Myelodysplastic Syndromes:
Diagnosis and Risk Assessment

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MDS Patient and Family Forum

June 29, 2024

UC San Diego
Moores Cancer Center

mds foundation
the myelodysplastic syndromes foundation, inc.

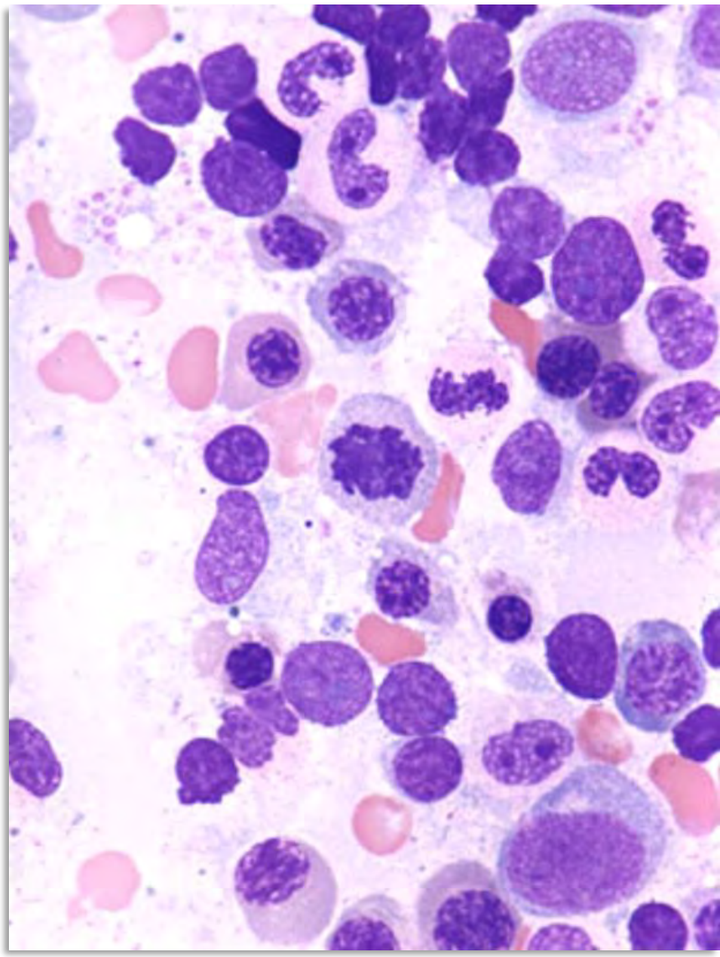
Overview

- Introduction to MDS
- Making the diagnosis
- Disease classifications
- Risk stratification
- Questions and Answers

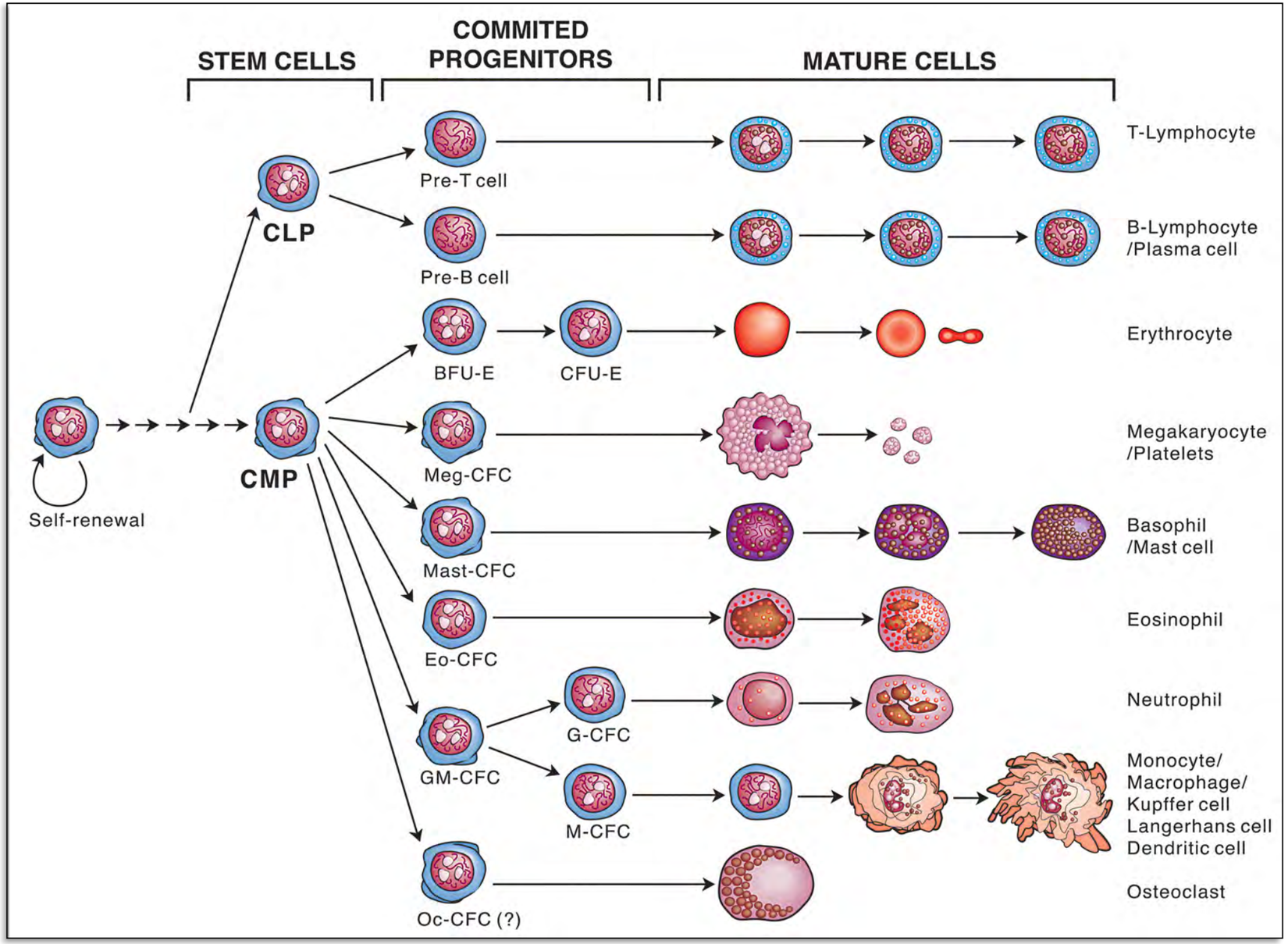
Introduction to MDS

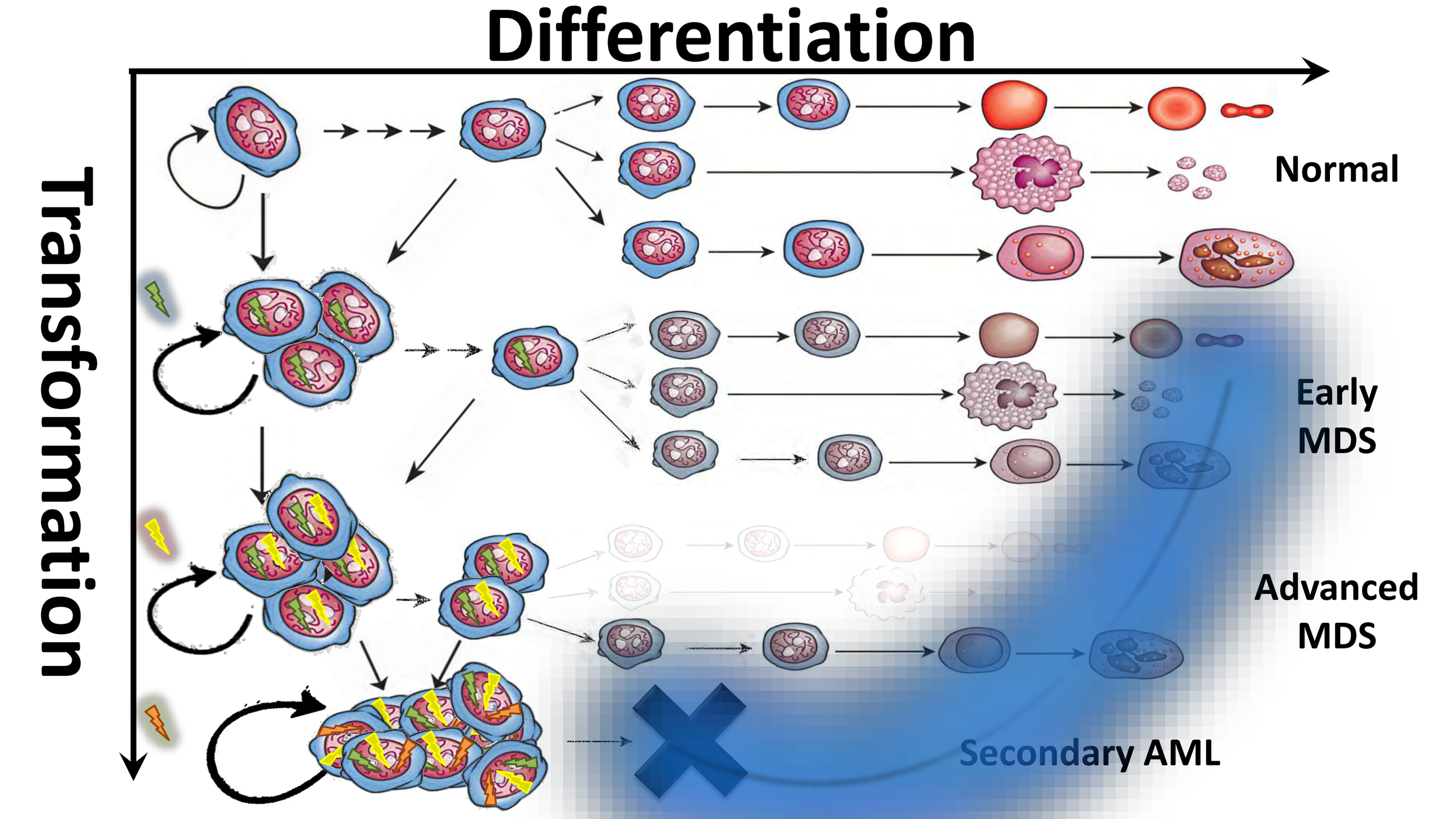
Myelodysplastic Syndromes

- Shared features:
  - Low blood counts
  - Clonal overgrowth of bone marrow cells
  - Risk of transformation to acute leukemia
- Afflicts 15,000 – 45,000 people annually
- Incidence rises with age (mean age 76)



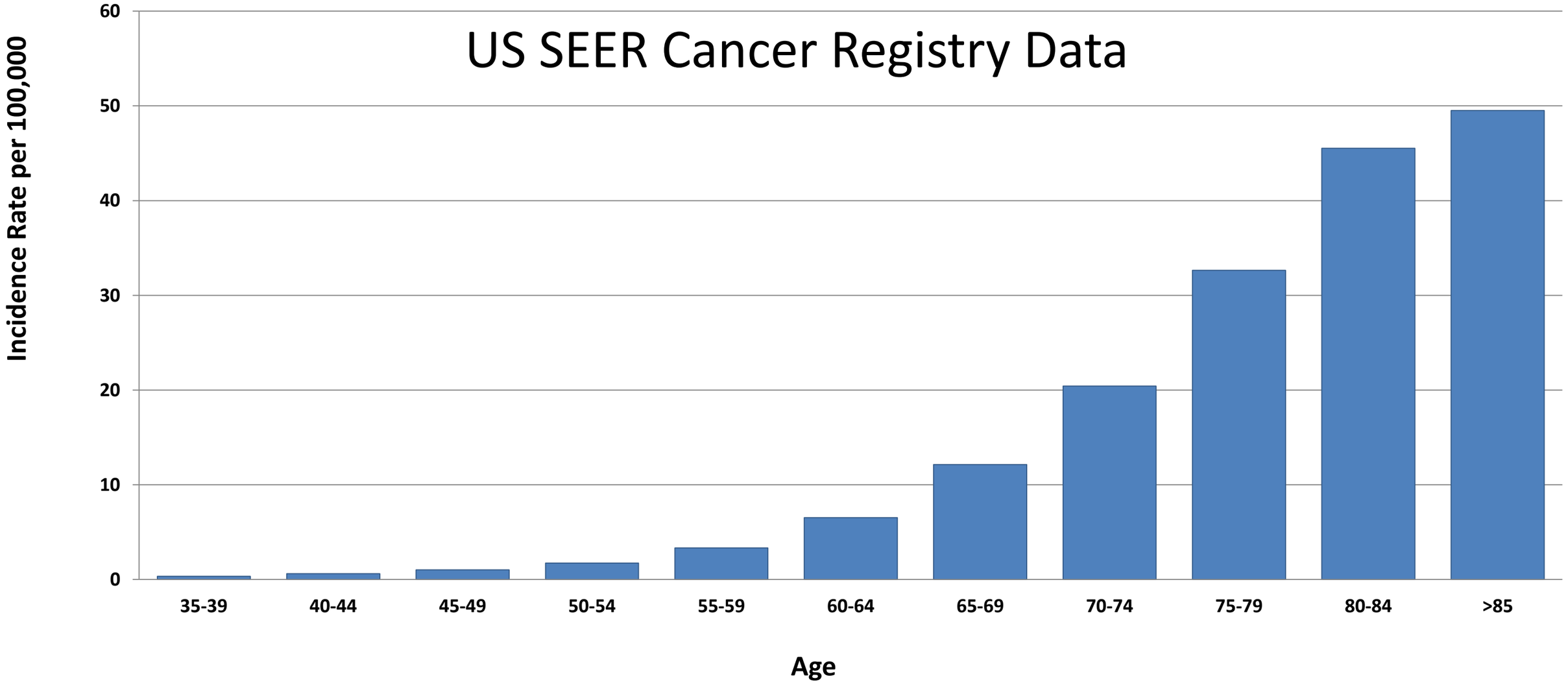
Normal Hematopoiesis




Differentiation
Transformation
Normal
Early MDS
Advanced MDS
Secondary AML

Who gets MDS?

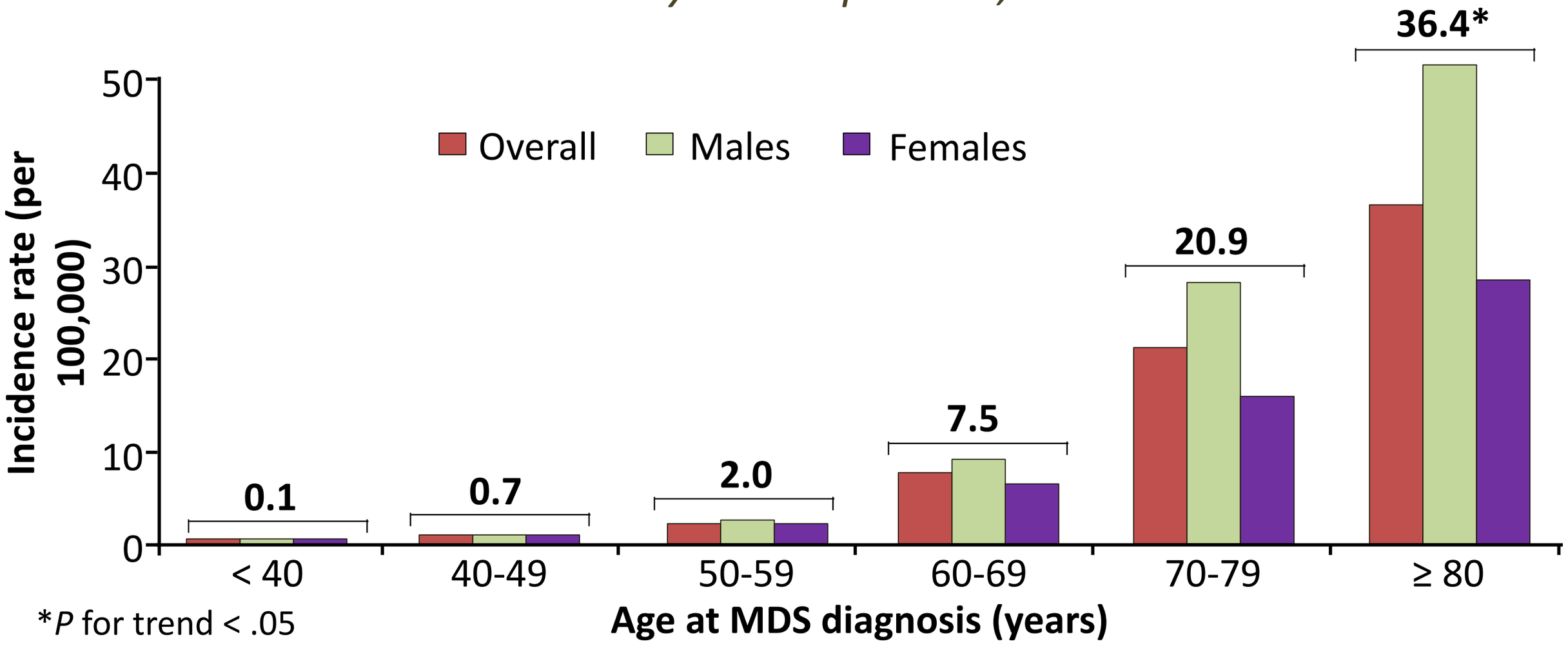
MDS Incidence Rates 2000-2008



http://seer.cancer.gov. Accessed May 1, 2013.

Age and Sex in MDS

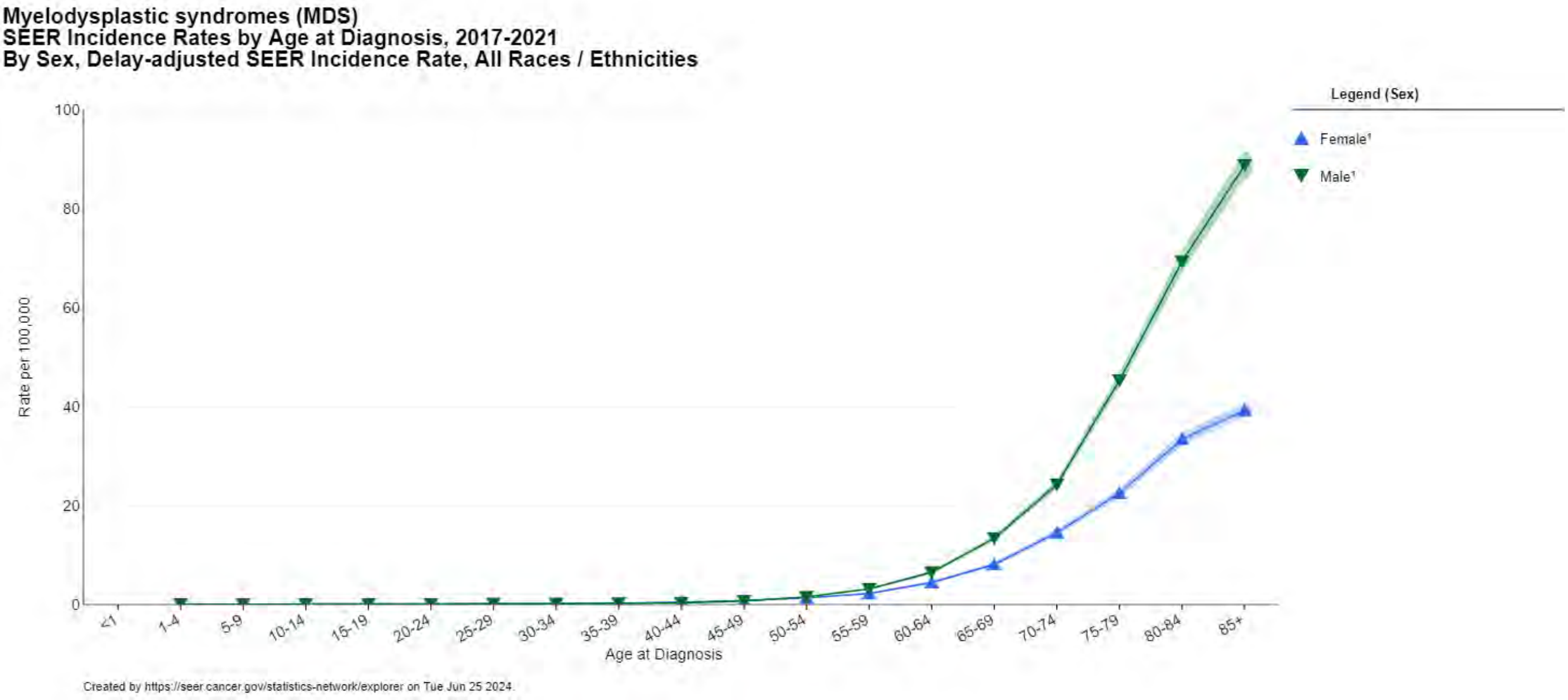
- *Overall incidence in this analysis: 3.4 per 100,000*



**P* for trend < .05

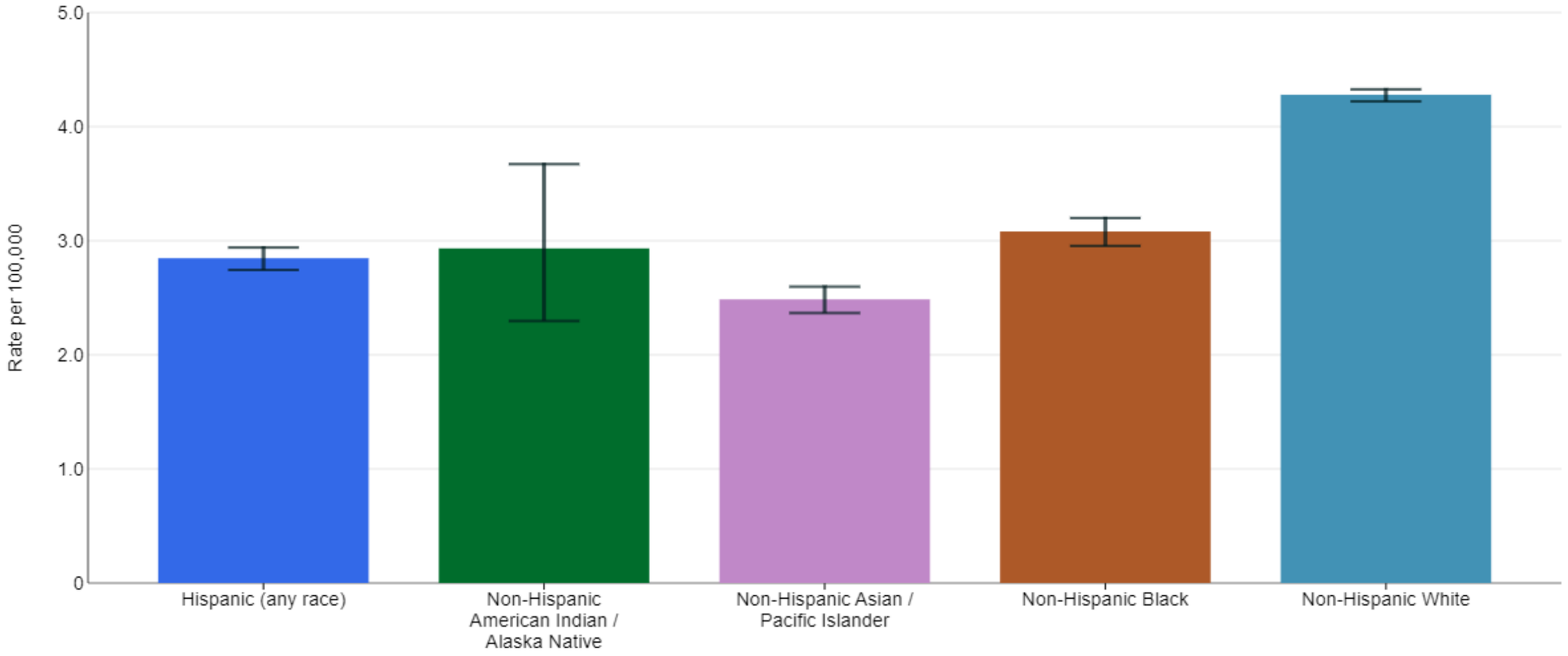
Rollison DE et al Blood 2008;112:45-52.

MDS Incidence Rates 2023



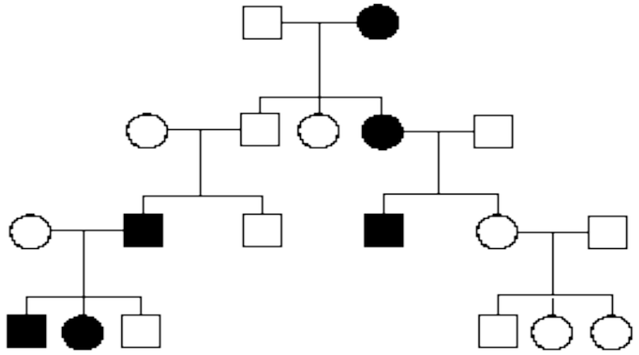
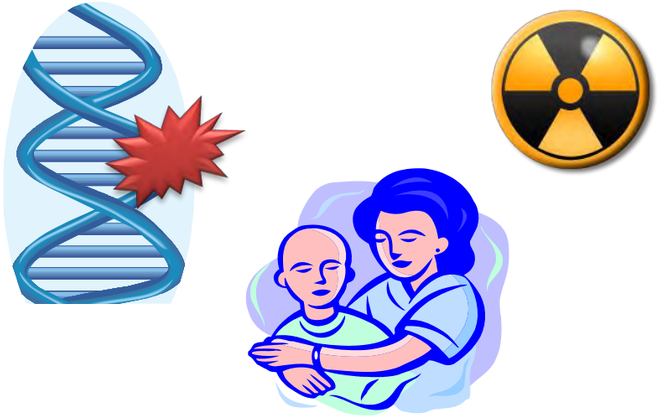
MDS Incidence 2023

Myelodysplastic syndromes (MDS)
SEER 5-Year Age-Adjusted Incidence Rates, 2017-2021
All Stages By Race/Ethnicity, Both Sexes, All Ages



Created by https://seer.cancer.gov/statistics-network/explorer on Tue Jun 25 2024.

Etiology of MDS

~10%	10-15%	**80%**
Familial or Congenital	**Topoisomerase II inhibitors** **Ionizing radiation** **DNA alkylating agents**	**“De novo”** (idiopathic, primary)
		
Often early onset and part of a larger syndrome	**Peaks 1-3 or 5-7 years following exposure**	Median age ~76 years; increased risk with **aging**

Making the Diagnosis

Who do we suspect?

Suspicion for MDS increases with:

- Age
- Prior cytotoxic or chemical/radiation exposures
- Number and severity of cytopenias (low blood counts)
- Family history
- Lack of an alternative explanations
- Evidence of dysplasia in peripheral blood

Myelodysplastic Syndromes

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Myelodysplastic Syndromes

NCCN Guidelines Index
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Discussion

INITIAL EVALUATION

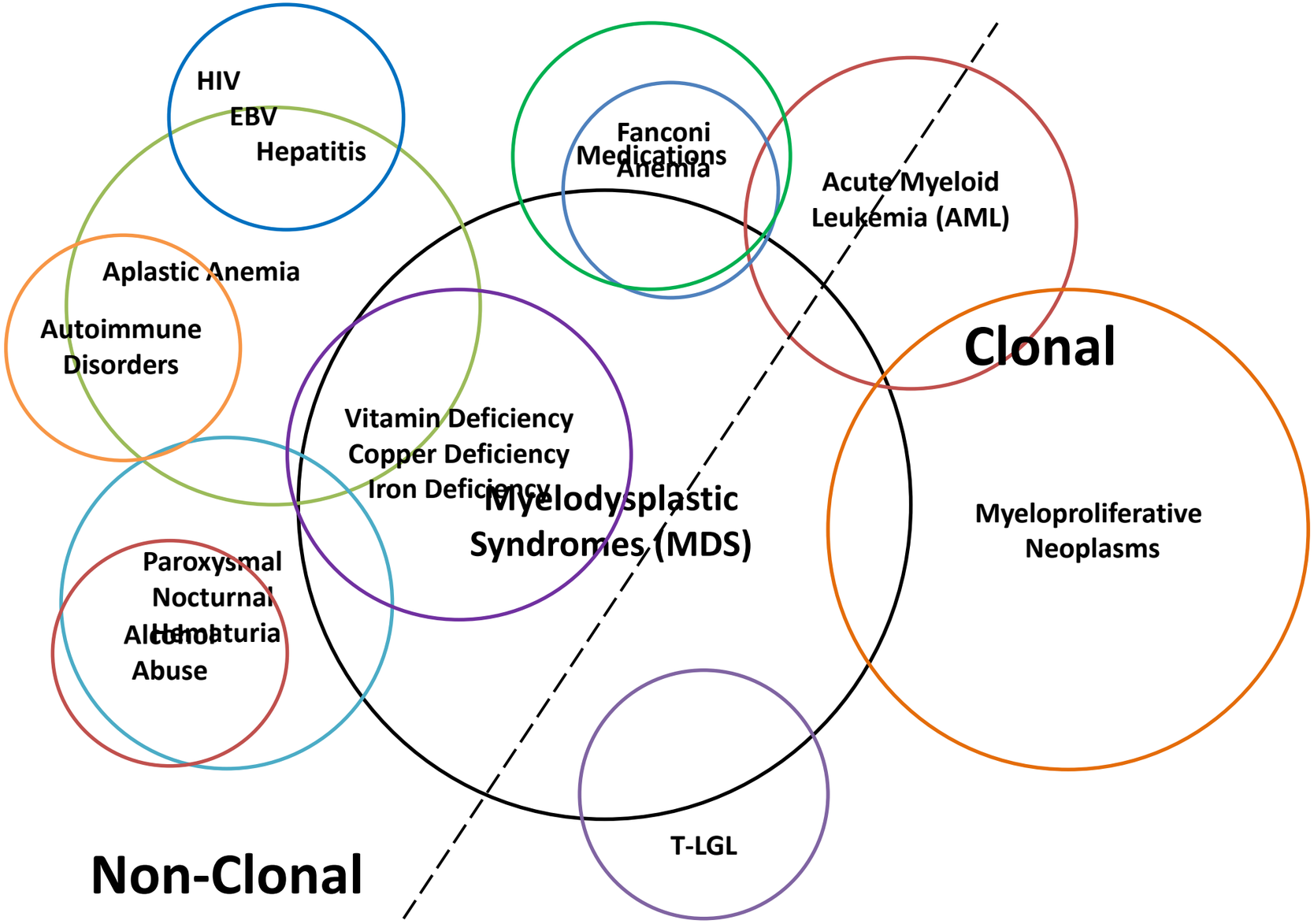
Cytopenia(s), suspect myelodysplasia[a] →

- H&P
- Complete blood count (CBC), platelets, differential, reticulocyte count
- Examination of peripheral blood smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping.[b] Consider testing bone marrow sample for fibrosis.
- Serum erythropoietin (prior to red blood cell [RBC] transfusion)
- RBC folate, serum B12[c]
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- Thyroid-stimulating hormone (TSH)
- Lactate dehydrogenase (LDH)
- Genetic testing for somatic mutations (ie, acquired mutations) in genes associated with MDS is highly recommended[d]
- Recommend additional molecular and genetic testing for hereditary hematologic malignancy predisposition in a subset of patients, particularly in younger patients[e]
- HIV testing if clinically indicated
- Consider evaluation of copper deficiency in patients with GI malabsorption, severe malnutrition, gastric bypass surgery, or patients on zinc supplementation
- Consider distinction from congenital sideroblastic anemia (CSA)[f]

→ **Diagnosis of MDS established based on morphologic, cytogenetic, and clinical criteria[g,h]** → See Additional Testing and Classification (MDS-2)

→ **Diagnostic criteria for MDS not met but cytopenias present** → See Spectrum of Indolent Myeloid Hematopoietic Disorders (MDS-F)

Diagnostic Overlap



Minimal Diagnostic Criteria

Cytopenia(s):

- Low hemoglobin, *or*
- Low neutrophil count, *or*
- Low platelet count

MDS "decisive" criteria:

- >10% **dysplastic cells** in 1 or more lineages, *or*
- 5-19% **blasts**, *or*
- Abnormal **karyotype** typical for MDS, *or*
- Specific **mutations** typical of MDS

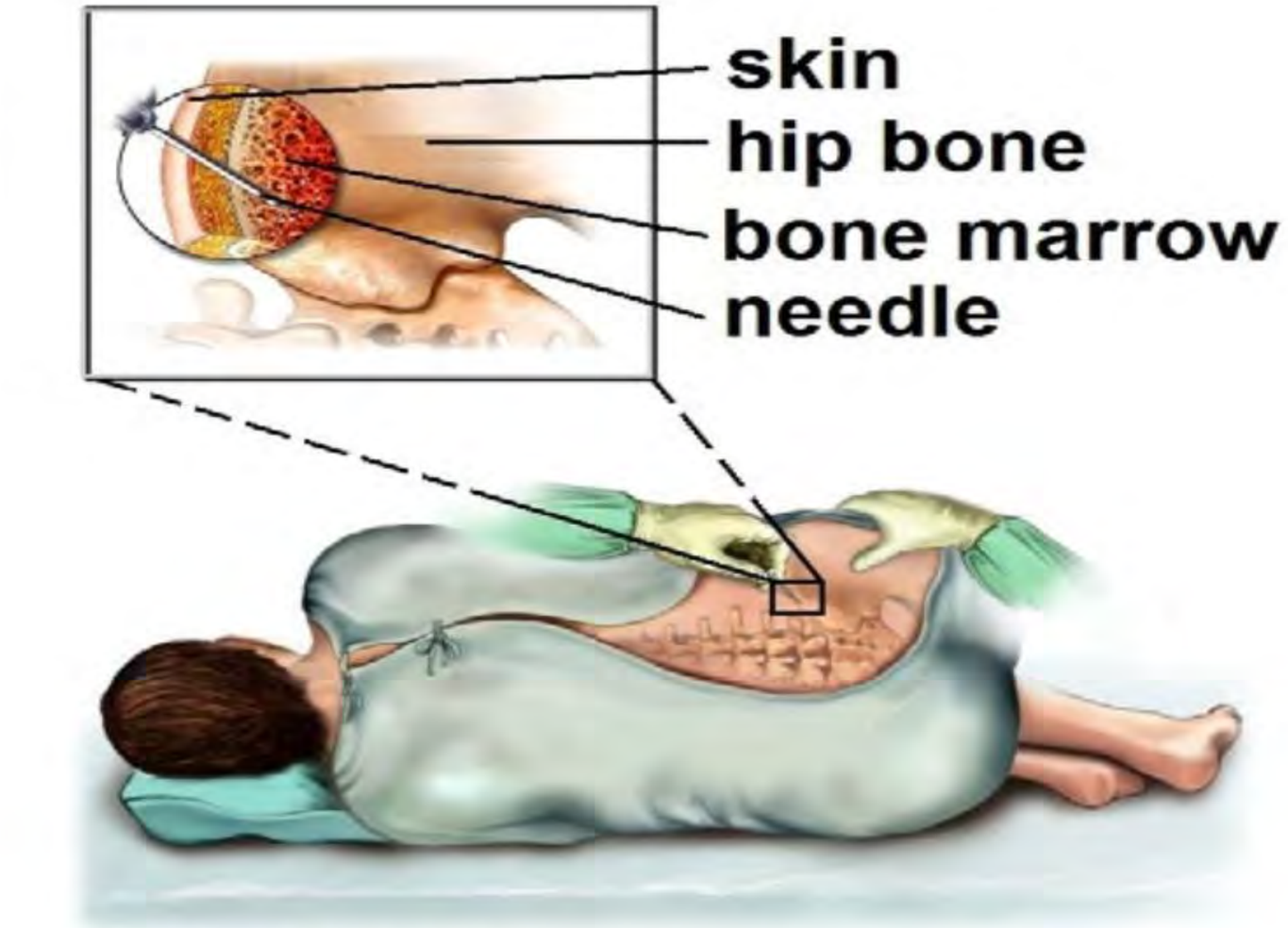
Other causes of cytopenias and morphological changes EXCLUDED:

- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE etc.)*
- *Congenital syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

Slide borrowed from Dr. David Steensma

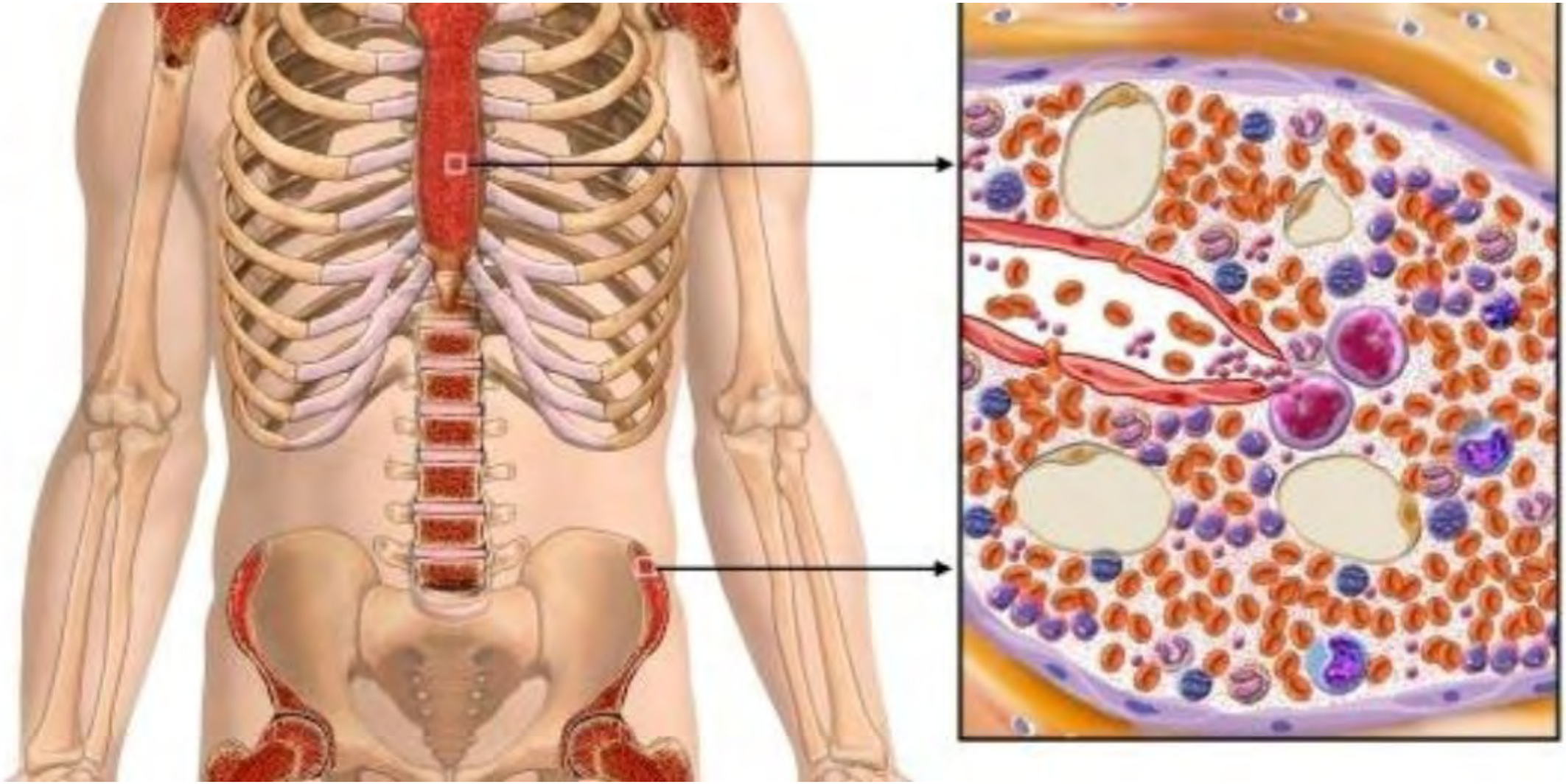
Valent P et al *Leuk Res* 2007;31:727-736.

Bone Marrow Biopsy



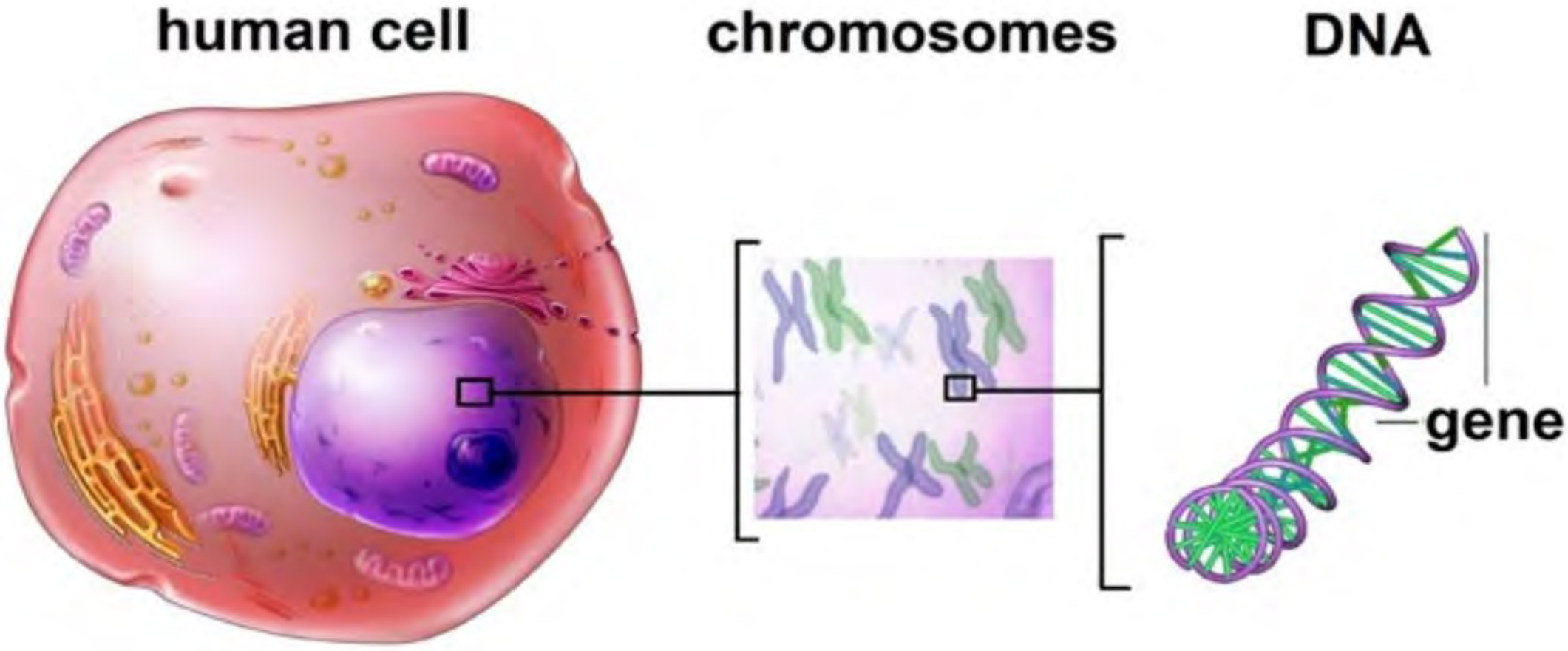
From: NCCN Guidelines for Patients: MDS

The Bone Marrow



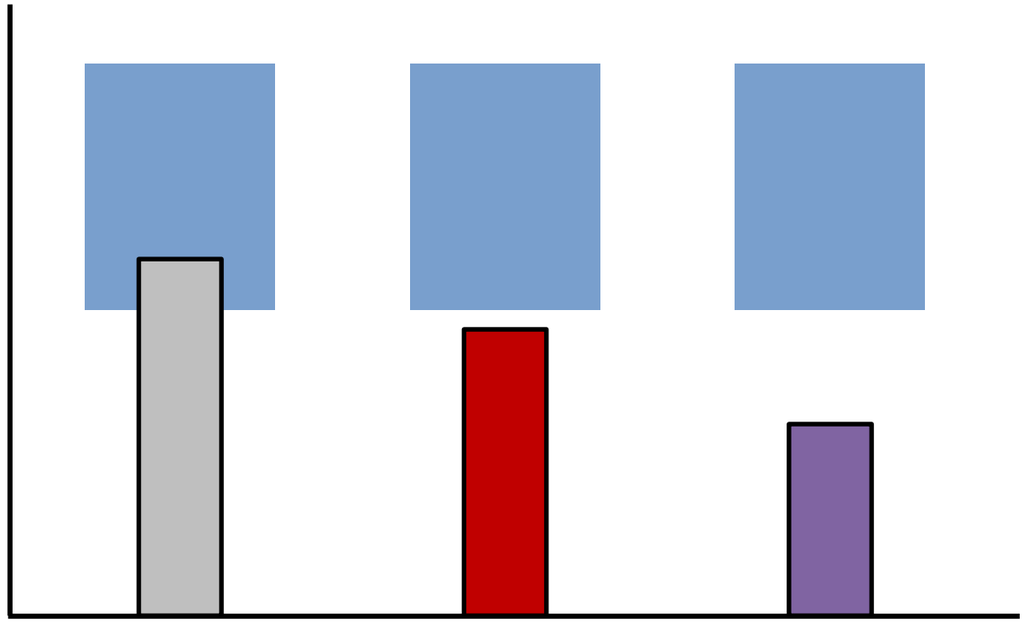
From: NCCN Guidelines for Patients: MDS

Chromosomes and Mutation Testing



Looking for Answers

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

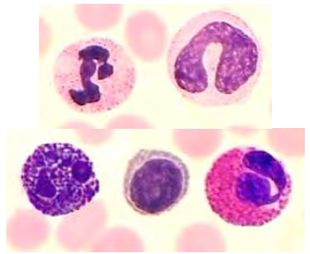


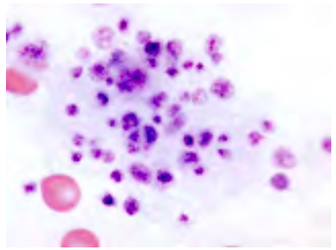
B12 level - Normal
Folate - Normal
Thyroid - Normal

No toxic medications

No alcohol use

No chronic illness





Making the Diagnosis

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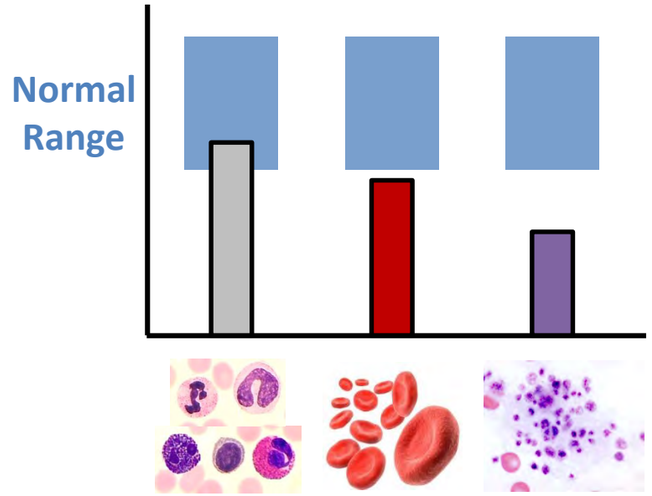
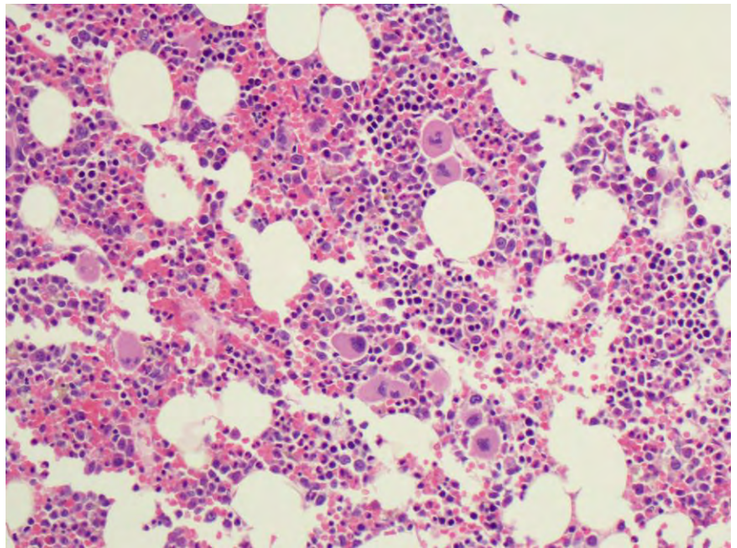


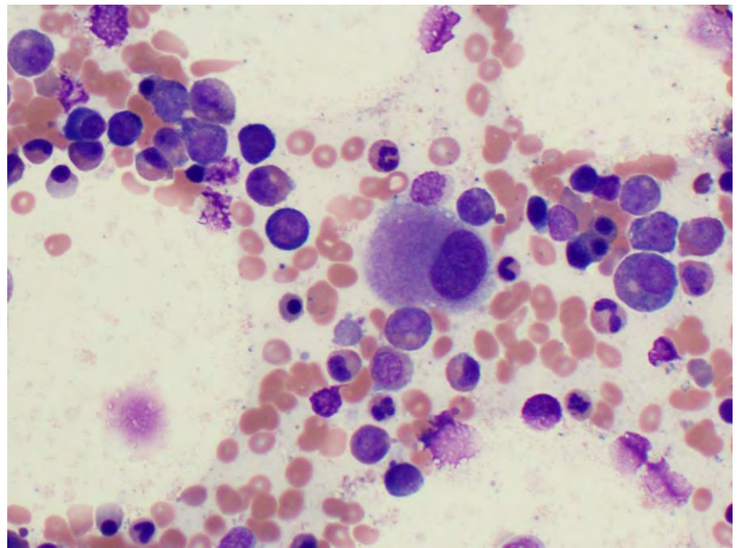
70% cellular marrow - 1% blasts in aspirate

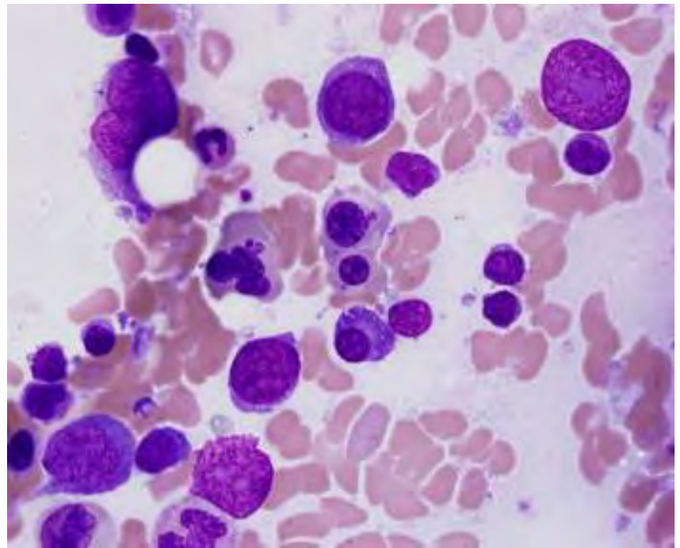
Dysmegakaryopoiesis >10% - <10% dyserythropoiesis

Normal Karyotype: 46,XX[20]

Mutations of *TET2* and *BCOR*

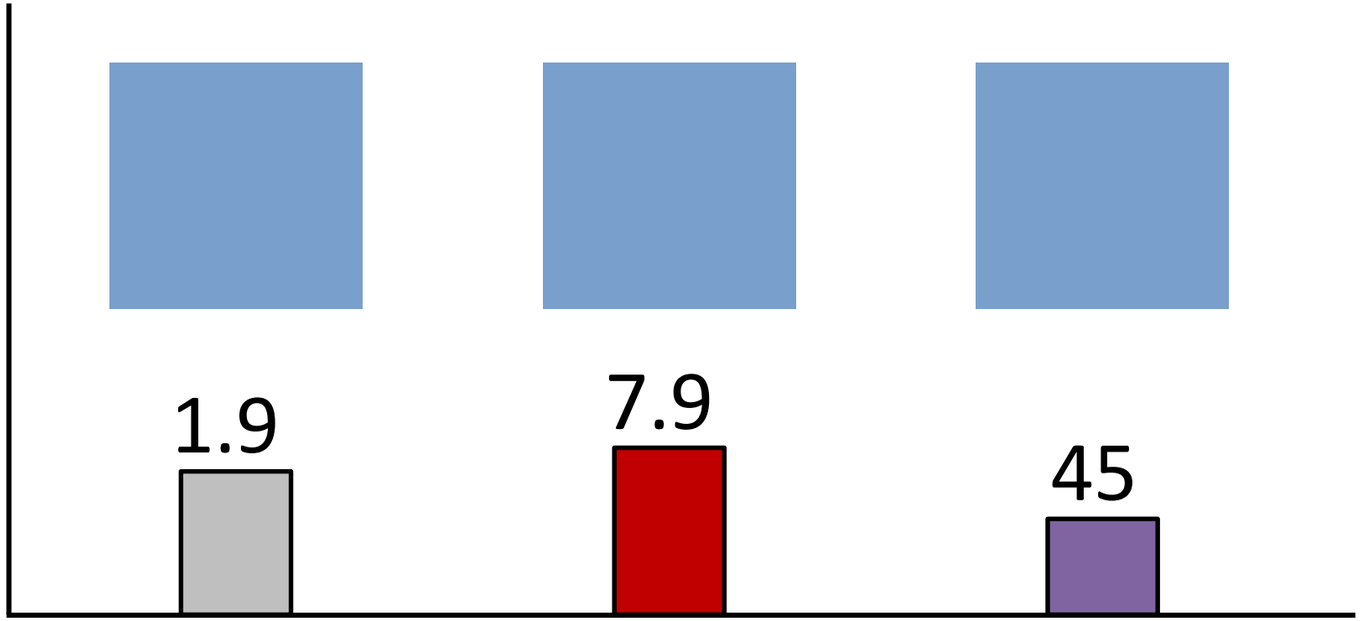






Another example

71 year-old man with big red cells and low blood counts that developed over the past 6 months.

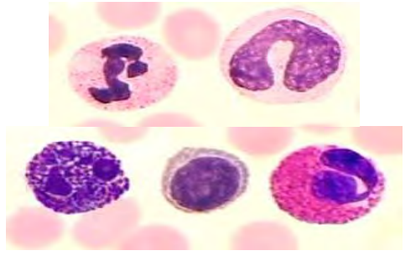


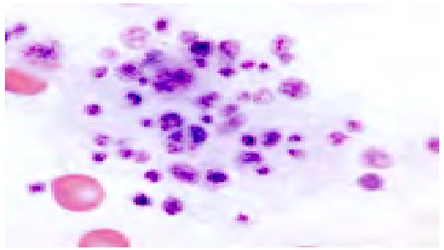
B12 level - Normal
Folate - Normal
Thyroid - Normal

No toxic medications

No alcohol use

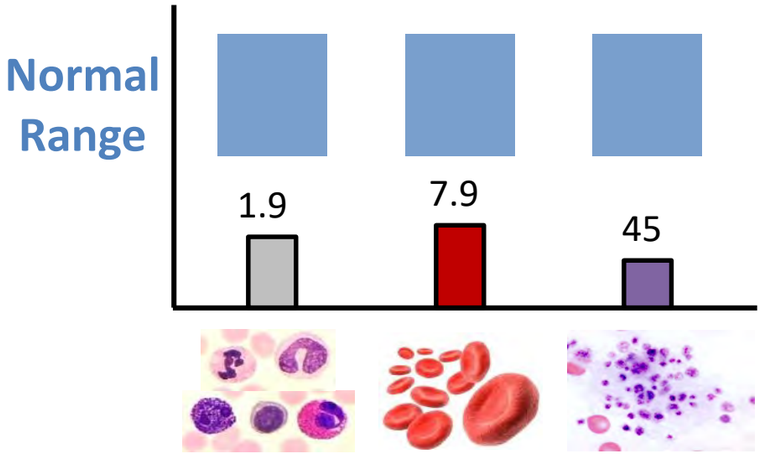
No chronic illness





Making the Diagnosis

71 year-old man with big red cells and low blood counts that developed over the past 6 months.



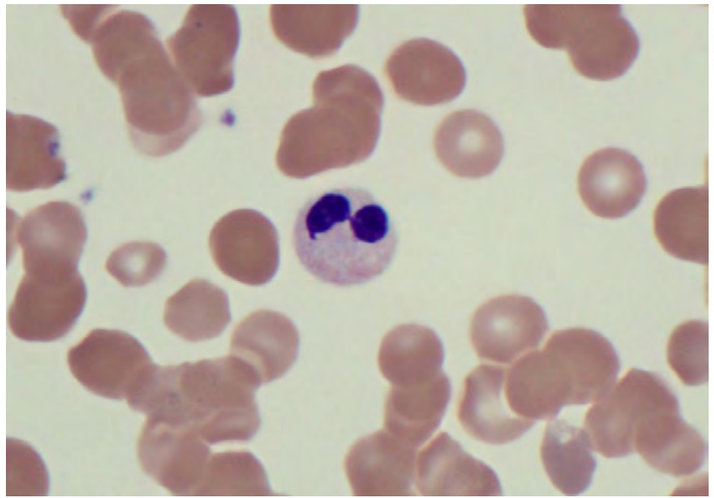
Hypercellular bone marrow (90%)

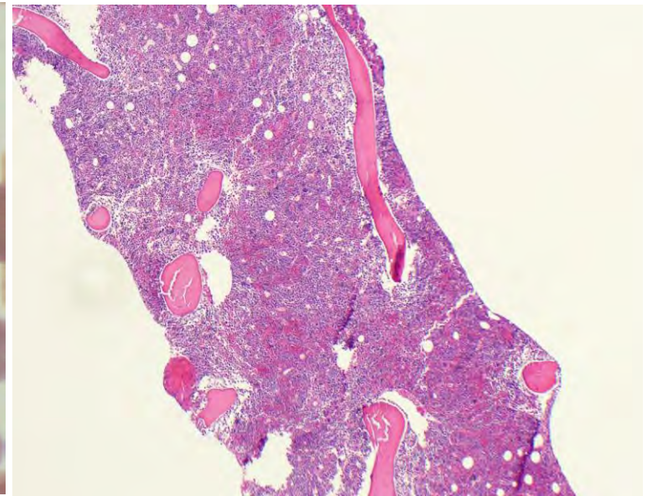
12% blasts in aspirate

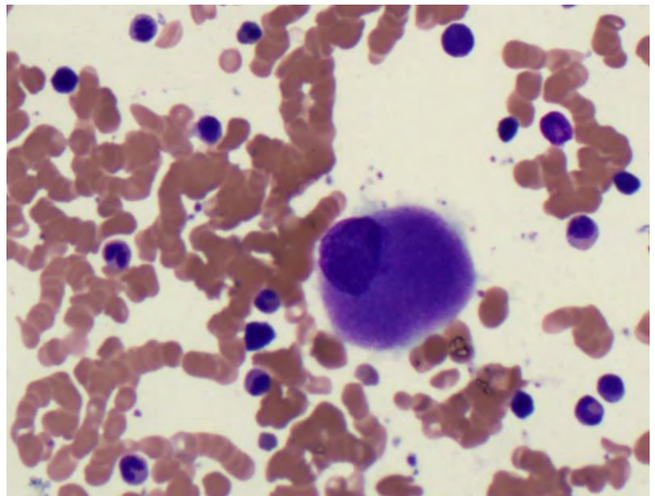
Dysplasia in all three cell types > 10%

Abnormal Karyotype: 46,XY,-7,del(17)(p12)[13]/46,XY[7]

Mutations in *TP53*, *RUNX1*, and *U2AF1*







Classification of MDS Subtypes

World Health Organization MDS categories (2016)

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD)[3]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occassions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts
MDS with excess blasts in transformation (MDS-EB-T)[2]	Cytopenias, 5%–19% blasts	Multilineage dysplasia, 20%–29% blasts, ± Auer rods

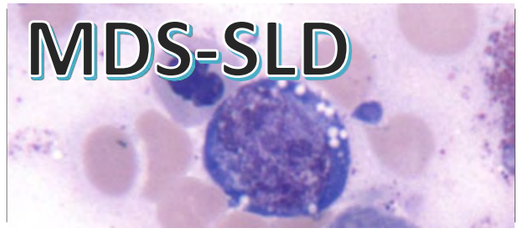
2016 WHO MDS Classification Disease Subtypes

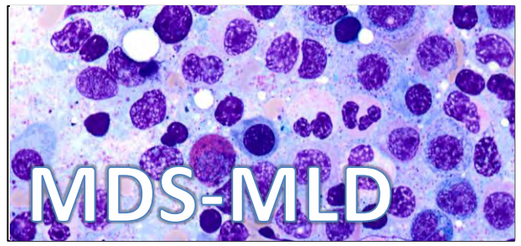
<5% BM blasts

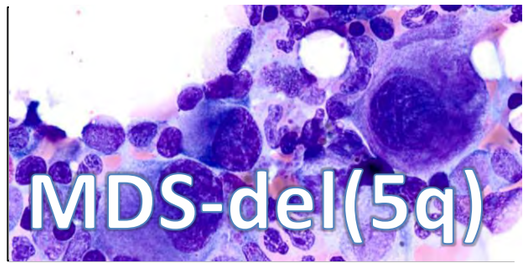
5-9% BM blasts

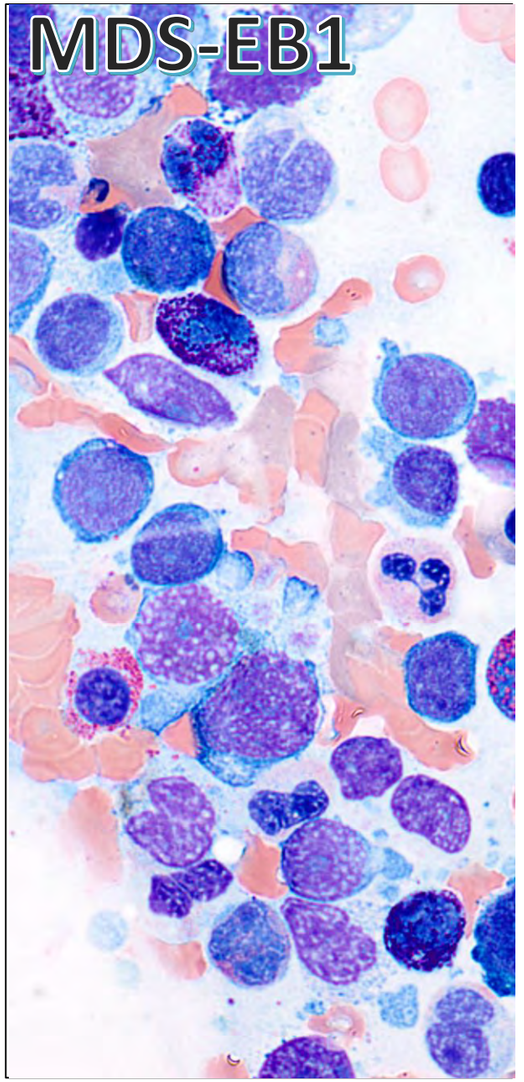
10-19% BM blasts

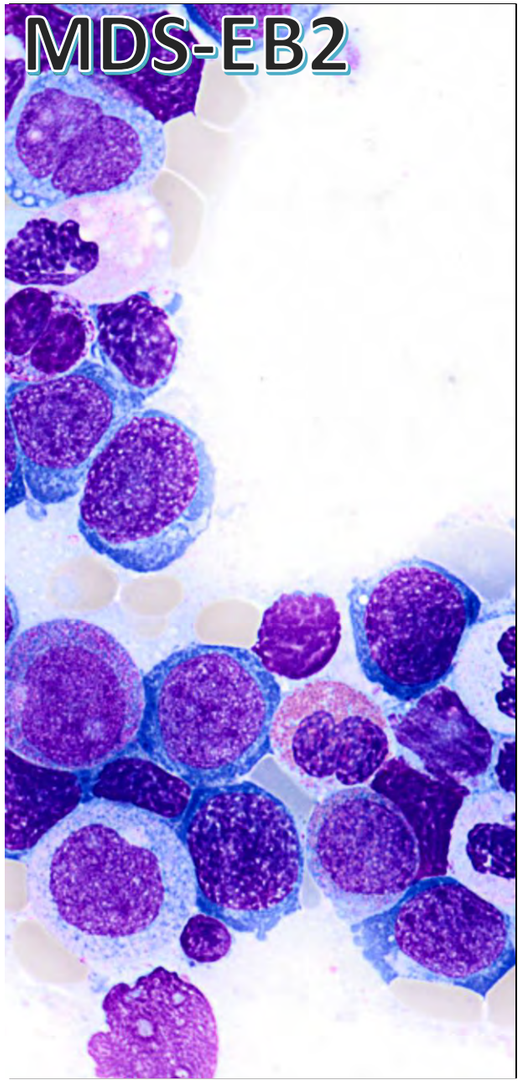
Single versus multilineage dysplasia, ring sideroblasts, isolated del(5q)





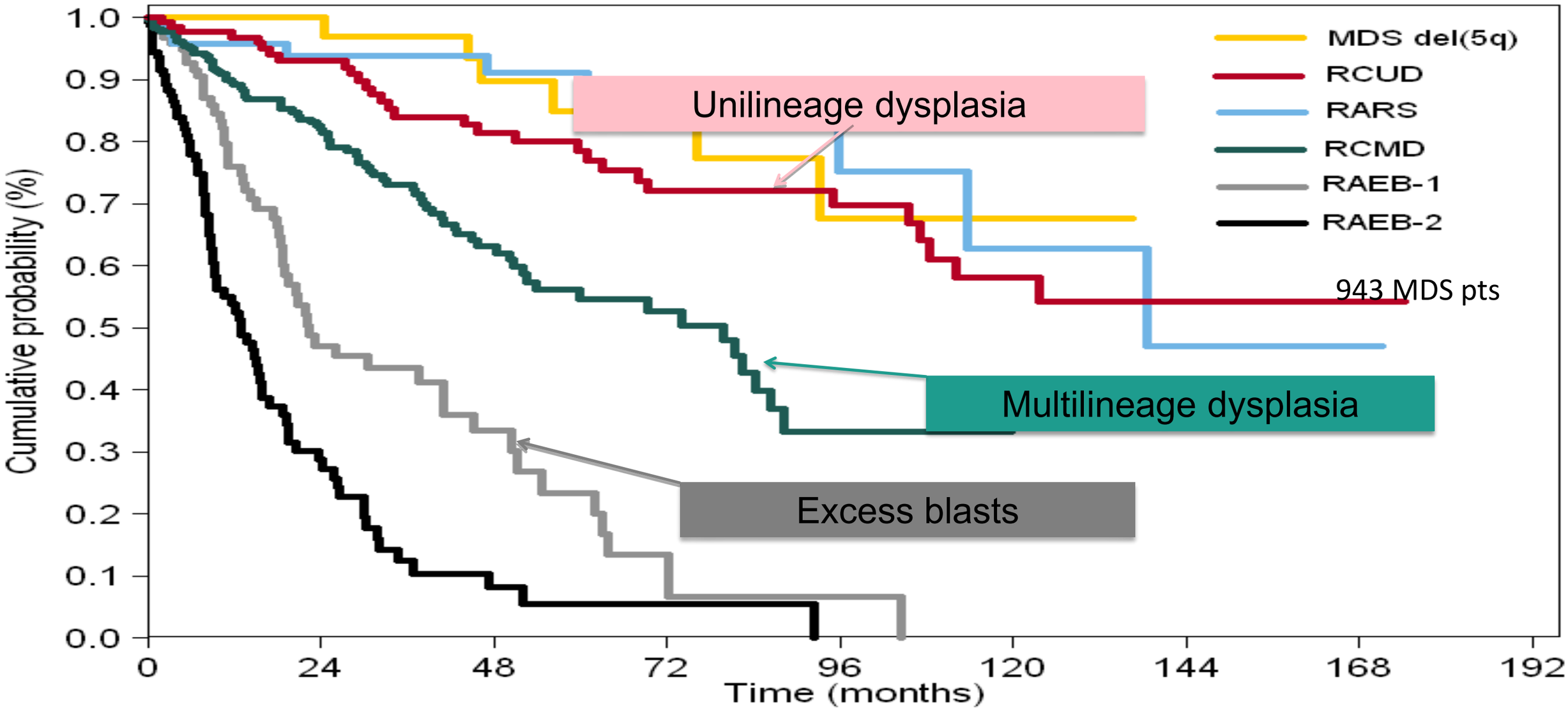






Courtesy Robert P Hasserjian

World Health Organization MDS categories (2016)



Cazzola. Haematologica. 2011 Mar;96(3):349-52.

Two new classifications of myeloid neoplasms in 2022

The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data

Daniel A. Arber, Attilio Orazi, Robert P. Hasserjian, Michael J. Borowitz, Katherine R. Calvo, Hans-Michael Kvasnicka, Sa A. Wang, Adam Bagg, Tiziano Barbui, Susan Branford, Carlos E. Bueso-Ramos, Jorge E. Cortes, Paola Dal Cin, Courtney D. DiNardo, Herve' Dombret, Eric J. Duncavage, Benjamin L. Ebert, Elihu H. Estey, Fabio Facchetti, Kathryn Foucar, Naseema Gangat, Umberto Gianelli, Lucy A. Godley, Nicola Gökbuget, Jason Gotlib, Eva Hellström-Lindberg, Gabriela S. Hobbs, Ronald Hoffman, Elias J. Jabbour, Jean-Jacques Kiladjian, Richard A. Larson, Michelle M. Le Beau, Mignon L-C. Loh, Bob Löwenberg, Elizabeth Macintyre, Luca Malcovati, Charles G. Mullighan, Charlotte Niemeyer, Olatoyosi M. Odenike, Seishi Ogawa, Alberto Orfao, Elli Papaemmanuil, Francesco Passamonti, Kimmo Porkka, Ching-Hon Pui, Jerald P. Radich, Andreas Reiter, Maria Rozman, Martina Rudelius, Michael R. Savona, Charles A. Schiffer, Annette Schmitt-Graeff, Akiko Shimamura, Jorge Sierra, Wendy A. Stock, Richard M. Stone, Martin S. Tallman, Jürgen Thiele, Hwei-Fang Tien, Alexandar Tzankov, Alessandro M. Vannucchi, Paresh Vyas, Andrew H. Wei, Olga K. Weinberg, Agnieszka Wierzbowska, Mario Cazzola, Hartmut Döhner and Ayalew Tefferi

Blood. 2022 Sep 15;140(11):1200-1228.

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

Leukemia. 2022 Jul;36(7):1703-1719.

2016 WHO MDS Classification Disease Subtypes

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5-9% BM blasts

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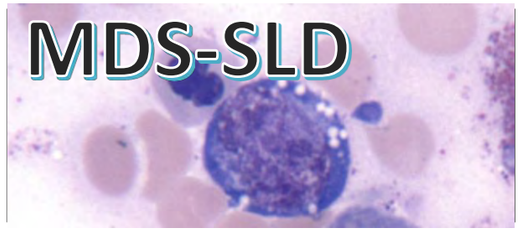
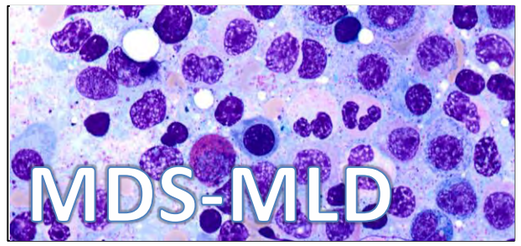
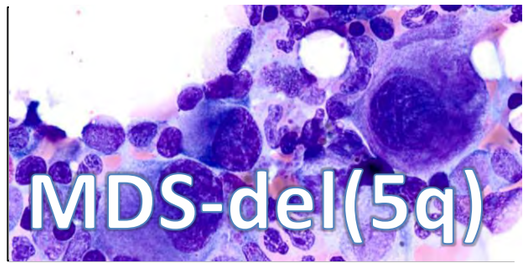
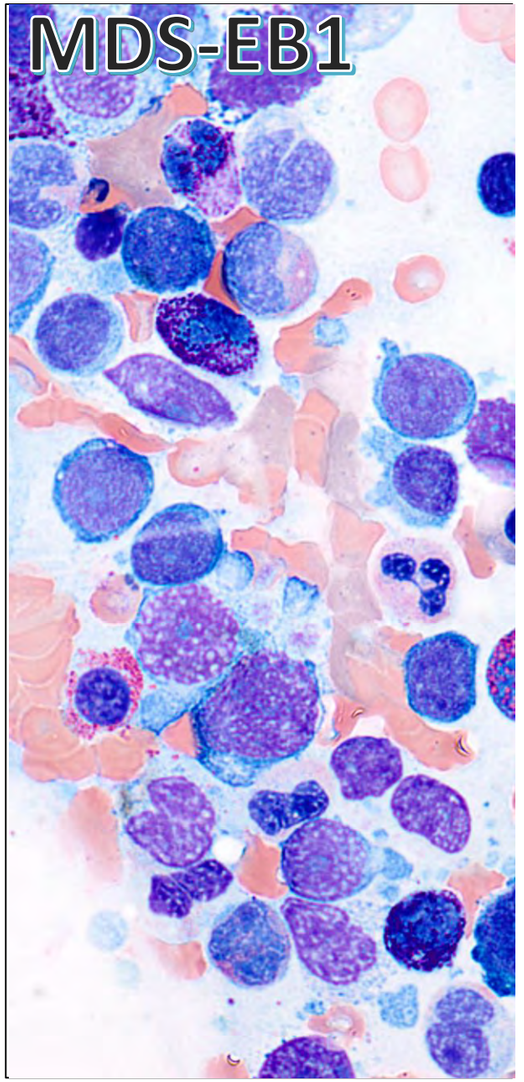
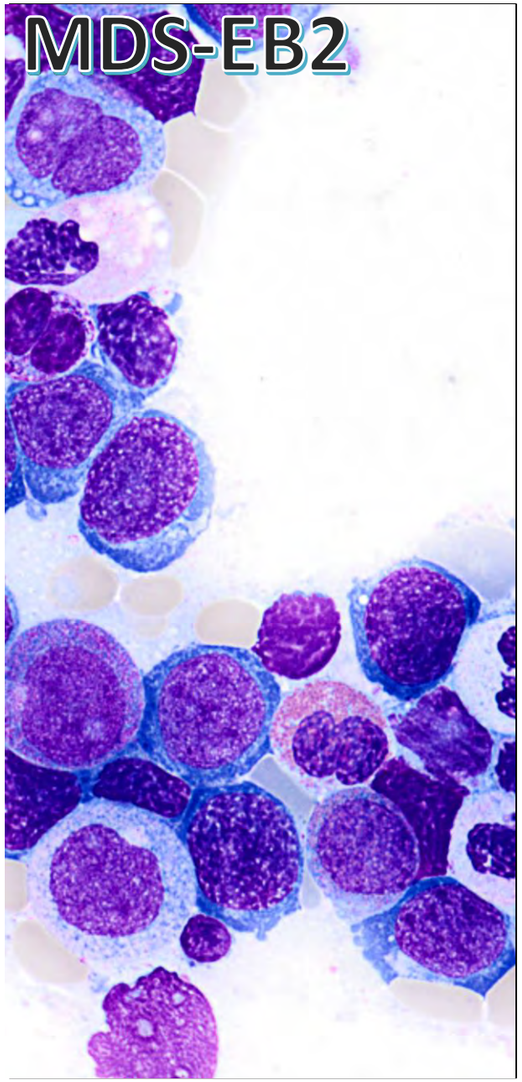
Single versus multilineage dysplasia, ring sideroblasts, isolated del(5q)











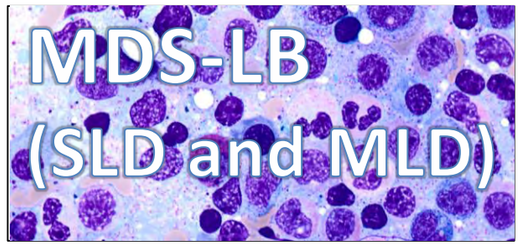
Courtesy Robert P Hasserjian

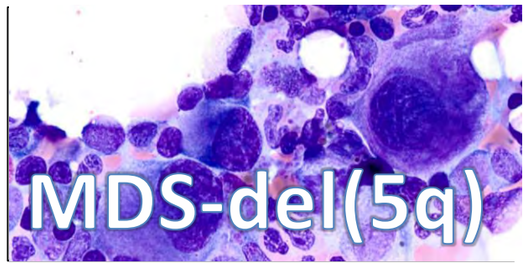
2022 WHO MDS Classification Disease Subtypes

MDS-bi TP53 (any blast %)

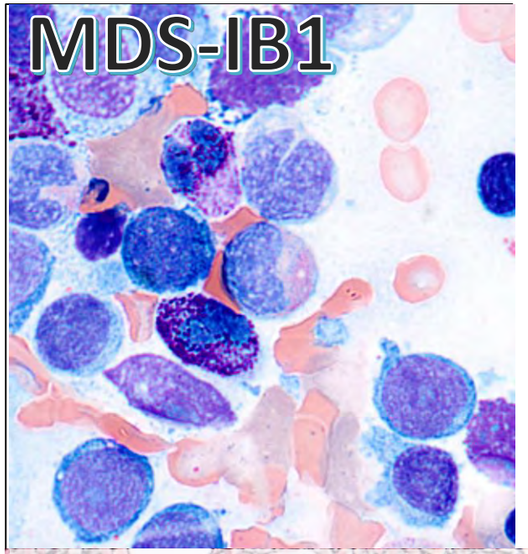
Single versus multilineage dysplasia, ring sideroblasts, isolated del(5q)

<5% BM blasts

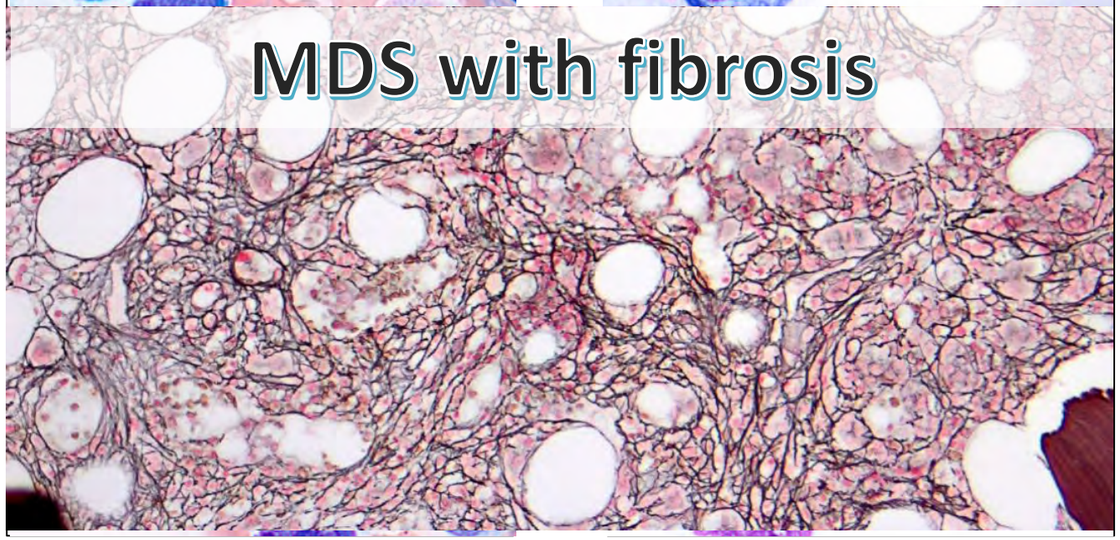




5-9% BM blasts



10-19% BM blasts



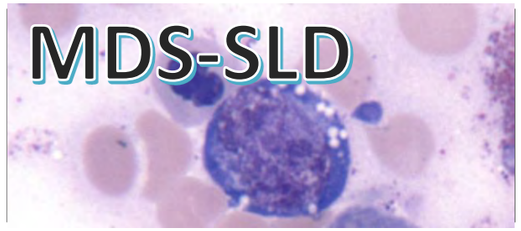
Courtesy Robert P Hasserjian

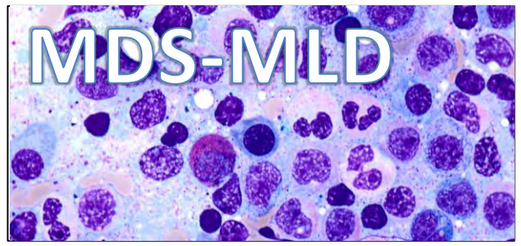
2022 ICC MDS Classification Disease Subtypes

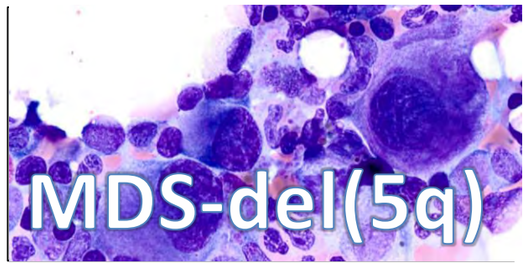
MDS-bi TP53 (any blast %)

Single versus multilineage dysplasia, ring sideroblasts, isolated del(5q)

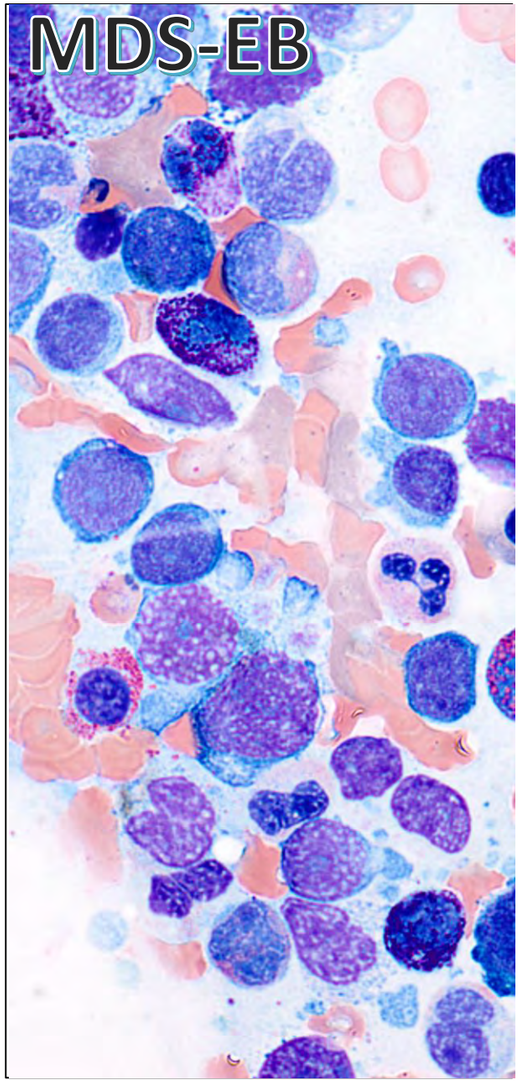
<5% BM blasts



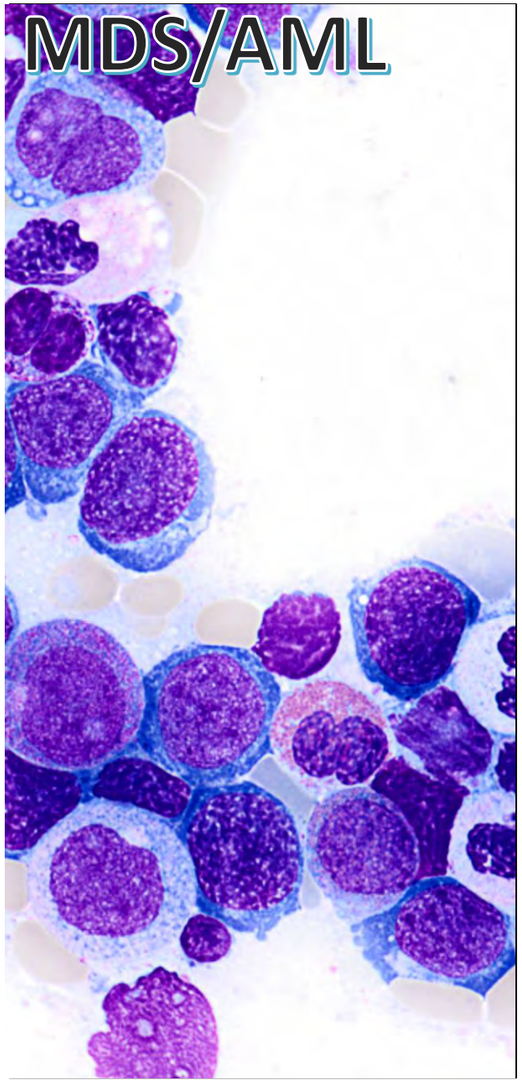




5-9% BM blasts



10-19% BM blasts



Courtesy Robert P Hasserjian

What questions should you ask about your diagnosis?

What did my bone marrow biopsy show?

- Did they find enough dysplastic cells to call it MDS?
- How many blasts were there?
- Did I have RING SIDEROBLASTS? If so, how many?
- Where the chromosomes normal or abnormal?
- What mutations were found, if any?

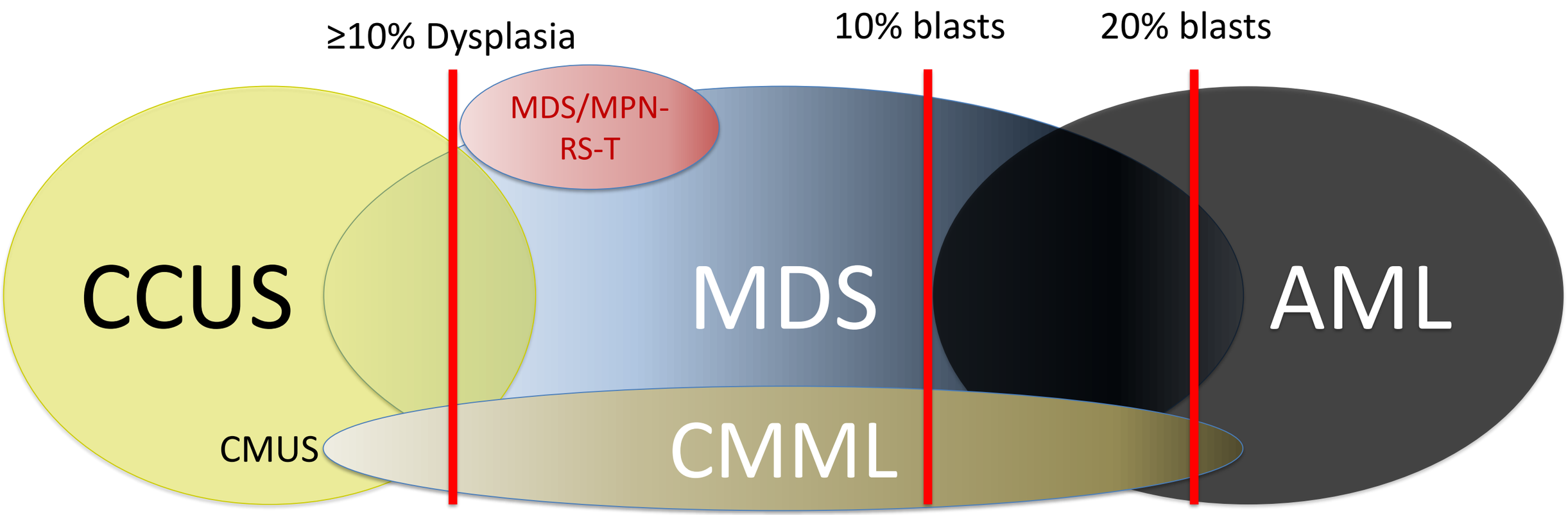
Was this consistent with MDS and if so, what subtype is it?

What if it’s abnormal but its not typical MDS?

MDS-related diagnoses:

- **Chronic Myelomonocytic Leukemia (CMML)**
- **MDS with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T)**
- **MDS with Germline Predisposition?**
- **Is it Acute Myeloid Leukemia (AML)?**
- **Is it a Clonal Cytopenia of Undetermined Significance (CCUS)?**

The Borders of MDS



Clonal cytopenias

Increasing blasts

Slide from Robert P Hasserjian

CCUS

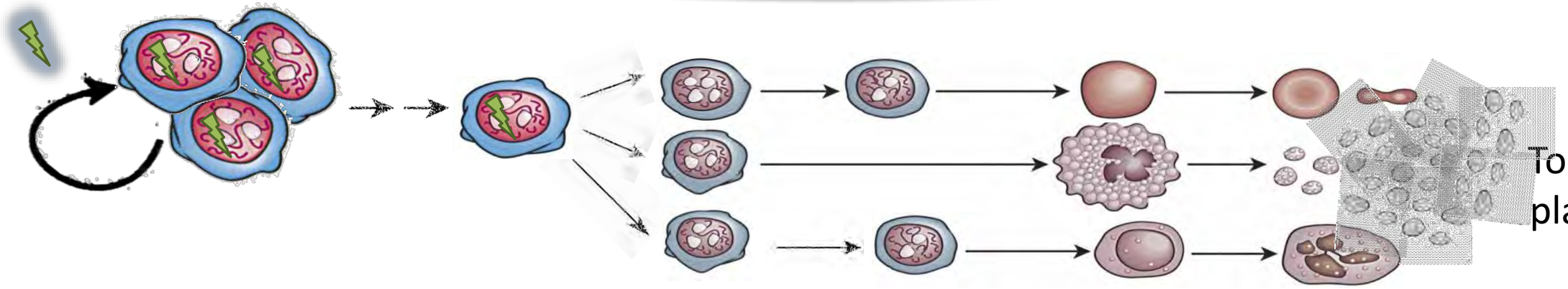
Clonal Cytopenia of Undetermined Significance

It is a potential pre-MDS, but how it evolves depends on several factors

1. Identification in blood (or marrow) DNA with one or more somatic gene mutations in ***myeloid malignancy driver*** genes of VAF ≥ 2%
2. Lack of evidence for a defined hematological disorder harboring the identified mutation(s)
3. Unexplained cytopenia(s) such as anemia (hemoglobin < 12 g/dL in females and < 13 g/dL in males), neutropenia (absolute neutrophil count < 1.8×10^9/L), and/or thrombocytopenia (platelets < 150×10^9/L) that is not explained by another condition (persistent >4 months ICC).

MDS + Ring Sideroblasts and Thrombocytosis

MDS/MPN-RS-T



- Can have dysplasia like MDS-RS
- Has ring sideroblasts like MDS-RS
- Can have low blood counts like MDS-RS
- Low risk of acute leukemia like MDS-RS
- Can share mutations with MDS-RS
- Similar range of prognosis to MDS-RS

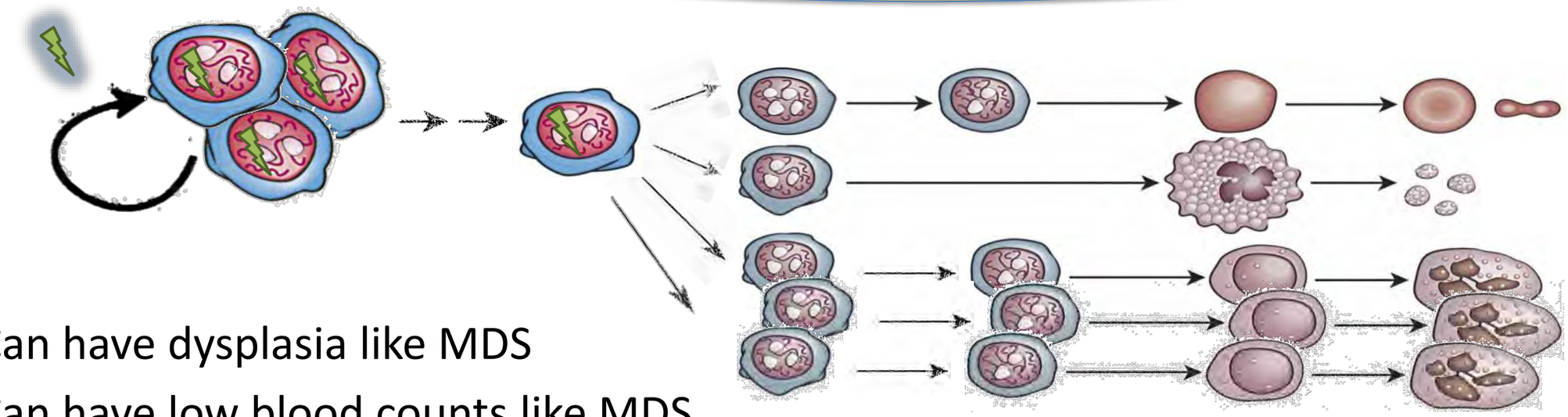
BUT, has some unique patterns with:

More *JAK2, CALR,* or *MPL* mutations

May have a higher risk of blood clots

Chronic Myelomonocytic Leukemia

CMML



Too many monocytes!

- Can have dysplasia like MDS
- Can have low blood counts like MDS
- Can become acute leukemia like MDS
- Can share mutations with MDS
- Similar range of prognosis to MDS
- Similar treatments as for MDS

BUT, has some unique patterns with:

More *TET2*, *ASXL1*, *SRSF2*, *NRAS*, *KRAS* mutations

Tends to be more inflammatory

Prognosis & Risk Assessment

Risk-Adapted Therapy

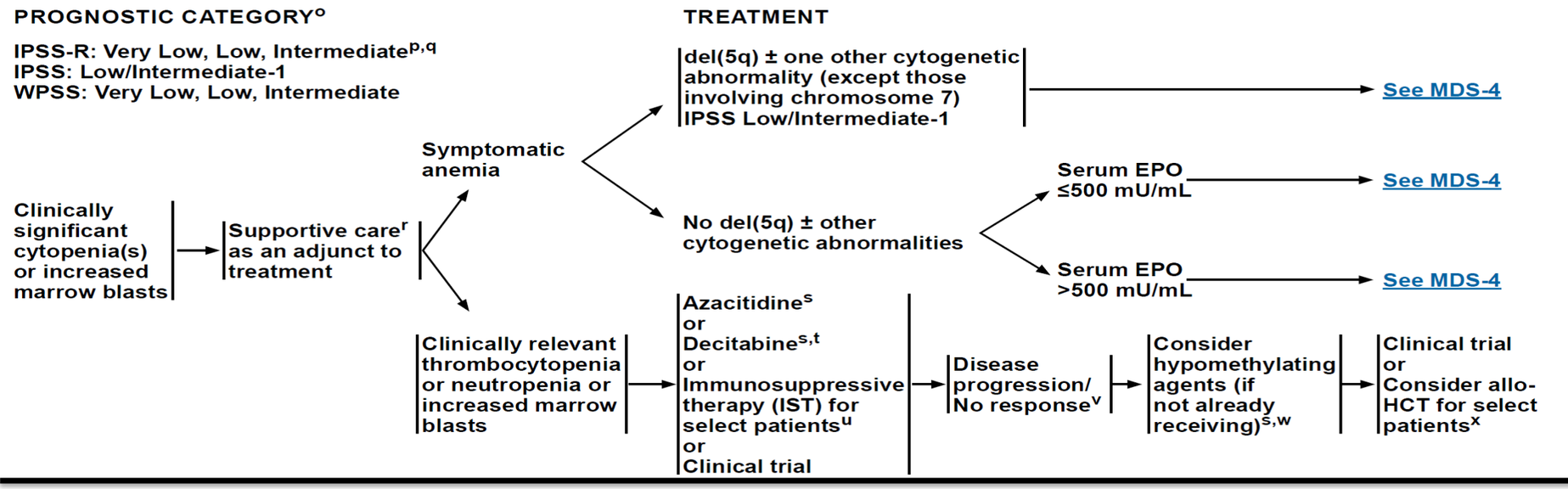
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

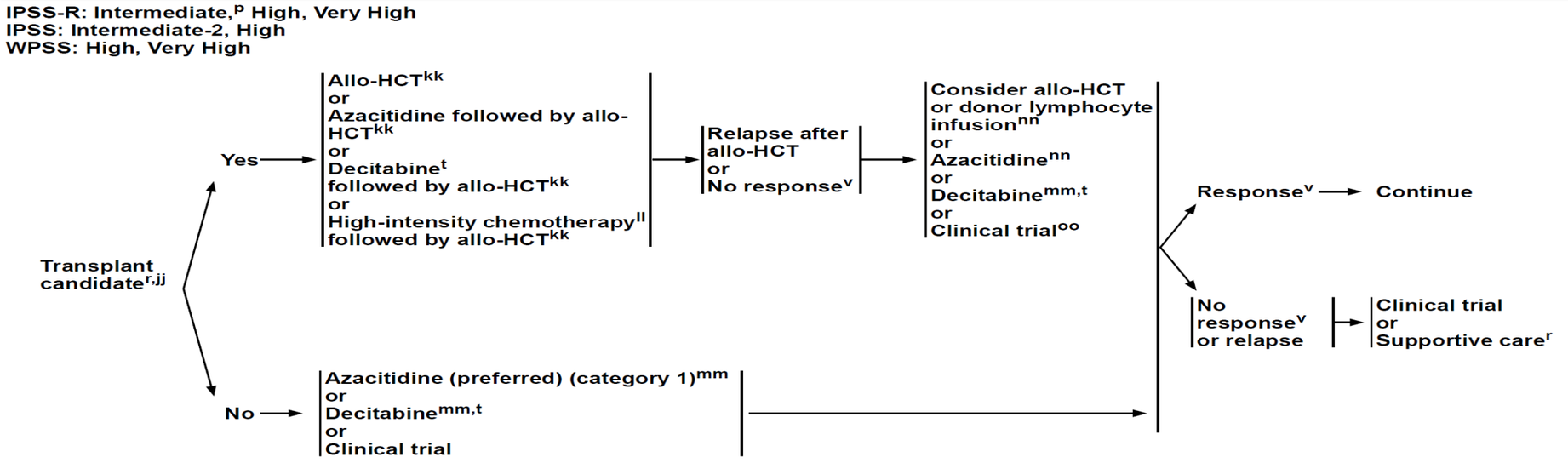
Lower Risk

- Observation
- ESAs/Luspatercept
- Lenalidomide
- Imetelstat
- Immune suppression



Higher Risk

- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials



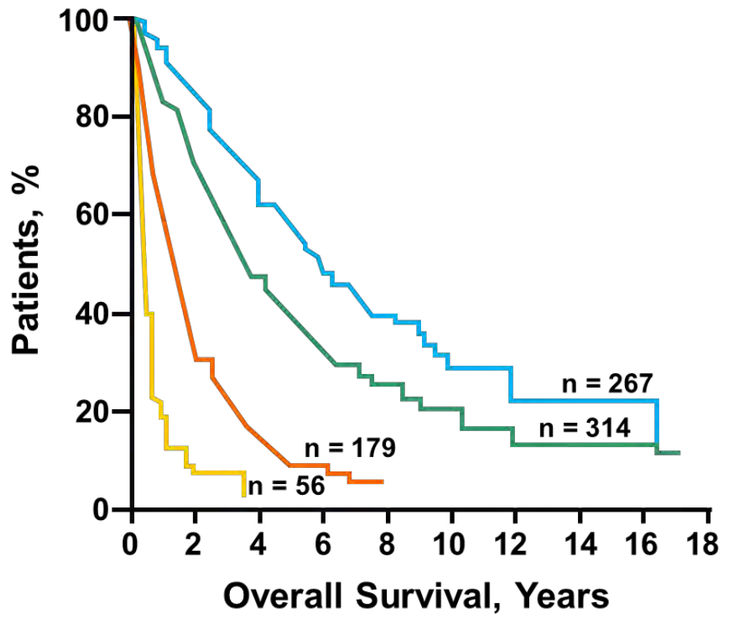
International Prognostic Scoring System

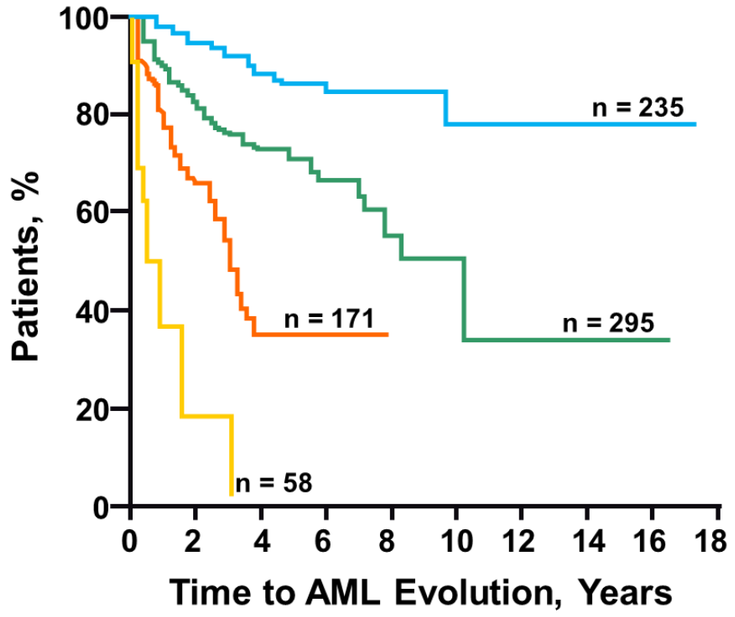
Cytogenetic Risk Group	IPSS Karyotype Abnormalities (7 categories)
Good	Normal, -Y, del(5q), del(20q)
Intermediate	+8, any other single or double abnormality
Poor	Complex with ≥ 3 abnormalities, anomaly of chromosome 7

IPSS Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Good	Intermediate	Poor		
	0	0.5	1		
Bone Marrow Blast %	≤ 5%	5%-10%		11% - 20%	21% - 30%
	0	0.5		1.5	2
Number of Cytopenias	0 or 1	2 or 3			
	0	0.5			

Definition of Cytopenias
Hemoglobin < 10 g/dL
Neutrophil Count < 1.80 x 10^9/L
Platelet Count < 100 x 10^9/L

IPSS Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Low	0	33%	5.7	9.4
Intermediate-1	0.5 - 1	38%	3.5	3.3
Intermediate-2	1.5 - 2	22%	1.1	1.1
High	≥ 2.5	7%	0.4	0.2





LOWER Risk

Low

Int-1

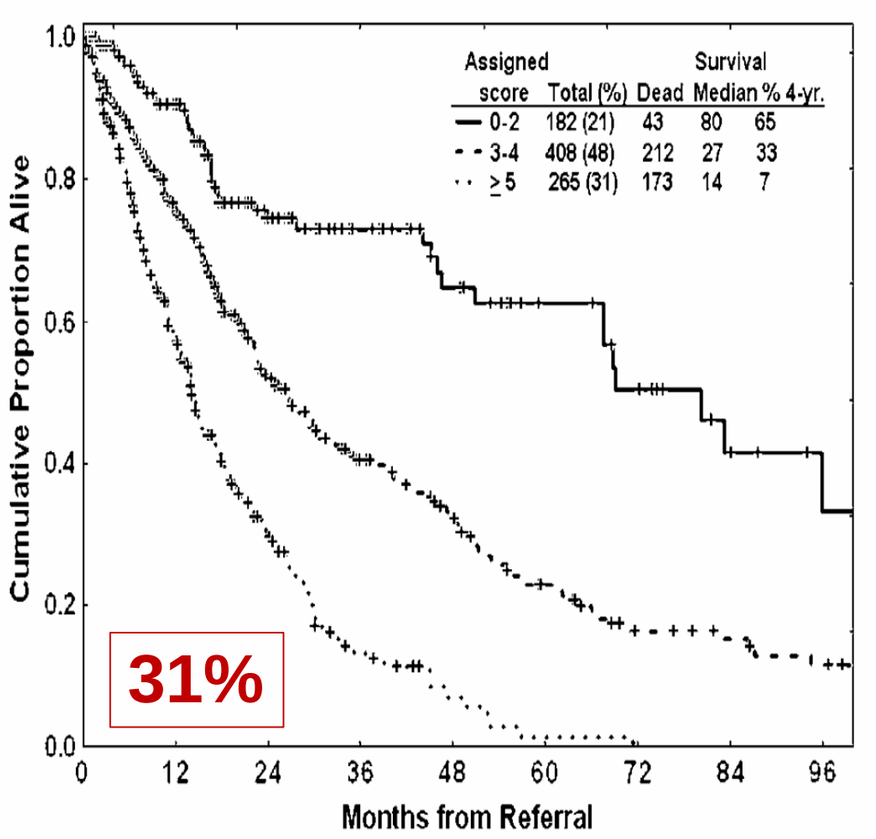
Int-2

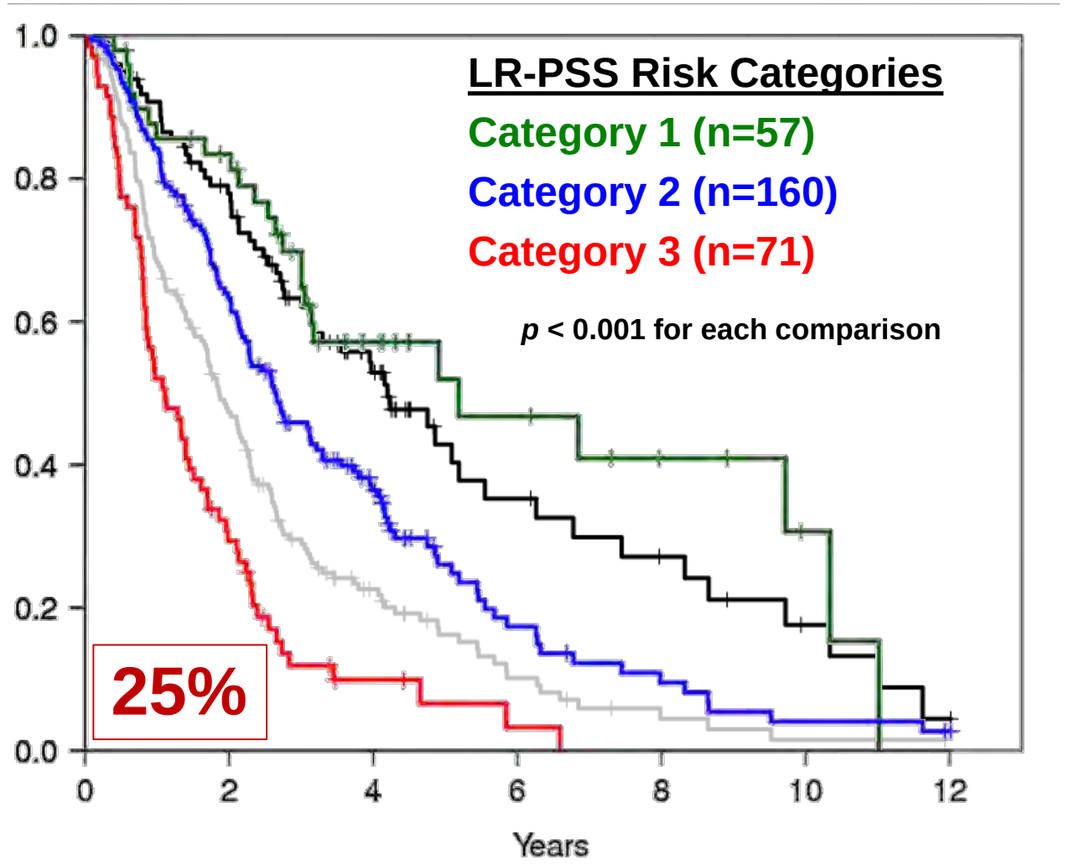
High

HIGHER Risk

Greenberg et al. *Blood*. 1997;89:2079-88.

MD Anderson Lower Risk PSS



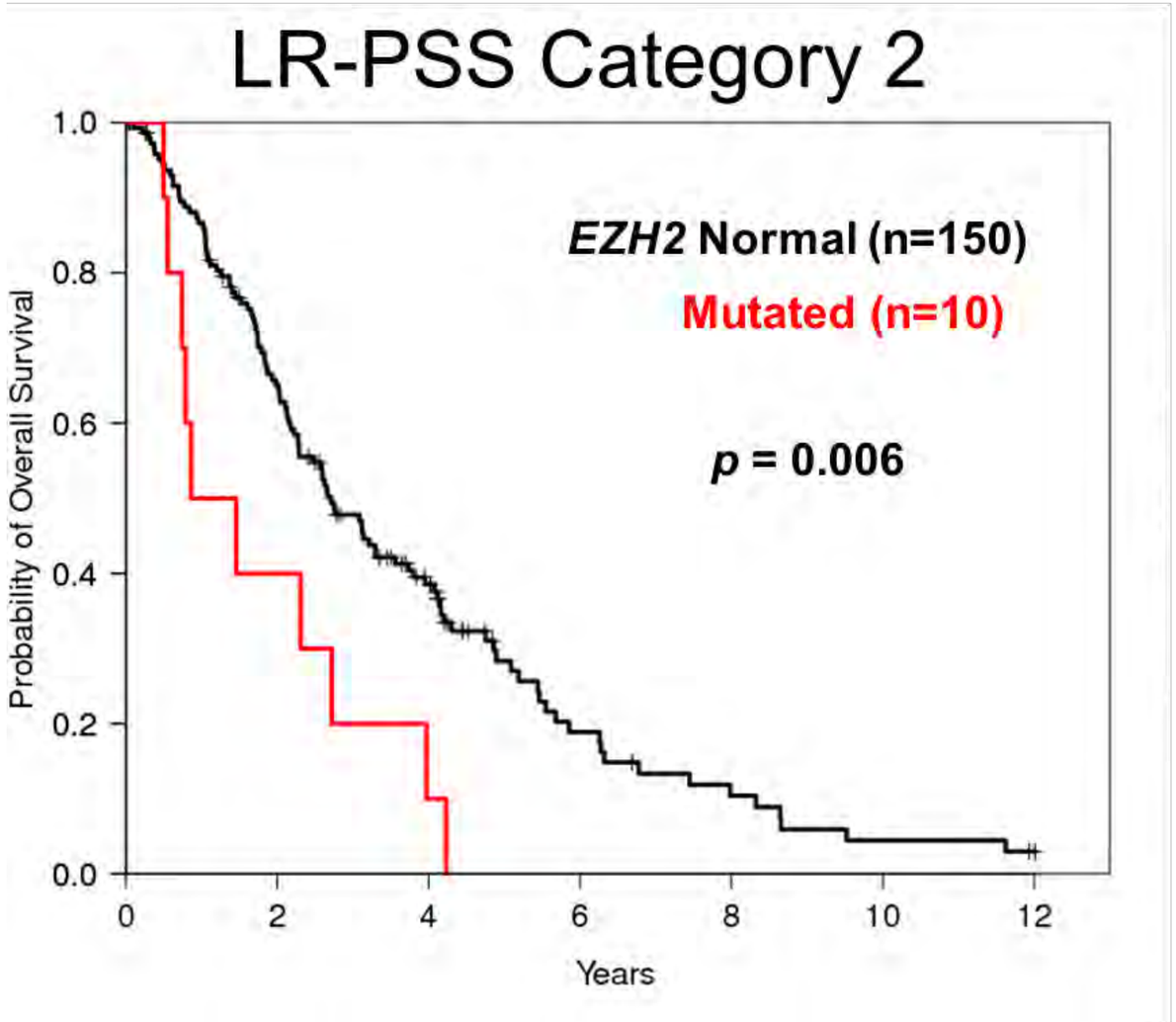


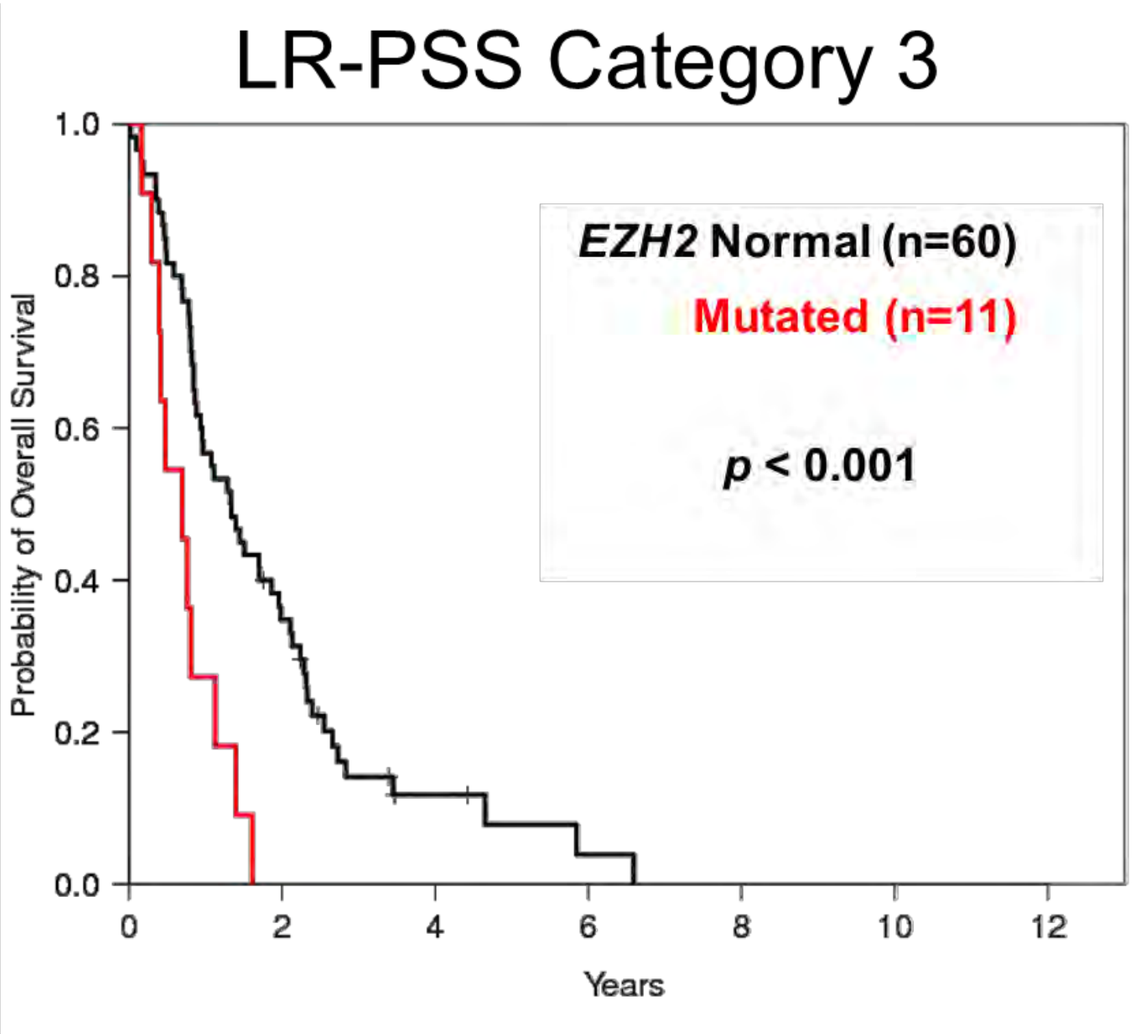
Allows for reweighting of risk factors and inclusion of new ones

Leukemia (2008) 22, 538–543

Bejar et al. *JCO*. 2012

Impact of *EZH2* Mutations in LR-PSS





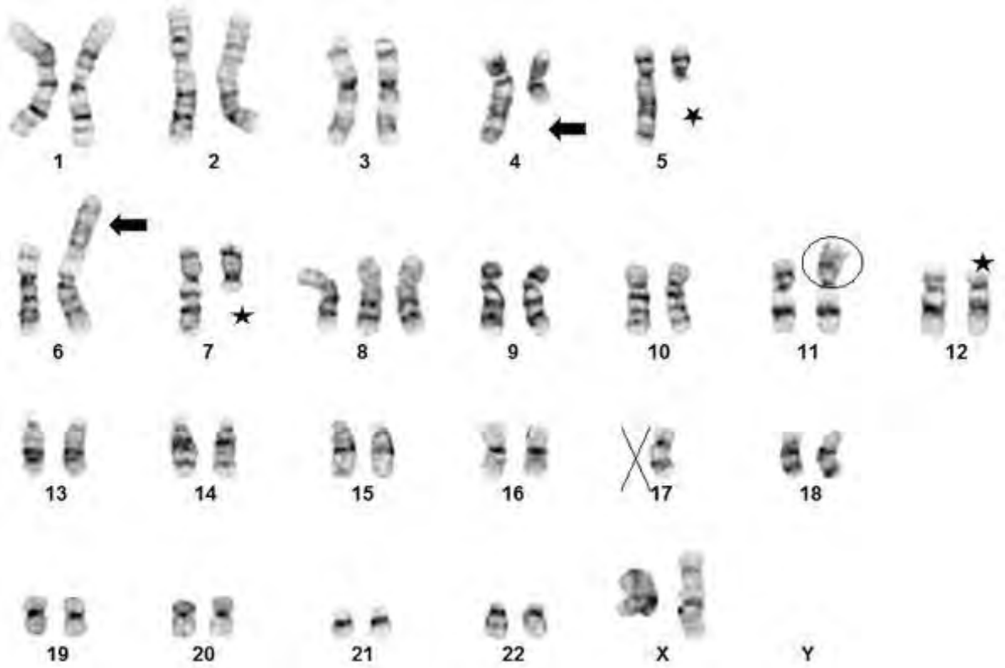
Kristen Stevenson & Donna Neuberg

Bejar et al. *JCO*. 2012

IPSS-Revised (IPSS-R)

Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities (19 categories)
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			



IPSS-R Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Very low	≤ 1.5	19%	8.8	Not reached
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3	3.2
High	> 4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

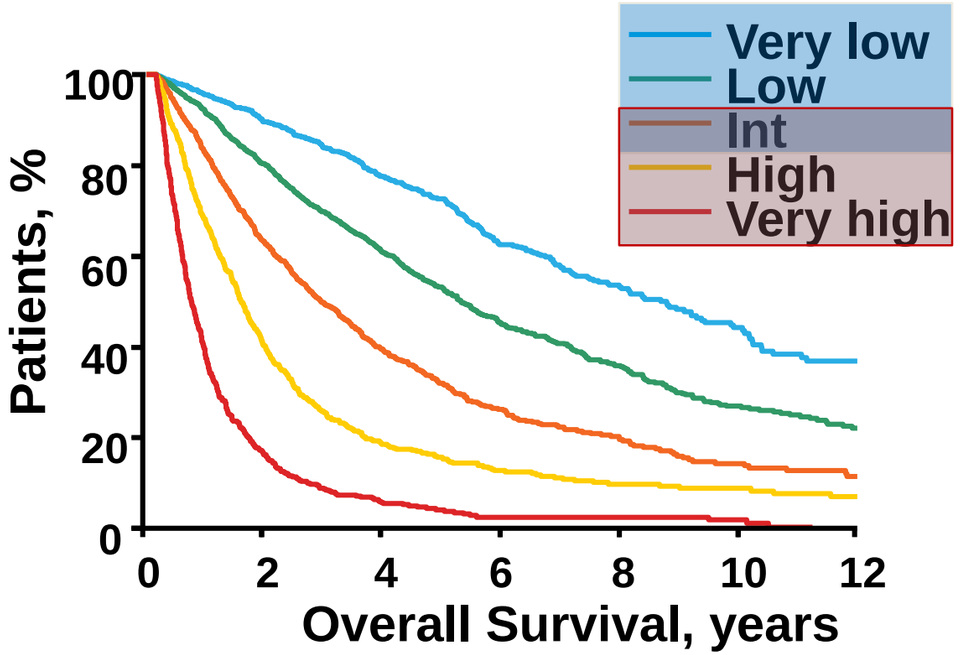
Greenberg et al. *Blood.* 2012:120:2454-65.

Revised IPSS (IPSS-R)

Risk group	Included karyotypes (19 categories)	Median survival, months	Proportion of patients in this group
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



LOWER Risk ≤3.5

HIGHER Risk >3.5

- **Considers only UNTREATED patients**
- **IPSS-R does not consider somatic mutations**
- **Somatic mutations are common in MDS**
- **Several mutated genes have prognostic significance independent of the IPSS-R**

Impact of Adverse Somatic Mutations on IPSS-R

Bejar R. *Haematologica*. 2014 Jun;99(6):956-64.

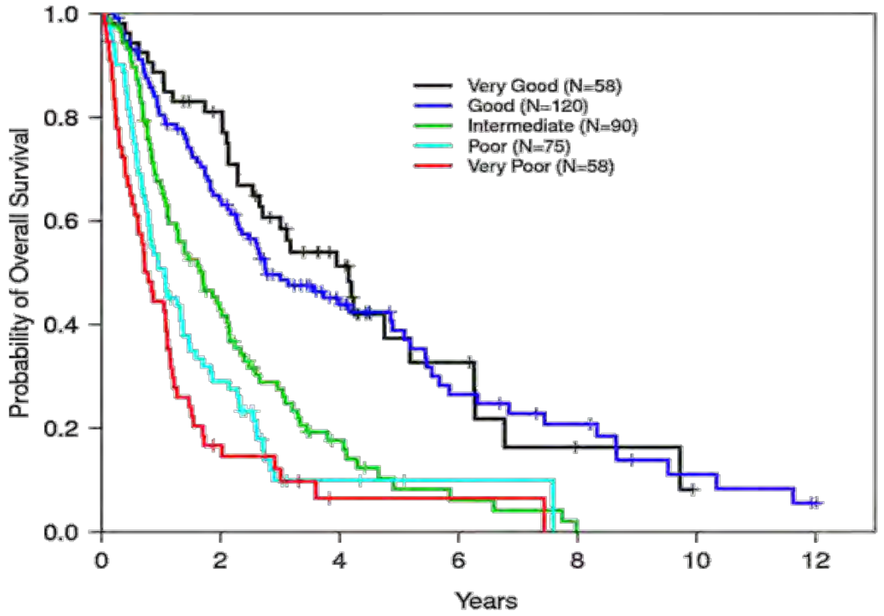
TP53

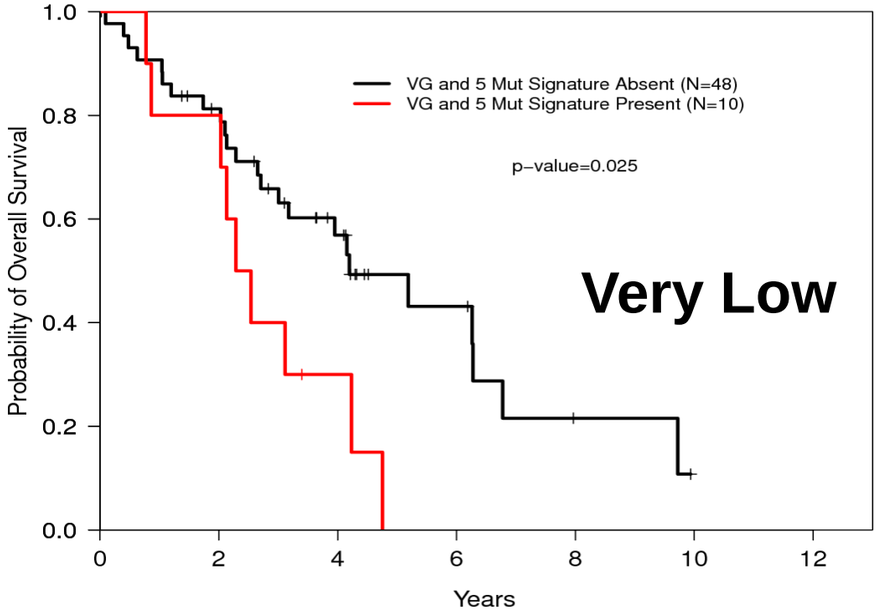
ETV6

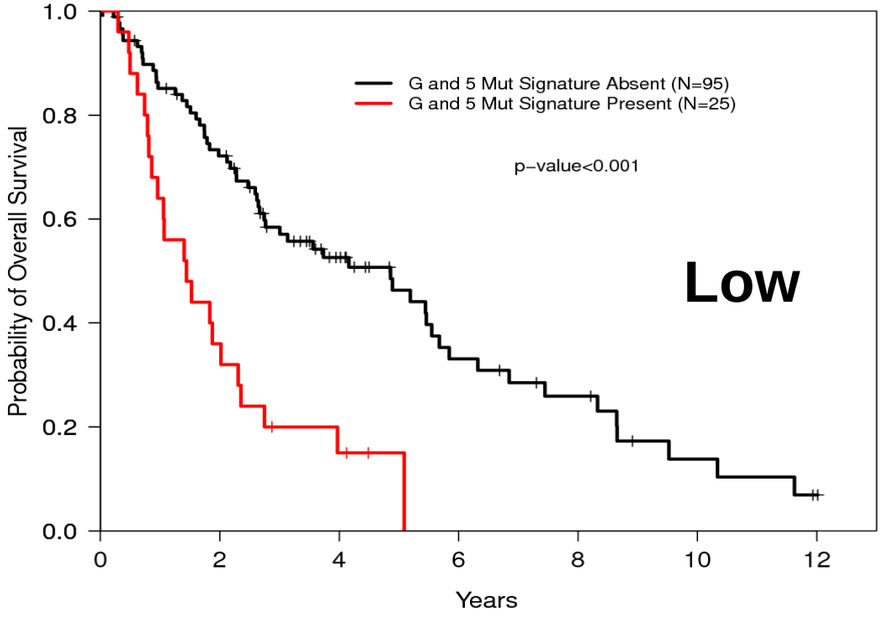
ASXL1

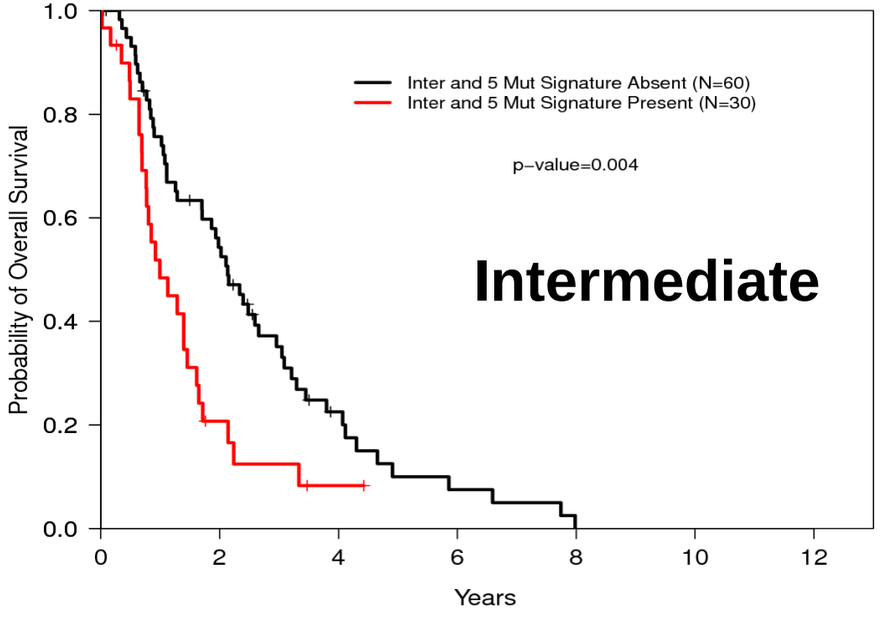
EZH2

RUNX1

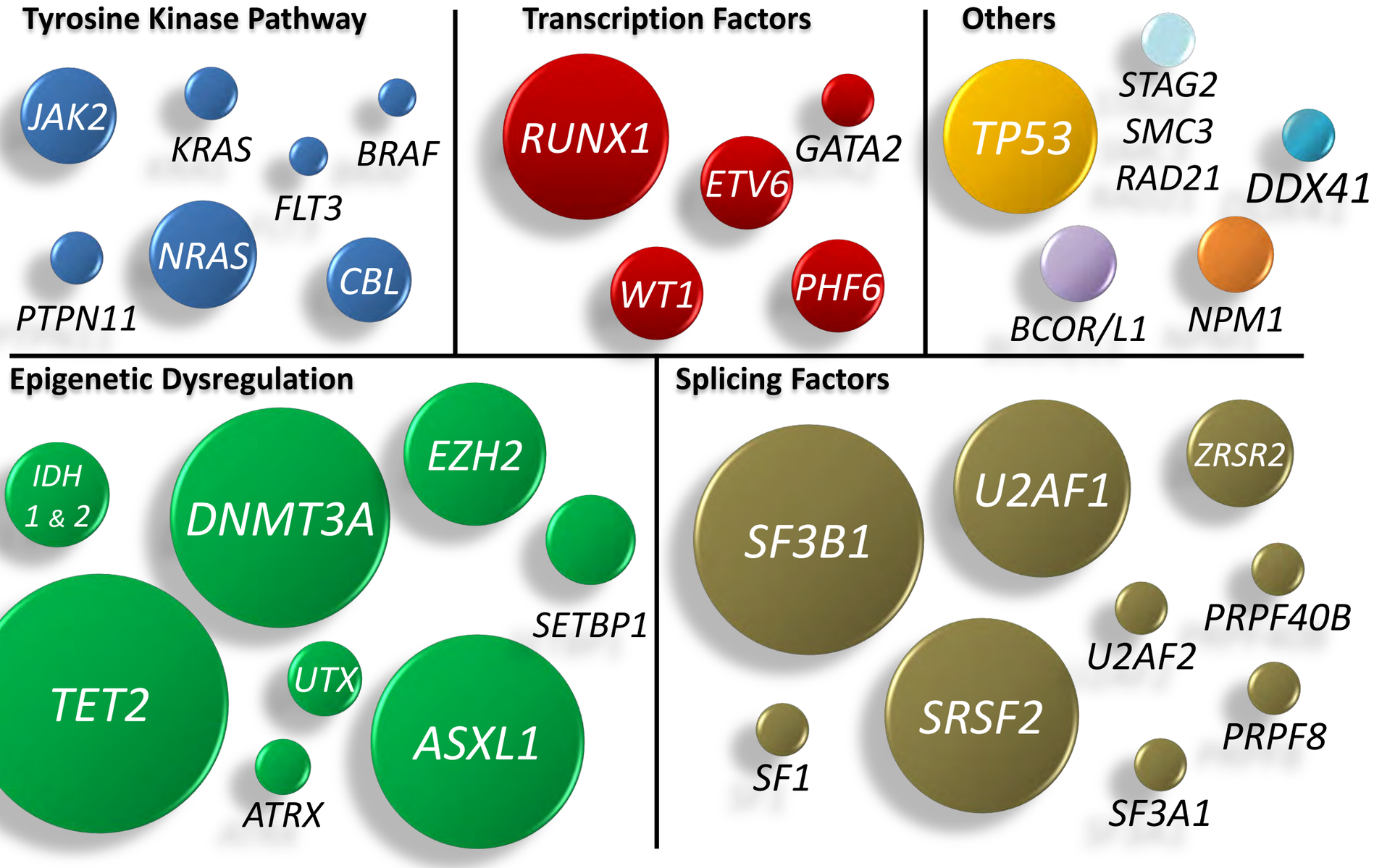








Most Frequently Mutated MDS Genes



Molecular Genetic Risk Stratification with the IPSS-M

How I risk stratify patients with MDS

International Working Group for the Prognosis of MDS (IWG-PM)

Study objective: **Integrate gene mutations into the International Prognostic Scoring System (IPSS/IPSS-R)**

IWG cohort (discovery)

n=2,957

Japan cohort (validation)

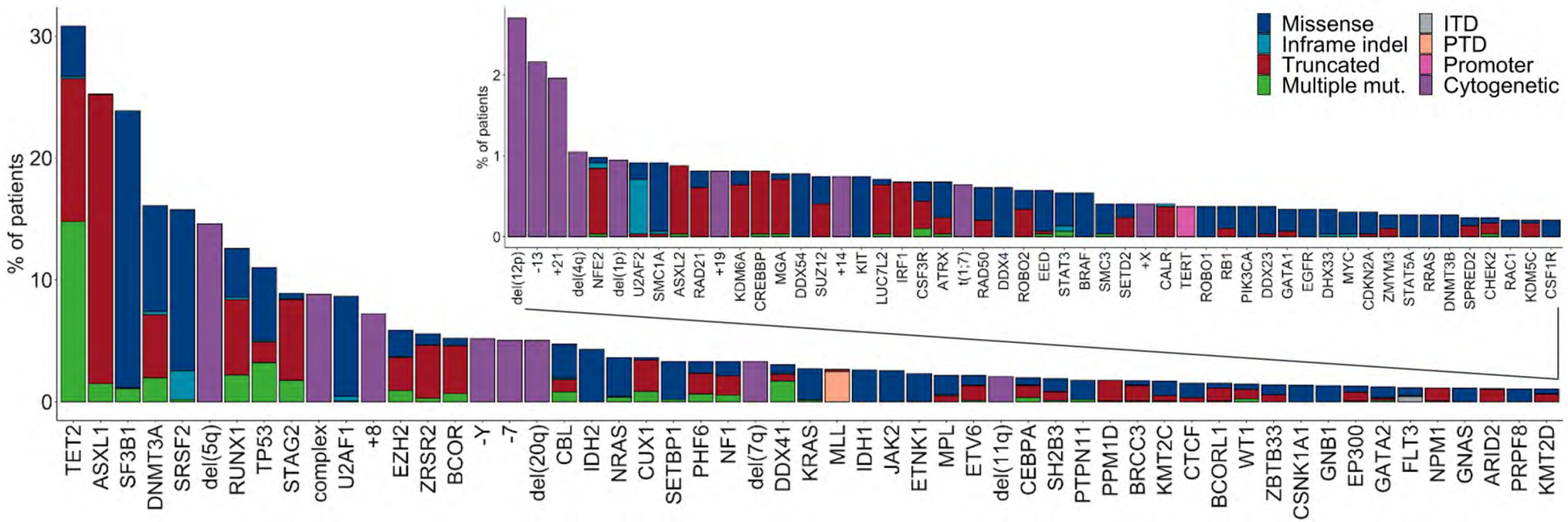
n=754

mds foundation
the myelodysplastic syndromes foundation, inc.

Slides courtesy of Dr. Elsa Bernard

Mutations in the IPSS-M cohort

Molecular characterization: Conventional cytogenetics | Oncogenic mutations from 152 genes (VAF>2%)
Dense copy number probes and SNP baits to capture aUPD/CN-LOH



- 48 genes mutated in >1% of patients.
- 94% of patients had at least one oncogenic lesion.
- Median 4 lesions per patient (range 0-20).

Considers Gene-Gene Interactions

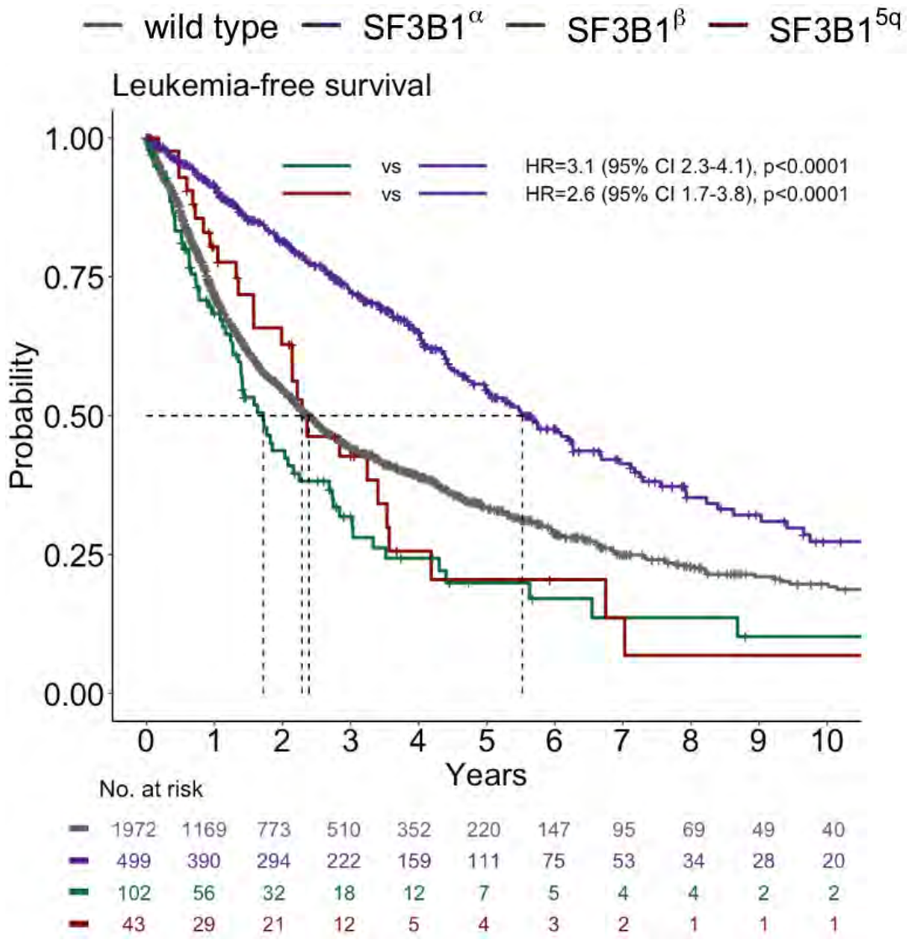
***SF3B1* mutations were associated with favorable outcomes.**

But this association was modulated by its pattern of co-mutations.

1. ***SF3B1*^{5q} (7%)**
Concomitant isolated del(5q)

2. ***SF3B1*$^{\beta}$ (15%)**
Co-occurrence of mutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*

3. ***SF3B1*$^{\alpha}$ (78%)**
Any other *SF3B1* mutations.



Malcovati et al. *Blood* 2011;2015;2021
Meggendorfer et al. *Haematologica* 2017
Malcovati et al. *Blood*. 2020 Jul 9;136(2):157-170.

Molecular IPSS (IPSS-M)

Model fit with a robust Cox multivariable regression adjusted for confounder variables

Category	Variable	Multivariable model: hazard ratio[#] (95% CI)	Weight w	Scaling x^{mean}
confounder	**Age**, in years	1.23 (1.05 - 1.43)	N/A	N/A
	Sex:Male	1.22 (1.06 - 1.41)	N/A	N/A
	Type:Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A	N/A
clinical	% **Bone Marrow Blasts**, in %	1.42 (1.30 - 1.55)	0.352	0.922
	min(**Platelets**,250), in x10^9/L	0.80 (0.72 - 0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171	9.87
cytogenetics	**IPSS-R category vector**[Δ]	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects 17 variables, 16 genes	***TP53***^{multi}	3.27 (2.38 - 4.48)	1.18	0.0710
	MLL^{PTD}	2.22 (1.49 - 3.32)	0.798	0.0247
	FLT3$^{ITD+TKD}$	2.22 (1.11 - 4.45)	0.798	0.0108
	SF3B1^{5q}	1.66 (1.03 - 2.66)	0.504	0.0166
	NPM1	1.54 (0.78 - 3.02)	0.430	0.0112
	RUNX1	1.53 (1.23 - 1.89)	0.423	0.126
	NRAS	1.52 (1.05 - 2.20)	0.417	0.0362
	ETV6	1.48 (0.98 - 2.23)	0.391	0.0216
	IDH2	1.46 (1.05 - 2.02)	0.379	0.0429
	CBL	1.34 (0.99 - 1.82)	0.295	0.0473
	EZH2	1.31 (0.98 - 1.75)	0.270	0.0588
	U2AF1	1.28 (1.01 - 1.61)	0.247	0.0866
	SRSF2	1.27 (1.03 - 1.56)	0.239	0.158
	DNMT3A	1.25 (1.02 - 1.53)	0.221	0.161
	ASXL1	1.24 (1.02 - 1.51)	0.213	0.252
	KRAS	1.22 (0.84 - 1.77)	0.202	0.0271
	SF3B1^{a}	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals[§] 1 variable, 15 genes	min(**Nres**,2) Possible values are 0,1 or 2	1.26 (1.12 - 1.42)	0.231	0.388

Adjusted for confounder variables
Age, sex, MDS type (primary, therapy-related)
Included in the fit but not in the score

Continuous clinical parameters
Marrow blasts, platelets, hemoglobin

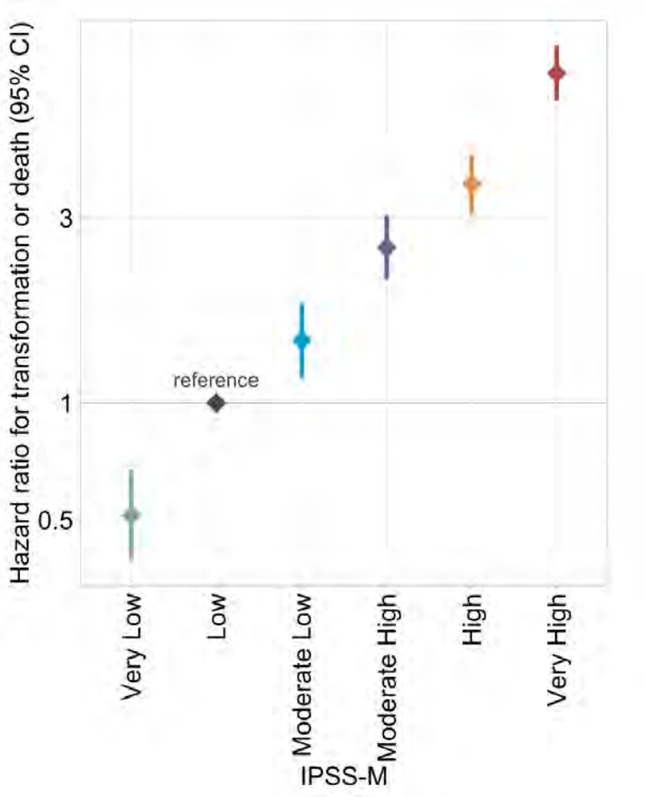
IPSS-R cytogenetic categories
Unchanged in the IPSS-M

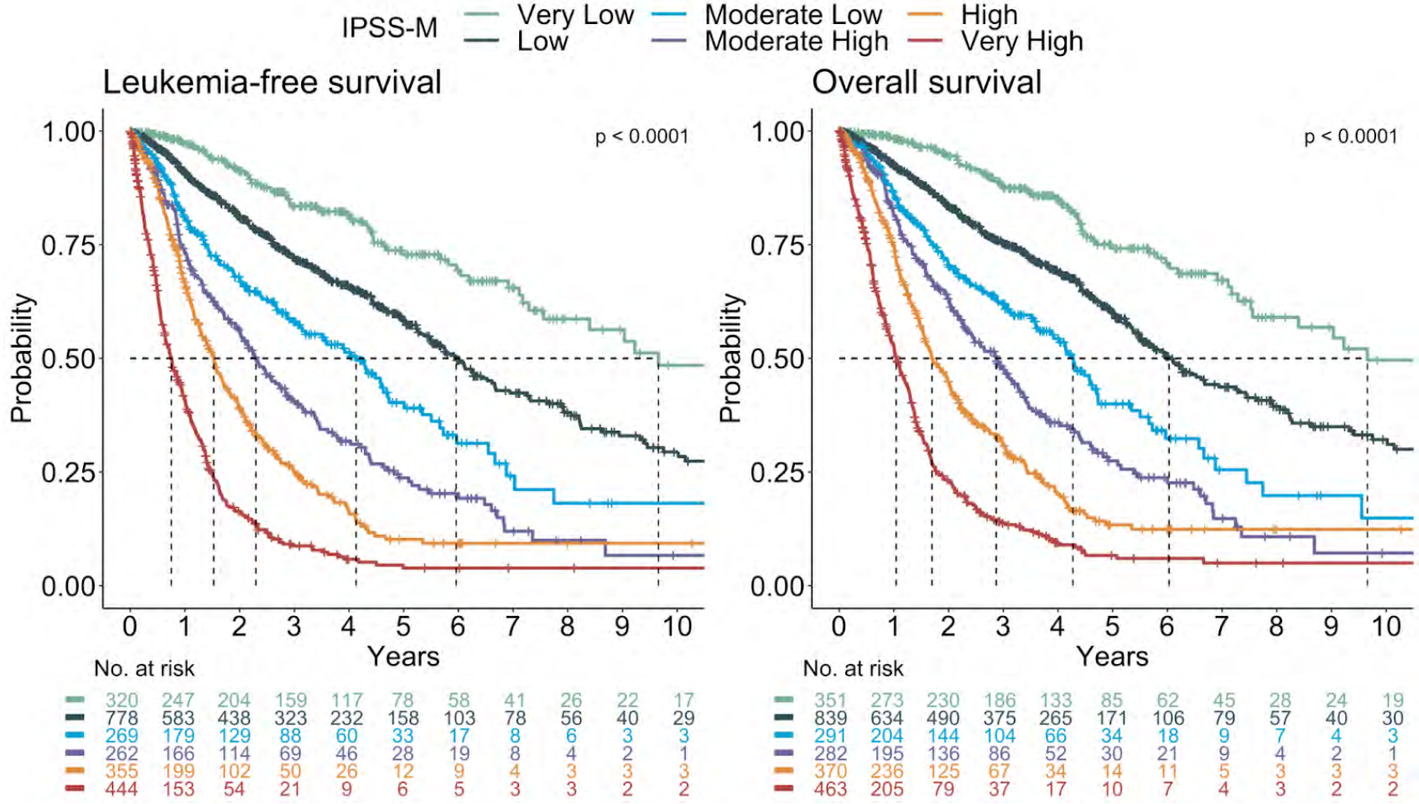
17 genetic variables from 16 main effect genes
Individual weights attributed to each variable

1 genetic variable from 15 residual genes
Number of mutated genes (0, 1 or 2)

IPSS-M Risk Categories

A six-category risk schema



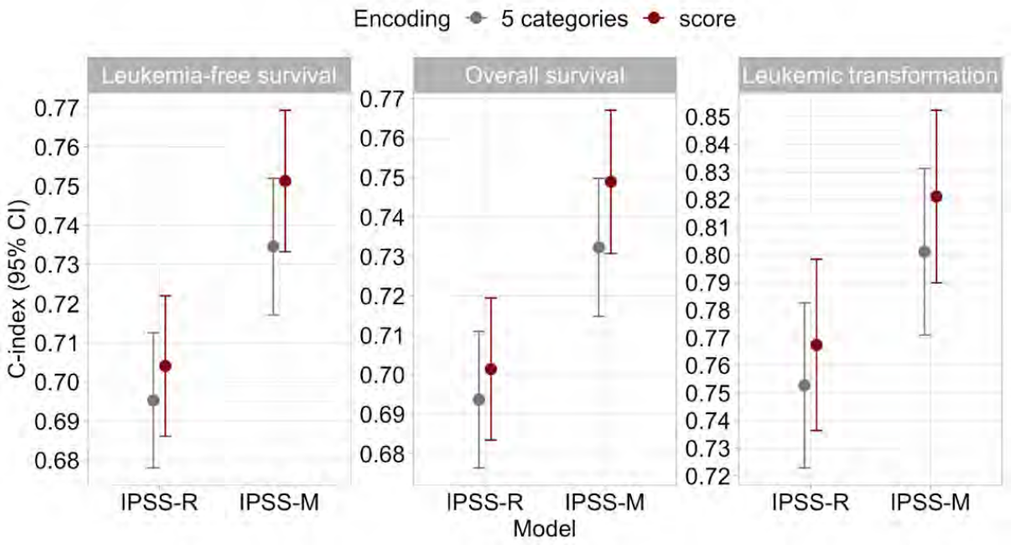


Very Low | Low | Moderate Low | Moderate High | High | Very High

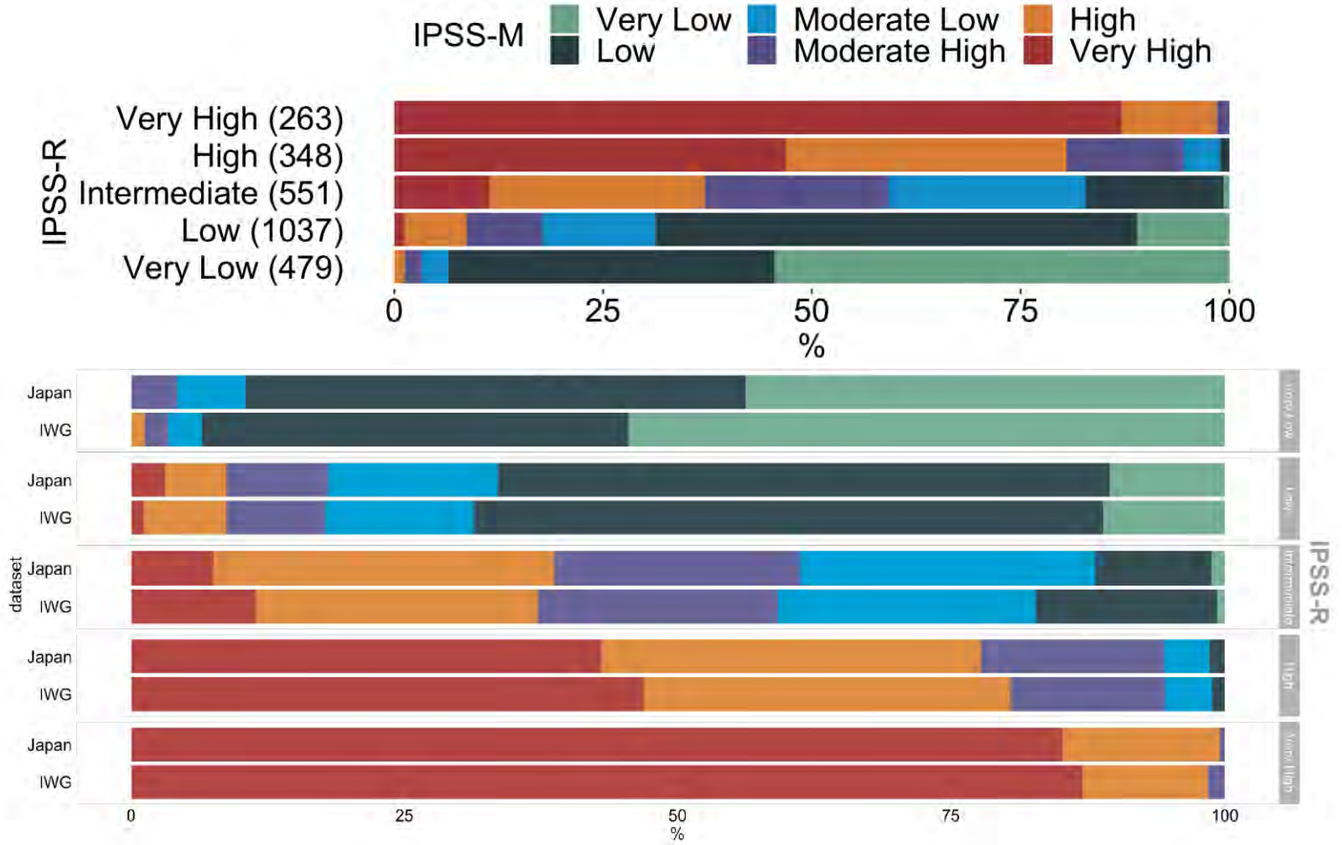
Prognostic separation of the IPSS-M risk categories

Mapping from the IPSS-R to the IPSS-M

Improved prognostic discrimination



Extensive patient re-stratification



Validation in Japanese Cohort →

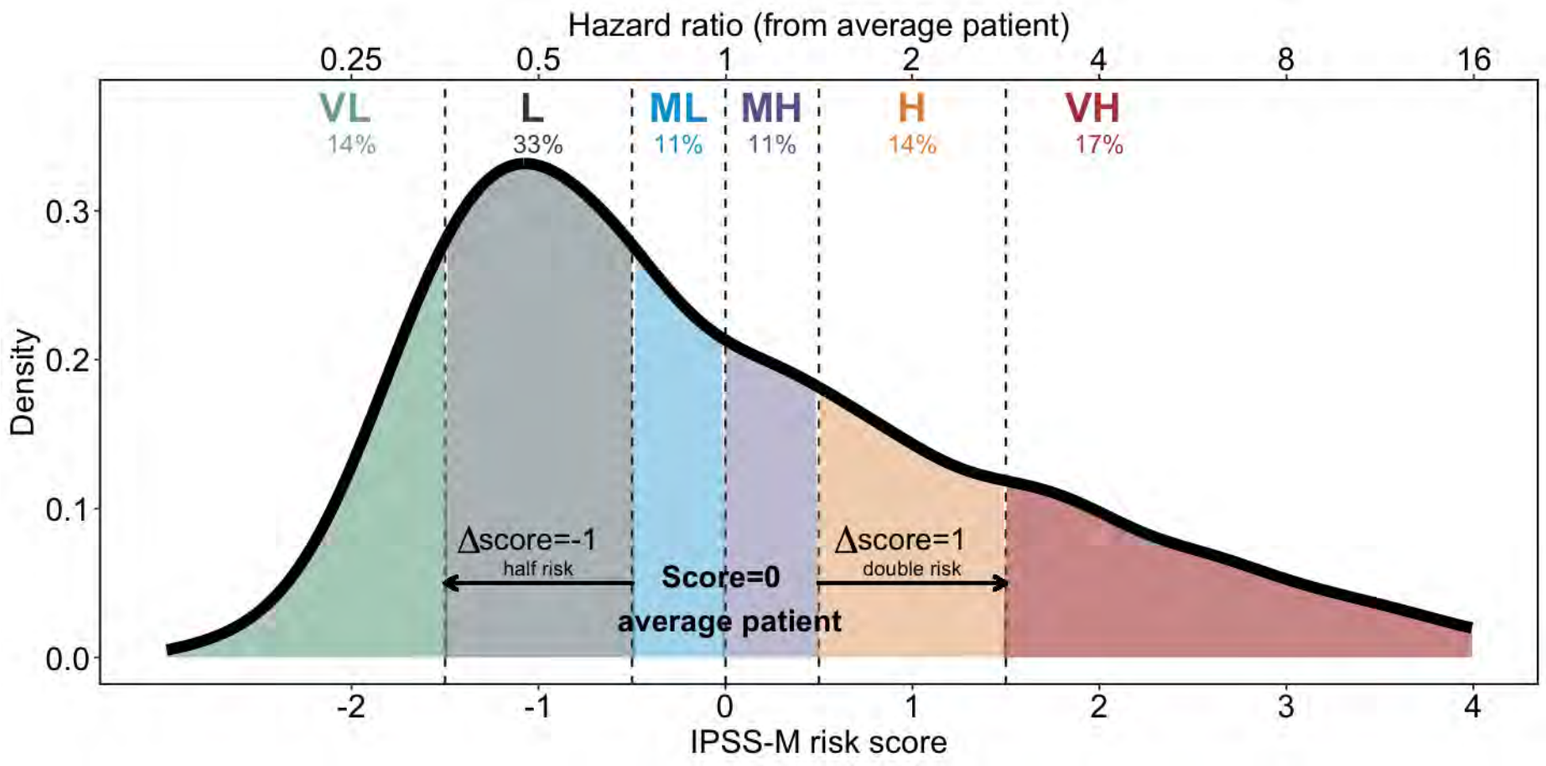
Five points increase in concordance index from IPSS-R to IPSS-M across all endpoints

46% (n=1,223) of patients were re-stratified

7% (n=196) of patients were re-stratified by more than one strata

IPSS-M Risk Categories

A six-category risk schema



Very Low | Low | Moderate Low | Moderate High | High | Very High

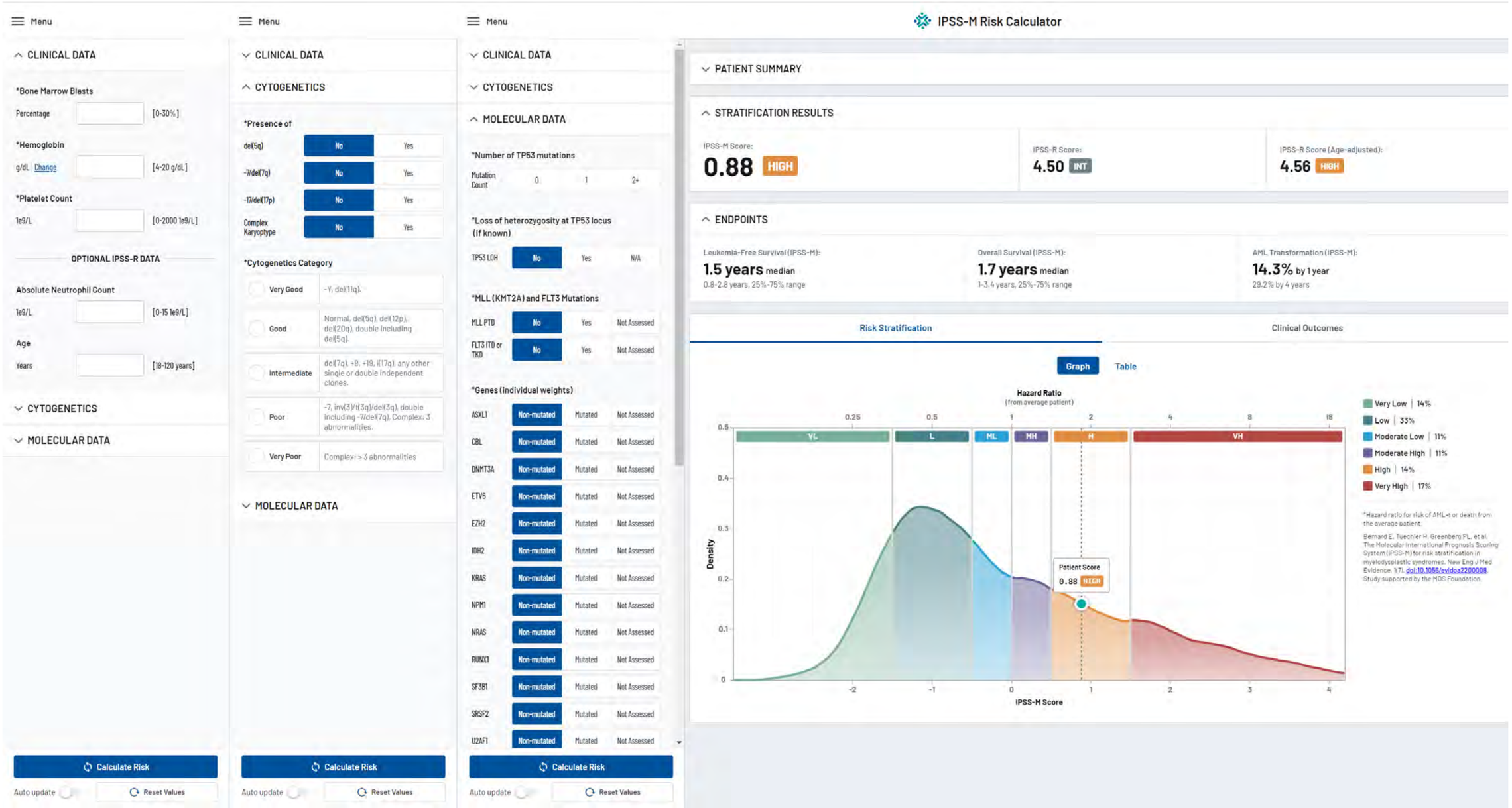
A point change of +1 implies a doubling of prognostic risk

Negative scores are LOWER RISK

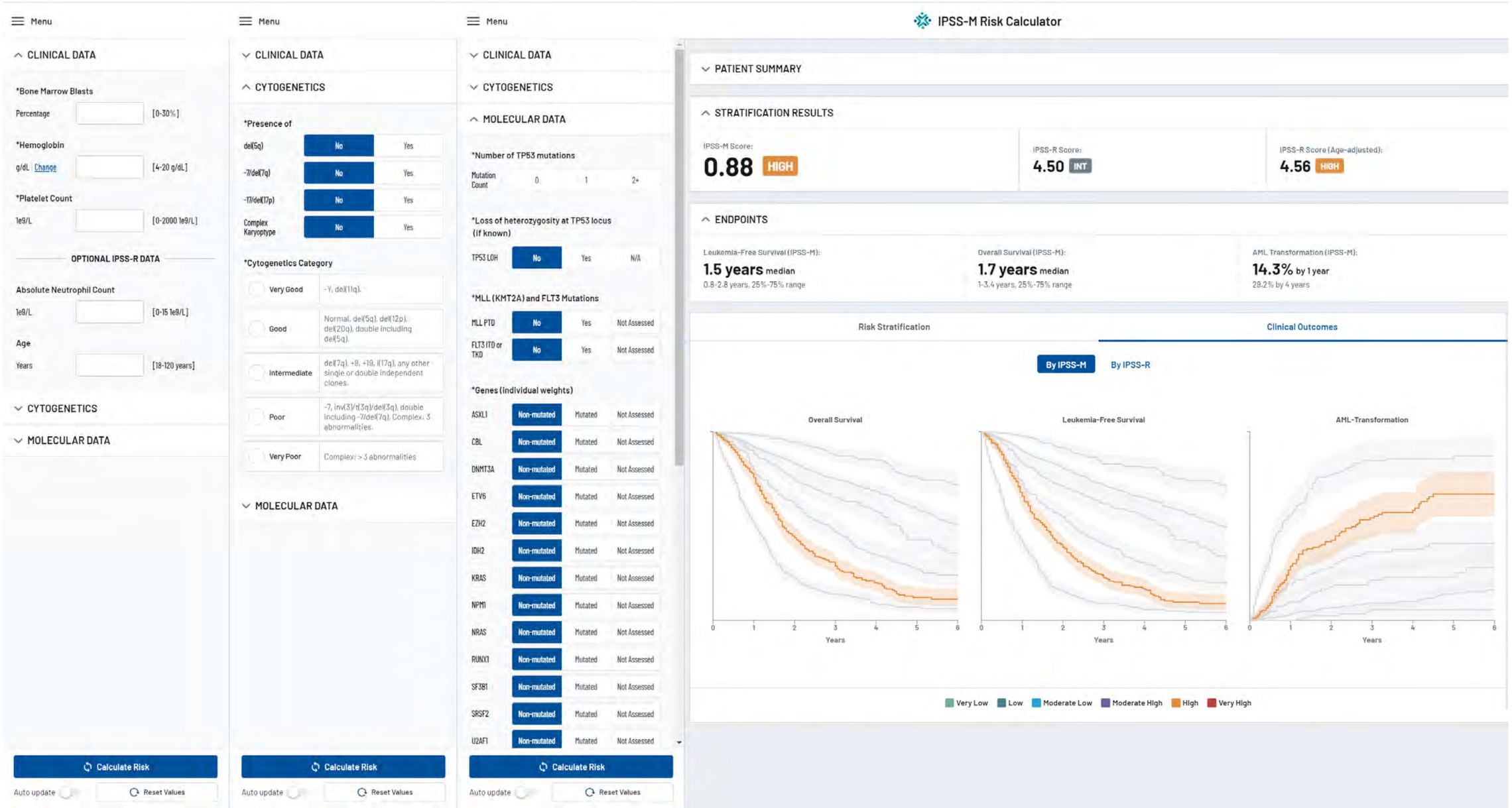
Positive scores are HIGHER RISK

IPSS-M Calculator

https://mds-risk-model.com/



https://mds-risk-model.com/



What if there are missing data?

Patient profile

Myelodysplastic Syndrome (MDS)

Risk Calculator Model

Input Patient Data

1 Clinical Data — 2 Cytogenetics — 3 Molecular Data

DNMT3A	Non-mutated	Mutated	Not Assessed
ETV6	Non-mutated	Mutated	Not Assessed
EZH2	Non-mutated	Mutated	Not Assessed
IDH2	Non-mutated	Mutated	Not Assessed
KRAS	Non-mutated	Mutated	Not Assessed
NPM1	Non-mutated	Mutated	Not Assessed
NRAS	Non-mutated	Mutated	Not Assessed
RUNX1	Non-mutated	Mutated	Not Assessed
SF3B1	Non-mutated	Mutated	Not Assessed
SRSF2	Non-mutated	Mutated	Not Assessed
U2AF1	Non-mutated	Mutated	Not Assessed

* Genes (number of residual mutations)

BCOR	Non-mutated	Mutated	Not Assessed
BCORL1	Non-mutated	Mutated	Not Assessed
CEBPA	Non-mutated	Mutated	Not Assessed
ETNK1	Non-mutated	Mutated	Not Assessed
GATA2	Non-mutated	Mutated	Not Assessed

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Reset Values Calculate Risk

Missing data

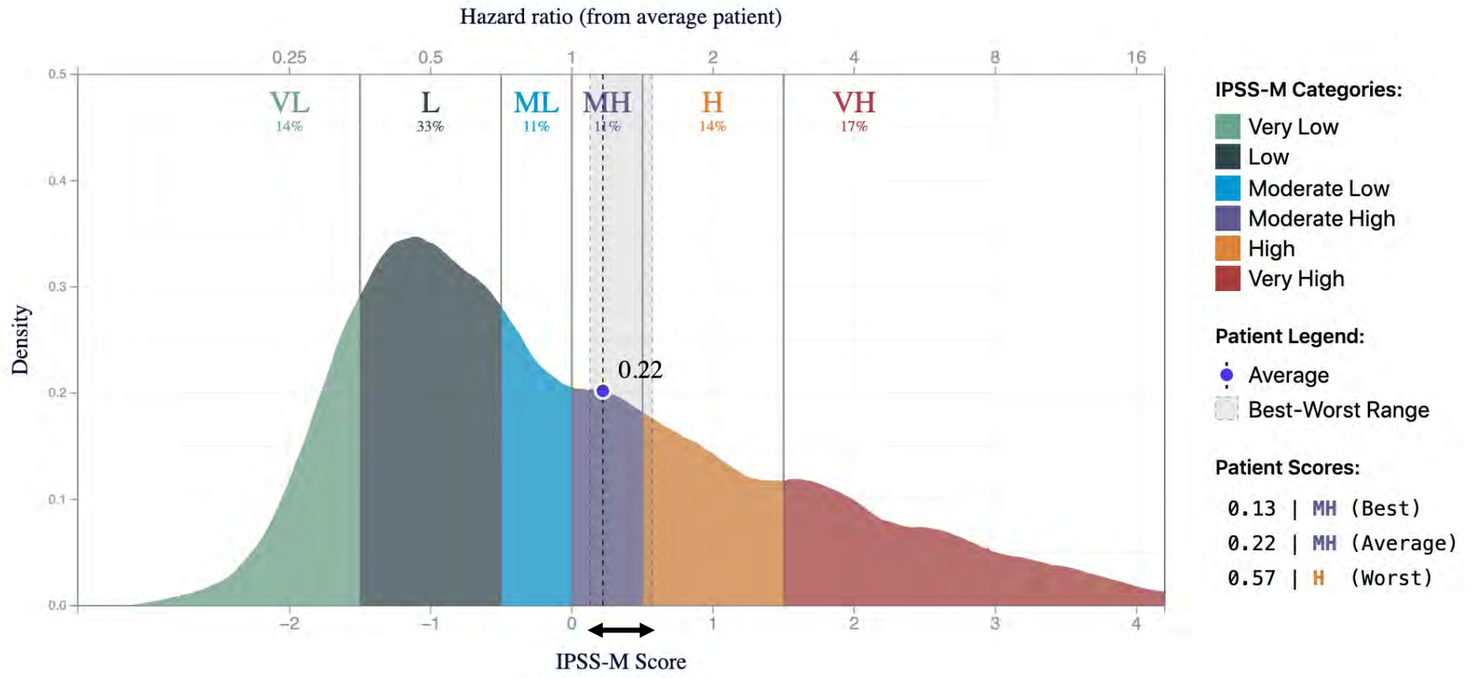
Patient-specific risk score & risk category

Stratification Results

IPSS-M Score:	IPSS-R Score:	IPSS-R Score (Age-adjusted):
0.22 | Moderate High	3.00 | Low	3.07 | Intermediate
0.13 | Moderate High (best), 0.57 | High (worst)		

Endpoints

Leukemia-Free Survival (IPSS-M)	Overall Survival (IPSS-M)	AML Transformation (IPSS-M)
2.3 years median	2.8 years median	9.5% by 1 year



Range of score

MDS Summary

- MDS are a broad range of bone marrow diseases caused by gene mutations that affect how blood cells grow and mature
- MDS can be very mild and slowly progressive or more severe and rapidly changing with an increased risk of becoming AML
- The IPSS-M is a new tool that helps predict MDS risk and can guide the timing and choice of therapy
- Knowing your MDS subtype, gene mutations, and risk group is key to understanding your treatment options and prognosis

Hematology at UC San Diego

MDS Center of Excellence at UC San Diego

Marla McArdle	Rosie Tan	- Bejar Clinic/Lab
Jennifer Galvan	Olivia Reynolds	
Michelle Don	Huanyou Wang	- Hematopathology
Edward Ball	James Mangan	- BMT Group
Tiffany Tanaka	Divya Koura	
Carolyn Mulroney	Caitlin Costello	
Fotis Asimakopoulos	Dimitri Tzachanis	
Aaron Goodman	Dan Kauffman	
Ayad Hamdan	Autumn Jeong	
Sandy Shattil	John Adamson	- Hematology Group
Catriona Jamieson	Michael Choi	
Erin Reid	Tom Kipps	
Benjamin Heyman	Annette Von Drygalski	
Srila Gopal	William Pearse	
Anthony Nguyen	Amanda Kagan	
Jenny Zhou		

All of our PATIENTS and INFUSION CENTER nurses and staff!

UC San Diego
MOORES CANCER CENTER

mds foundation
the myelodysplastic syndromes foundation, inc.

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AMERICAN SOCIETY OF HEMATOLOGY

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LEUKEMIA & LYMPHOMA SOCIETY®
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