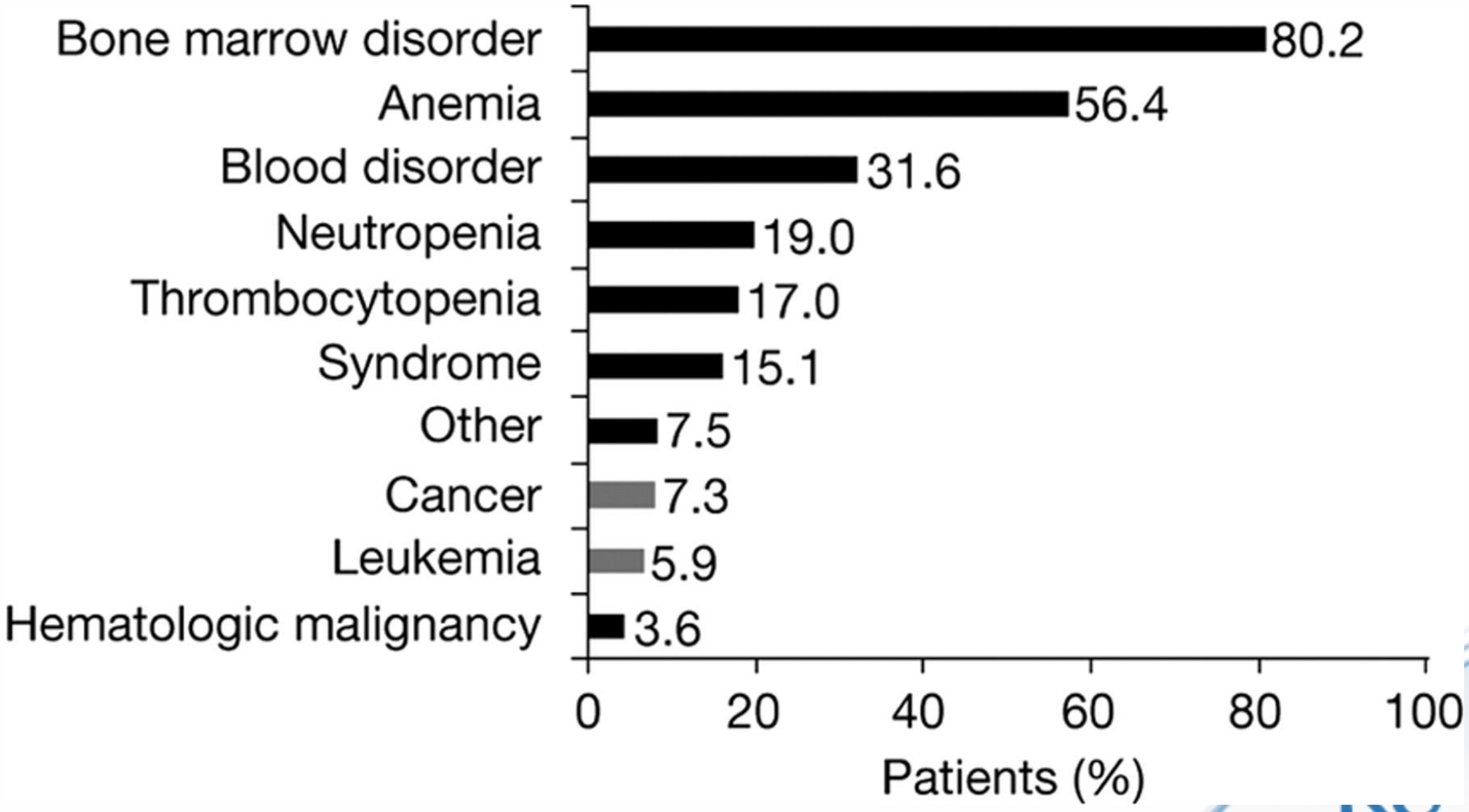
How myelodysplastic syndrome was first described to patients.

Note that patients could select more than one answer.



Sekeres M A et al. The Oncologist 2011;16:904-911

Myelodysplastic Syndromes

- Recognized for over 50 years, termed Preleukemia, Smoldering Leukemia, Oligoblastic Leukemia, and Refractory Anemia.

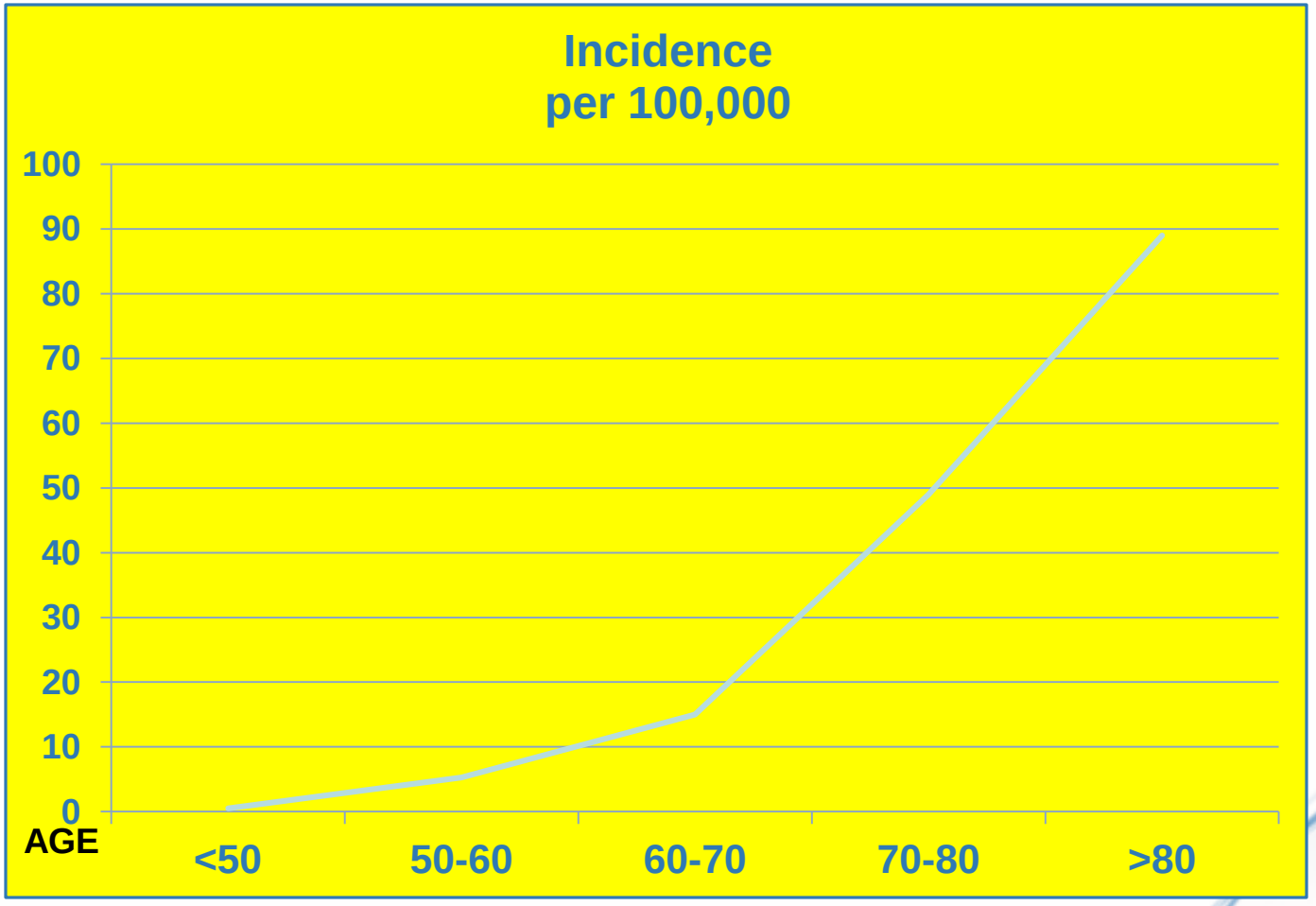
- Denotes a variable risk of progression to:…
    - BM failure
    - AML:
  - Severe cytopenia, increased blasts, or cytogenetic abnormalities correlate with poor outcomes not different from acute leukemia.
  - Lack of these features is associated with long survival.

Epidemiology

- The precise incidence of de novo MDS is not known. Believed to be underestimated.
- 2004 SEER data
  - Estimated to be 3.3 (2-12.6) per 100,000
  - >60,000 individuals in USA
  - >10,000 new cases /year
  - Overall relative 3-year survival was 45%.
- The median age is ≥65 years, with a male predominance
- Incidence increases with age

Rollison D et al. Blood. 2008;112(1):45.
Williamson PJ, et al. Br J Haematol. 1994;87(4):743.

Epidemiology



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Clinical Presentation and Diagnosis

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Clinical Presentation and Diagnosis

- No specific associated symptoms or signs.

- Most diagnoses are made subsequent to abnormal routine laboratory testing showing quantitative changes of one or more blood elements .

Definitions:

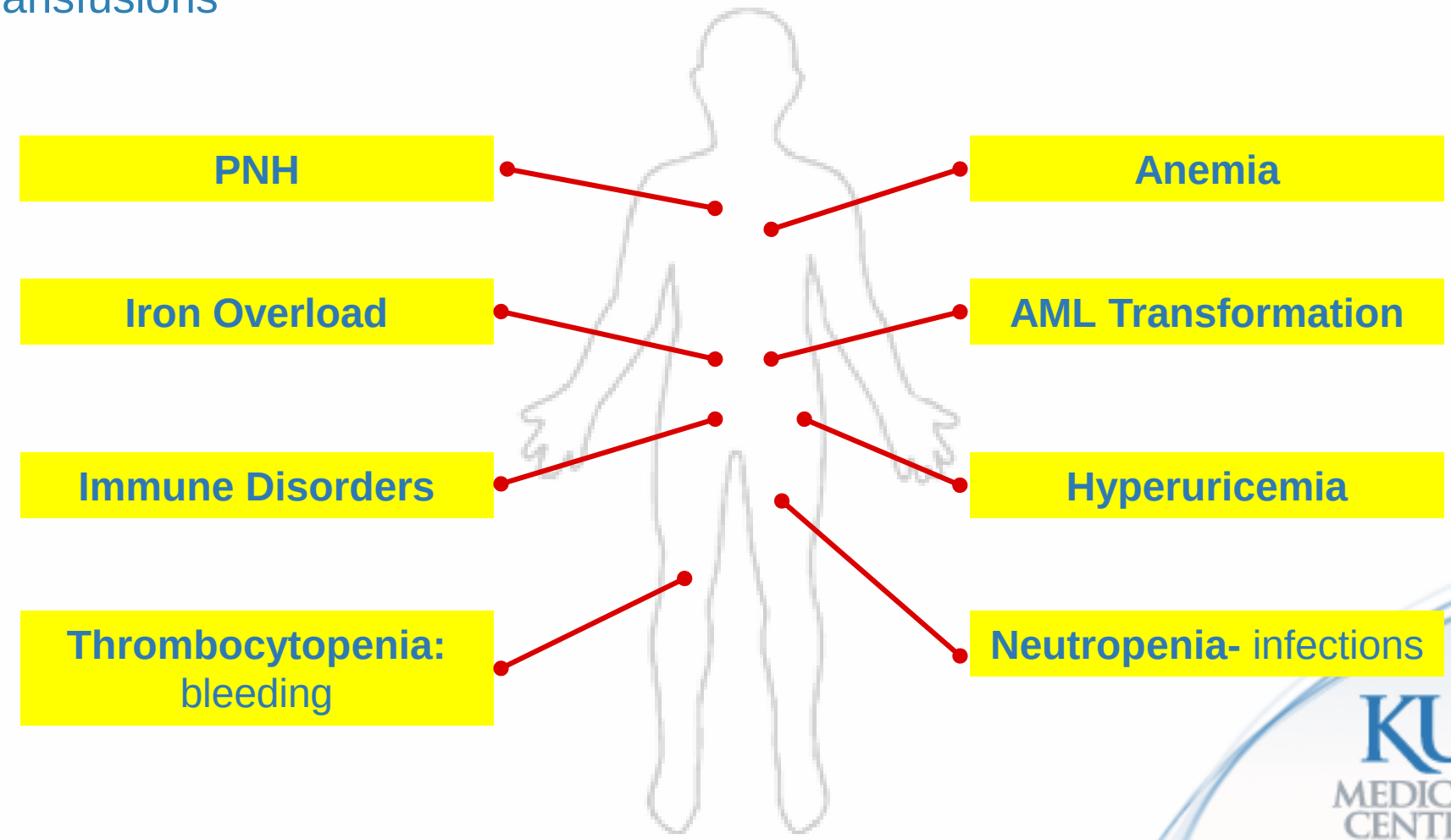
ANEMIA : decreased Red Blood Cells /Hemoglobin

THROMBOCYTOPENIA: decreased Blood Platelets

NEUTROPENIA: decreased White Blood Cells (Neutrophils)

Clinical Features of MDS

Anemia is hallmark - challenging to treat, many will require RBC transfusions



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Clinical Presentation and Diagnosis

- Symptoms are related to the degree of anemia, less commonly due to thrombocytopenia, and neutropenia.
- Associated constitutional symptoms, or autoimmune deregulation are uncommon.

Clinical Presentation and Diagnosis

- Findings at time of diagnosis:
  - Anemia is almost uniformly present: 95-100%
  - Pancytopenia 50 %
  - Isolated neutropenia, thrombocytopenia, or monocytosis in the absence of anemia: Less than 5 %

Predisposing Factors

- Advanced age
- Mutagen exposure:
  - Chemotherapy
    - Alkylators
    - Topoisomerase II inhibitors
  - Radiation exposure
  - Hematopoietic cell transplantation
  - Environmental
    - Benzene
    - Tobacco use: (HR 1.68, 3.17)
- Other primary hematologic disorders:
  - Aplastic anemia
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Myloproliferative disorders
- Heridatory predisposition:
  - DNA repair defects
  - Congenetal and genetic disorders
- Obesity (HR 1.15 and 2.18)

Ma X, et al. Am J Epidemiol. 2009;169(12):1492.

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Diagnosis and Classification

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Diagnosis and Classification

- Careful evaluation of the peripheral smear.
- Evaluation of the duration of abnormal blood counts and other potential causes
- Exclusion of confounding factory: nutritional deficiencies, co-morbidities, chronic infections or autoimmune disorders.

Diagnosis and Classification

- Diagnosis is confirmed by a BM biopsy and aspirate.
-
  - Identify and quantify dysplastic features, and involved lineages.
  - Assess marrow cellularity, fibrosis, and topography
  - Sample for cytogenetic studies
  - Molecular testing, mutation analysis and DNA sequencing
  - Classification
  - Has prognostic relevance.

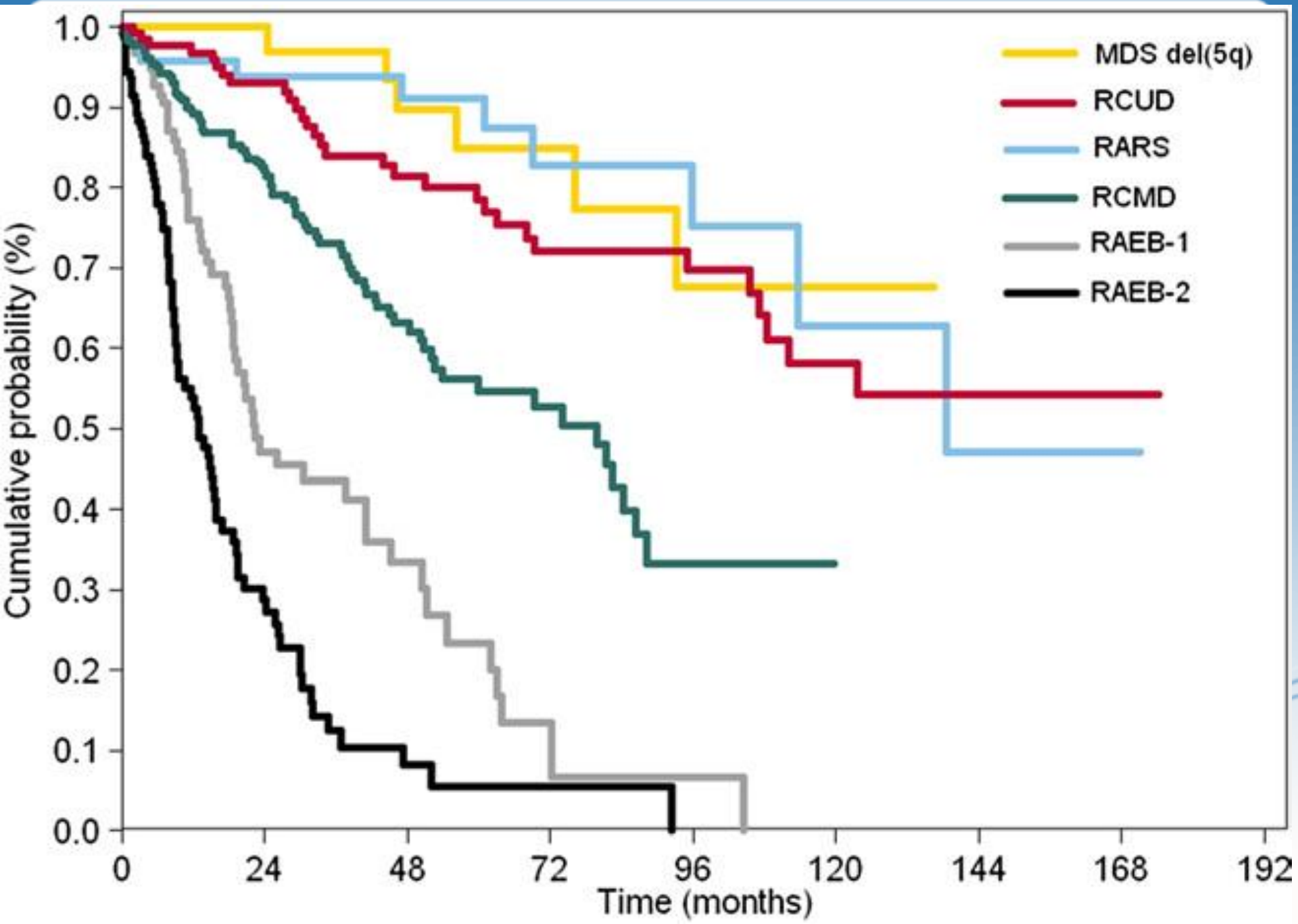
Table 1. FAB Classification of Myelodysplastic Syndromes

	Peripheral Blood		Bone Marrow		
Category	Monocytes (10^9/L)	Blast (%)	Ringed Sideroblasts (%)	Blast (%)	Auer Rods
Refractory anemia (RA)	≤1	≤1%	≤15%	<5%	—
RA with ring sideroblasts (RARS)	≤1	≤1%	>15%	<5%	—
RA with excess of blasts (RAEB)	≤1	<5%	Ringed sideroblasts may be seen	5%–20%	—
Chronic myelomonocytic leukemia (CMML)	>1	<5%	Ringed sideroblasts may be seen	0%–20%	—
RAEB "in transformation" (RAEB-t)	≤1	≥5%	Ringed sideroblasts may be seen	21%–30%	+

Bennett JM, et al. Br JHaematol. 1982;51:189–99.

2008 WHO[m] Classification of MDS[n]

Subtype	Blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD)[o]	Single or bicytopenia	Dysplasia in ≥ 10% of one cell line, < 5% blasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia, no blasts	≥ 15% of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), < 1 x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ± 15% ring sideroblasts, < 5% blasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s), ≤ 2%-4% blasts, < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, No Auer rods, 5%-9% blasts
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), 5%-19% blasts, < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia Auer rods, ± 10%-19% blasts
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), < 5% blasts

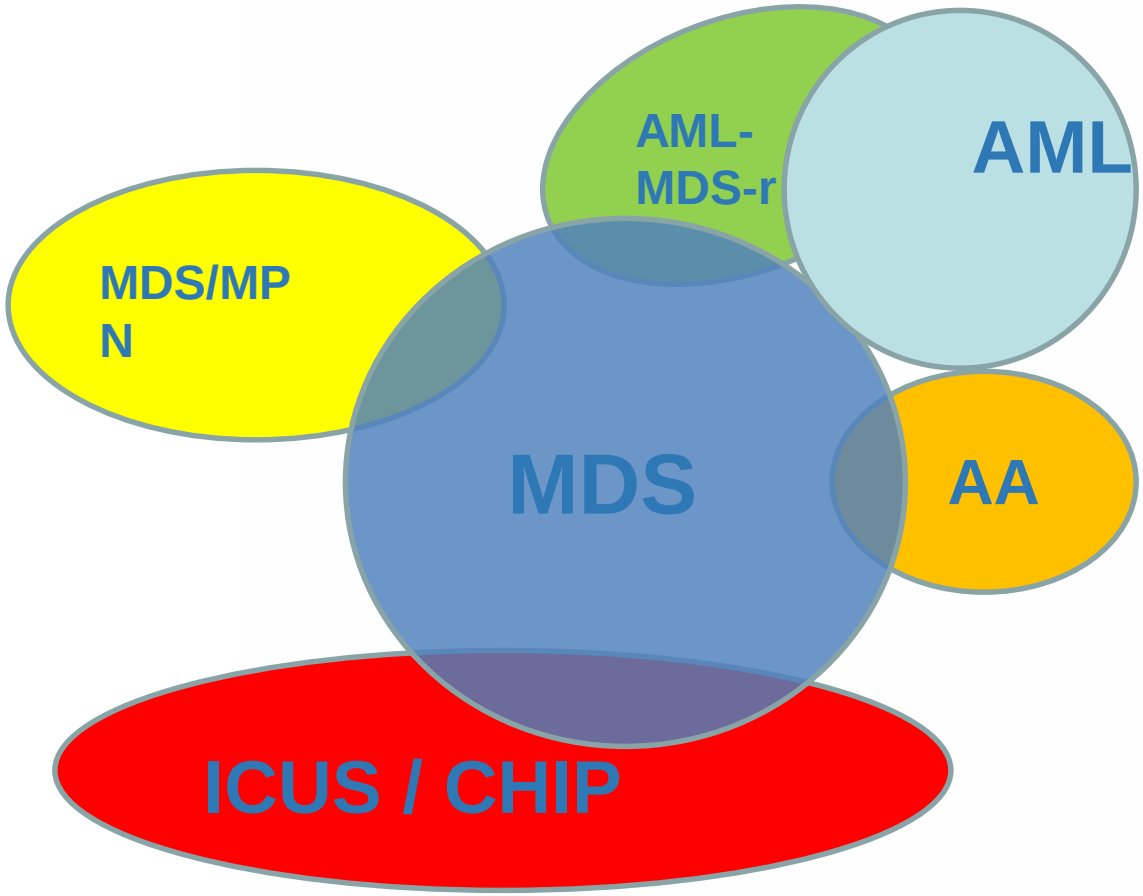

MDS del(5q)
RCUD
RARS
RCMD
RAEB-1
RAEB-2
Cumulative probability (%)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
Time (months)

WHO Classification 2016

MDS subtype	Abbreviation	Notes
MDS with single lineage dysplasia	MDS-SLD	1 dysplastic lineage and 1–2 cytopenias
MDS with multilineage dysplasia	MDS-MLD	2–3 dysplastic lineages and 1–3 cytopenias
MDS with ring sideroblasts	MDS-RS	≥ 15% ring sideroblasts, or ≥ 5% ring sideroblasts if mutation of SF3B1 present
MDS with excess blasts	MDS-EB	5–9% BM blasts (MDS-EB-1) or 10–19% BM blasts (MDS-EB-2)
MDS unclassified	MDS-U	
MDS with isolated del(5q)	-	del(5q) cytogenetic abnormality alone or with 1 additional abnormality other than −7 or del(7q)

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification

Subtype
Chronic myelomonocytic leukemia-1 (CMML-1)
CMML-2
Atypical chronic myeloid leukemia (CML), BCR-ABL1 negative
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN, unclassifiable ('Overlap syndrome')



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Prognosis

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Prognosis

- International Prognostic Scoring System (IPSS) was developed by The International MDS Risk Analysis Workshop.

	Points				
Variable	**0**	**0.5**	**1**	**1.5**	**2**
Marrow blasts (%)	<5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenias†	0 or 1	2 or 3			
IPSS Risk Group					**Score**
Low					0
Intermediate 1					0.5–1.0
Intermediate 2					1.5–2.0
High					2.5–3.5

*Good: normal, del(5q) only, del(20q) only, –Y only; Poor: very complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities.
†Cytopenias: hemoglobin <10 g/dL, neutrophil count < 1.8 × 10^9/L, platelet count < 100 × 10^9/L.

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

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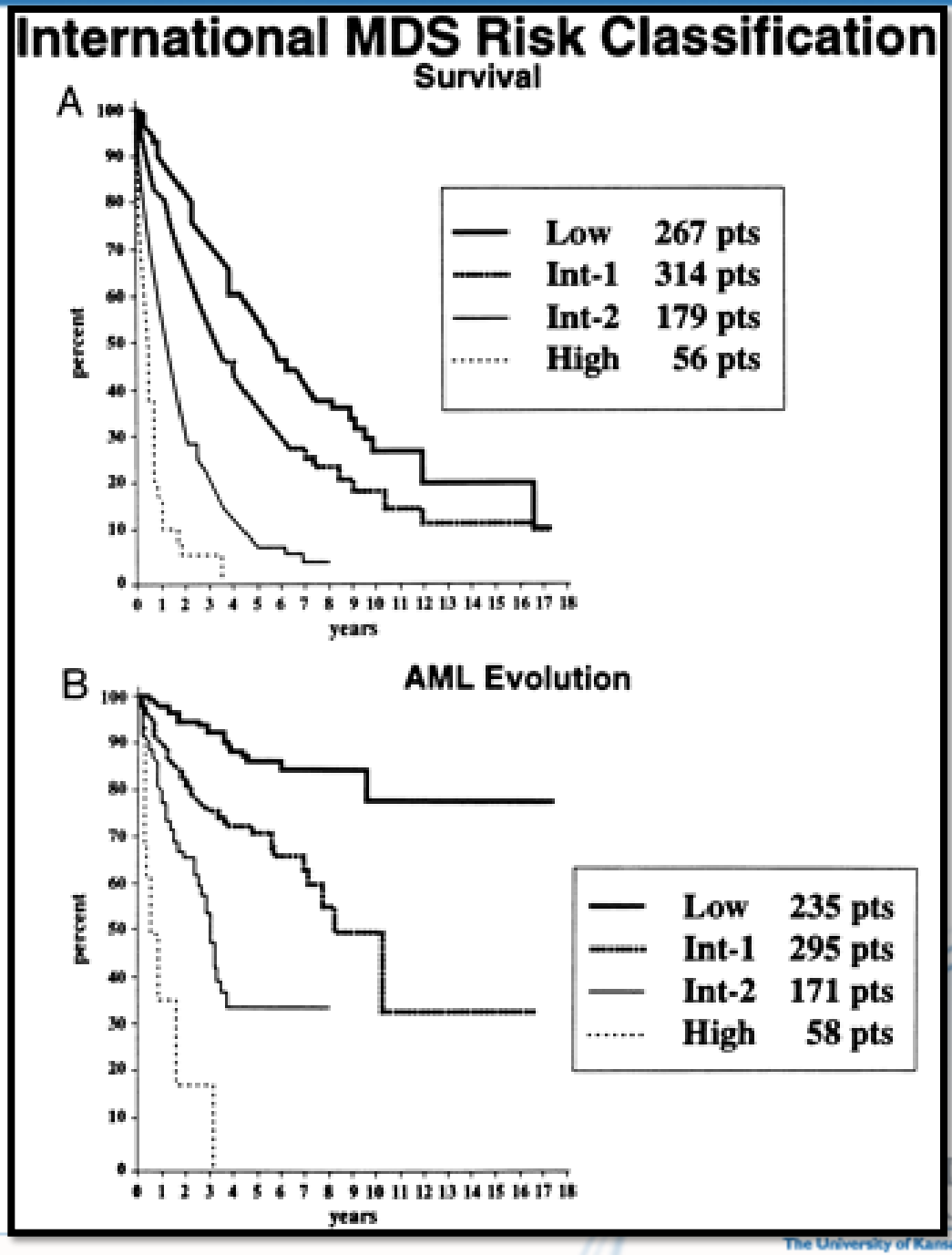
Time in Years	Median OS	AML in 25%
low risk	5.7	9.4
Int-1	3.5	3.3
Int-2	1.2	1.1
high risk	0.4	0.2

Age	Median OS
< 60	11.8
> 60	4.8
> 70	3.9



IPSS-Revised

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					

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

Prognostic subgroups (% patients)	Cytogenetic abnormalities
Very good (4%*/3%^)	-Y, del(11q)
Good (72%*/66%^)	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate (13%*/19%^)	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor (4%*/5%^)	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
Very poor (7%*/7%^)	Complex: >3 abnormalities

Greenberg PL, et al. Blood. 2012 June 27, 2012

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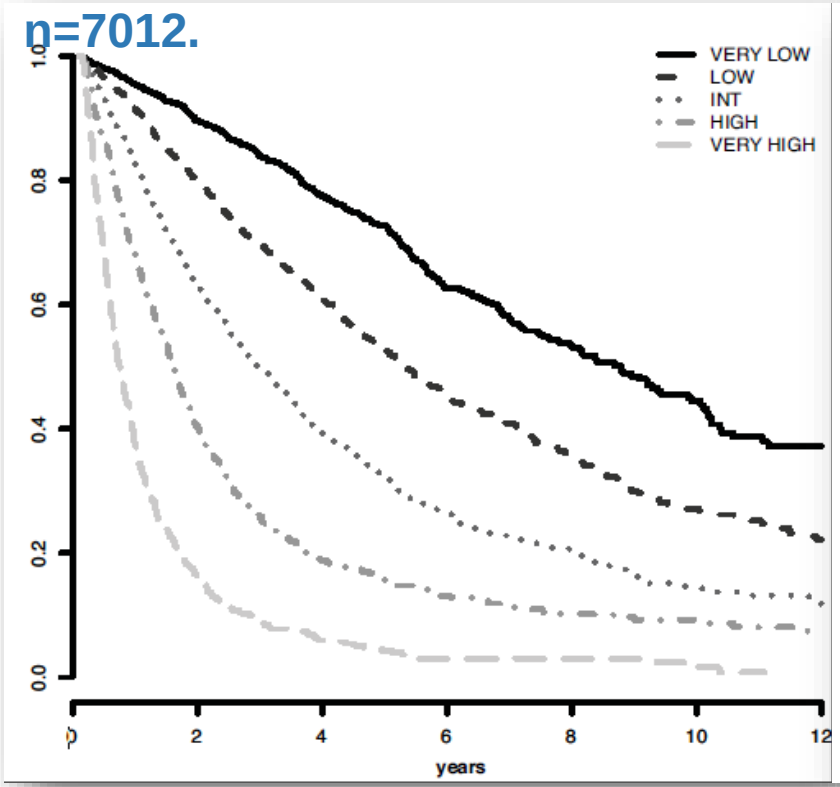
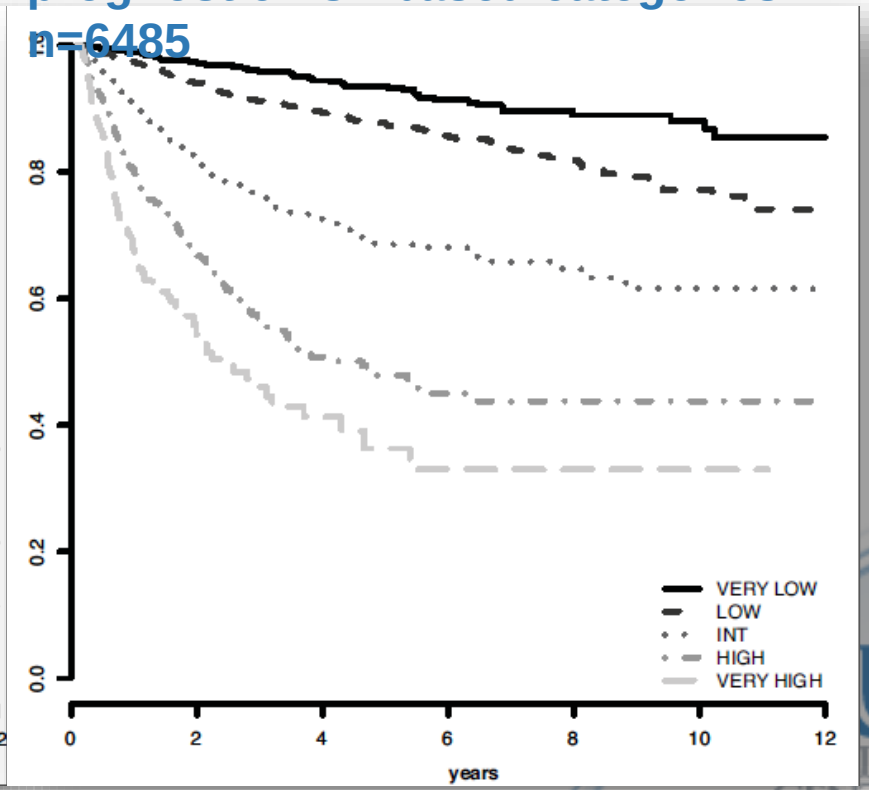
IPSS-R	7012	100	Median OS	AML 25%
Very Low	1313	19	8.8	NR
Low	2646	38	5.3	10.8
Intermediate	1433	20	3.0	3.2
High	898	13	1.6	1.4
Very High	722	10	0.8	0.7

Survival based on IPSS-R prognostic risk-based categories. n=7012.



AML evolution based on IPSS-R prognostic risk-based categories. n=6485



Greenberg PL, et al. Blood. 2012 June 27, 2012

Other Prognostic Models

- **WHO PROGNOSTIC SCORING SYSTEM (WPSS)**
- **MD ANDERSON CANCER CENTER MDS MODEL**
- **Individual risk factors:**
  - Increased age
  - Poor performance status, presence of comorbidities
  - Total WBC >20,000/microL, Eosinophilia (>350/microL) and basophilia (>250/microL)
  - Absolute lymphocyte count <1200/microL
  - Severity of anemia, Transfusion dependence
  - Refractory or severe (<30,000/microL) thrombocytopenia
  - CD34 positivity of bone marrow nucleated cells
  - Gene expression profiling
  - **Increased DNA methylation**
  - Following treatment failure with decitabine
  - Increased expression of the Wilms' tumor gene (WT1)
  - Increased serum beta-2 microglobulin concentration
  - **Mutations of the FLT3, EZH2, or ETV6 genes , Absence of TET2 mutations**
  - Presence of marrow fibrosis

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