Understanding your MDS risk score

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Case 1 - Mary

- 66 yo woman with anemia and low white blood cell count
- She has a bone marrow biopsy and is told she has myelodysplastic syndrome with excess blasts-1
- What does this mean?
- How can we try to determine how this might behave?

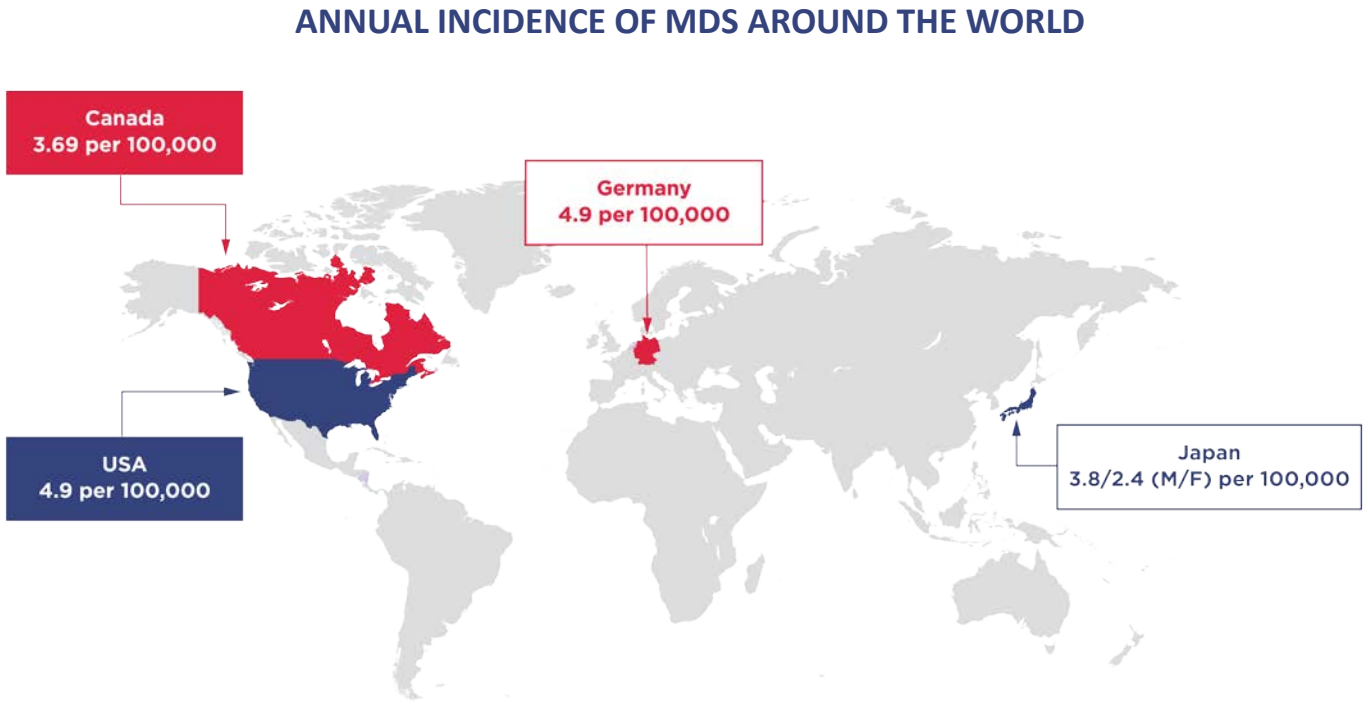
Canadian and Global Incidence of MDS

> 350,000 patients have MDS worldwide[1]

In Canada, it is estimated that there are 10,000 – 40,000 patients who have been diagnosed with MDS[2]

- Approximately 1,800 – 5,900 new cases are diagnosed each year in Canadians >65 years[2]

The highest incidence rates are found in the U.S, Japan, and Germany[3]

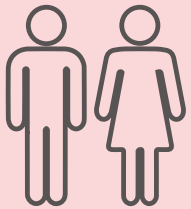


MDS, myelodysplastic syndromes.

[1]Research and Markets. Global Myelodysplastic Syndrome (MDS) Market 2017-2027: Prevalence Forecast, Licensing and Acquisition Deals & Drug-Specific Revenue Forecasts. Available at: https://www.globenewswire.com/news-release/2018/01/22/1298306/0/en/Global-Myelodysplastic-Syndrome-MDS-Market-2017-2027-Prevalence-Forecast-Licensing-and-Acquisition-Deals-Drug-Specific-Revenue-Forecasts.html. [2]Leukemia & Lymphoma Society of Canada. Blood Cancer in Canada. 2016. [3]Slack J, et al. Journal of Applied Laboratory Medicine. 2018;03:378-383.

DEMOGRAPHICS OF MDS

The incidence of MDS varies depending on:



Sex

MDS affects more males than females[1]

Race

MDS affects individuals of all races but the incidence rate is highest in White individuals[1]

Age

The median age of diagnosis for MDS is 76 years[2]
Incidence rates increase drastically in individuals >80 years[3]

*Based on data from the United States
MDS, myelodysplastic syndromes.
[1]Rollison DE, et al. Blood. 2008;112;45-52. [2]Wells R, et al. Canadian Medical Association Journal. 2016;188(10):751. [3]SEER Cancer Statistics Review 1975-2016. Section 30. National Cancer Institute. Available at https://seer.cancer.gov/csr/1975_2016/results_merged/sect_30_mds.pdf#search=mds.

RISK FACTORS FOR DEVELOPING MDS

Most cases of MDS occur *de novo* but a number of risk factors have been identified:

Environmental/ Lifestyle

Occupational benzene exposure (e.g., petrochemical industry), or through cigarette smoke (increases MDS risk for as long as 15 years from time of quitting)[1,2]

Therapy-Related*

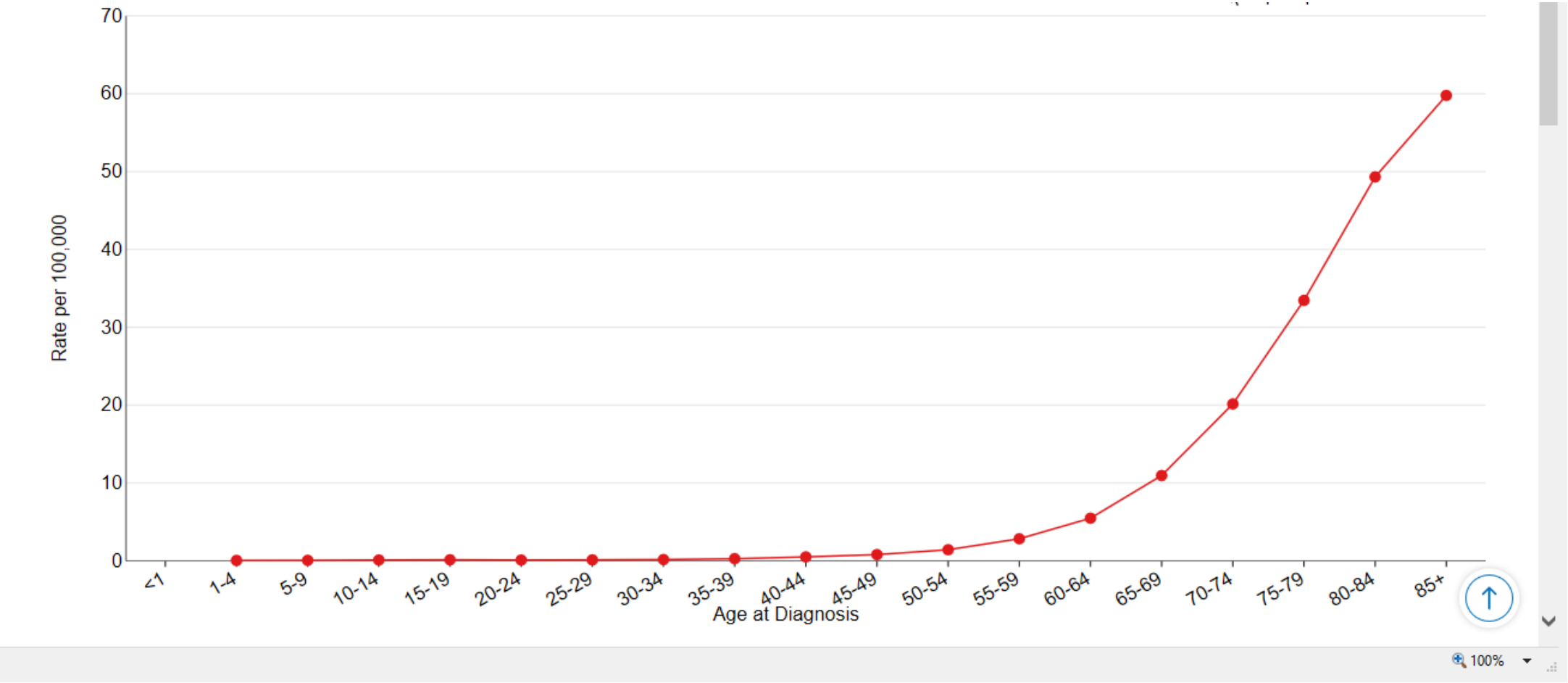
Therapy-related MDS (t-MDS) constitutes **10 – 15%** of all MDS cases[3]
T-MDS is typically considered higher-risk, with greater resistance to treatment, and worse prognosis[4]

Other

Family history of hematopoietic cancers, certain inherited blood disorders†, and a BMI >25 increase an individual's risk of developing MDS[1,3,5]

*Developed after chemotherapy and/or radiotherapy treatment for other cancers. †Such as Fanconi anemia, congenital neutropenia.
BMI, body mass index; MDS, myelodysplastic syndromes; t-MDS, therapy-related MDS.
[1]Strom SS, et al. Leukemia. 2005;19:1912-1918. [2]Schnatter AR, et al. J Natl Cancer Inst 2012. 104:1724-1737. [3]Steensma DP. Mayo Clinic Proceedings. 2015;90:969-983. [3]Fukumoto JS, Greenberg PL. Critical Reviews in Hematology Oncology. 2005;56:179-192. [5]Ma X, et al. American Journal of Epidemiology. 2009;169:1492-1499.

Incidence rates of MDS by age at diagnosis, SEER database 2013-2017



https://seer.cancer.gov

Environmental exposures & High risk professionals[1]

Environmental exposures

Professional	Adjusted OR	95% CI	*P*
Petrol	2·5	(0·9–7·7)	0·8
Aromatic polycyclic hydrocarbons	1·8	(0·7–4·6)	0·93
Exhaust gases	1·0	(0·5–1·9)	0·27
Dyes	2·3	(0·5–13·9)	0·77
Plastic fumes and dusts	3·5	(0·7–34·5)	0·09
Wood dusts	1·0	(0·3–3·3)	0·71
Pesticides	3·2	(1·1–11·2)	0·21
Fertilizers	2·9	(1·2–8)	0·96
Cereal dust	2·6	(1·2–6)	0·58
Poultry	15	(2·3–631·5)	0·1
Cotton and flax dusts	3·4	(1·6–8·2)	0·013
Radiation	2.25	(1.1 - 4.7)	NR

High risk professionals

Professional	Adjusted OR	95% CI	*P*
Agricultural workers	3·66	(1·9–7·0)	0·0001
Textile operators	3·66	(1·7–7·9)	0·001
Health professionals	10·0	(2·1–48·7)	0·004
Living next to an industrial plant	2·45	(1·5–4·1)	0·007
Commercial and technical sales representatives	4·45	(1·4–14·6)	0·013
Smoking	1·74	(1·1–2·7)	0·015
Machine operators	2·69	(1·2–6·0)	0·015
Oil use	1·10	(1·0–1·2)	0·029

1. Occupational and environmental risk factors of the myelodysplastic syndromes in the North of France, C Nisse et al, Br J Haematol, 2001 Mar;112(4):927-35

COMMON SIGNS AND SYMPTOMS OF MDS

MDS can be asymptomatic and discovered during routine blood work[1]

Low blood counts associated with MDS may manifest as signs and symptoms leading to a diagnosis[1]

Common Signs and Symptoms of MDS[1,2]
Fatigue, weakness
Loss of sense of well-being
Pale
Shortness of breath with exertion
Frequent severe infections
Easy bruising and/or bleeding (e.g., nosebleeds, gum bleeds)
Weight loss
Loss of appetite
Fever

MDS, myelodysplastic syndromes.

[1]Mayo Clinic. Myelodysplastic Syndromes. Available at: https://www.mayoclinic.org/diseases-conditions/myelodysplastic-syndrome/symptoms-causes/syc-20366977. [2]Canadian Cancer Society. Myelodysplastic Syndromes. Available at: https://www.cancer.ca/en/cancer-information/cancer-type/leukemia/leukemia/myelodysplastic-syndromes/?region=on.

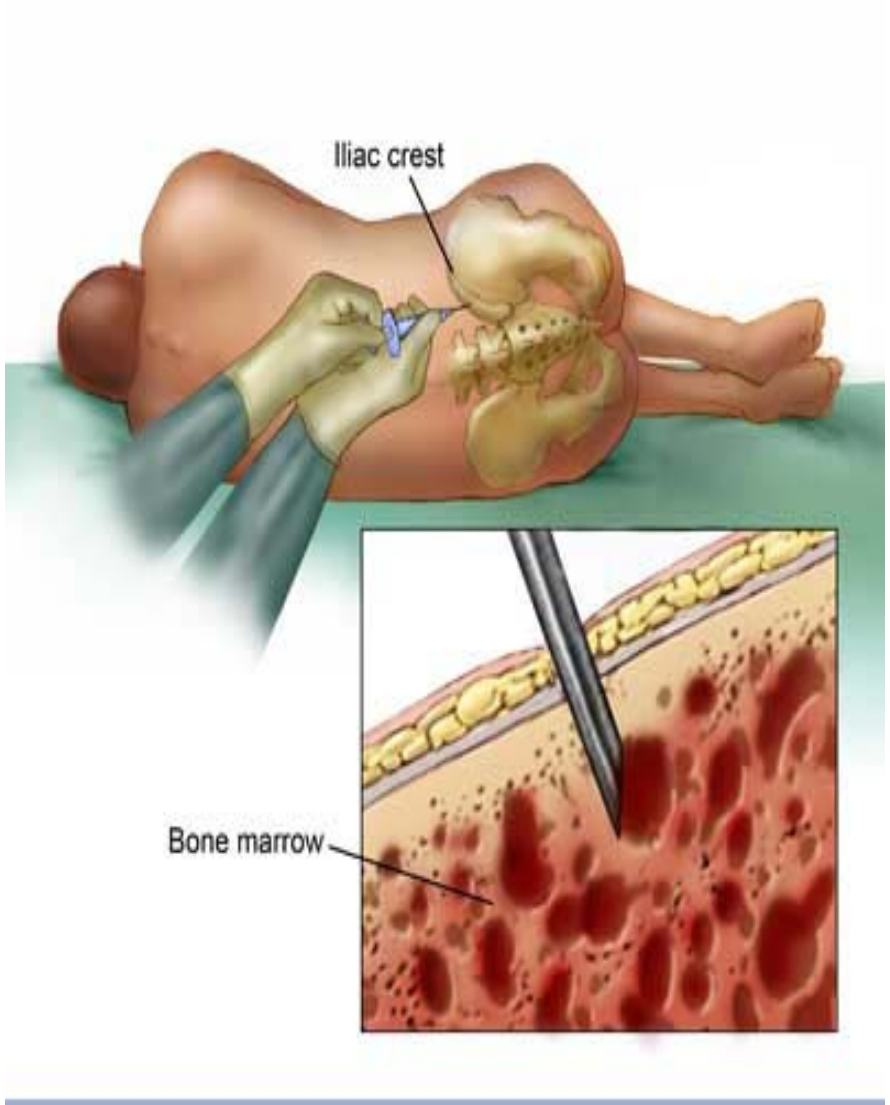
SYMPTOMS ASSOCIATED WITH LOW BLOOD COUNTS

MDS is characterized by cytopenias

- **Anemia** is the most common cytopenia in MDS
- **Thrombocytopenia (low platelets)** is observed in ~50% of patients with lower risk MDS
- Neutropenia (low neutrophils, a type of white blood cell) is observed in ~50% of patients with MDS

Anemia	Thrombocytopenia	Neutropenia
Fatigue Weakness Lightheadedness Shortness of breath Rapid heartbeat Pallor Chest pain Confusion	Petechiae Easy or excessive bruising Abnormal or excessive bleeding from nose or mouth Unusually heavy menstrual flow Blood in urine or stool Bleeding in the gastrointestinal tract Neurological symptoms including headache, confusion or balance difficulties in severe cases	Fever Frequent, severe or unusual infections

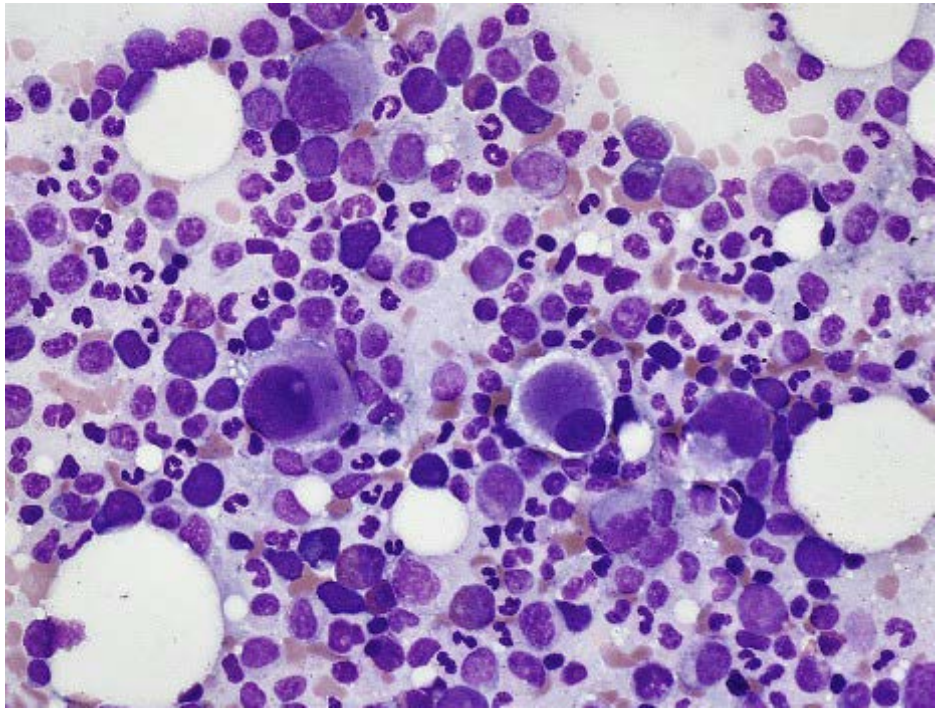
Bone Marrow Biopsy



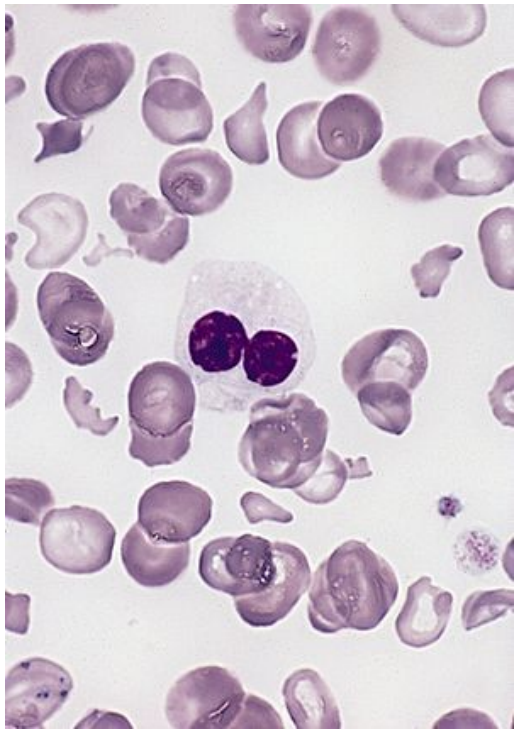
- Examination of marrow from posterior superior iliac crest by:
  - Microscopy
  - Stains for immunohistochemistry
  - Flow cytometry
  - Chromosome testing
  - Molecular testing
    - Usually acquired mutations but some are inherited

www.mayoclinic.org

Bone marrow examination



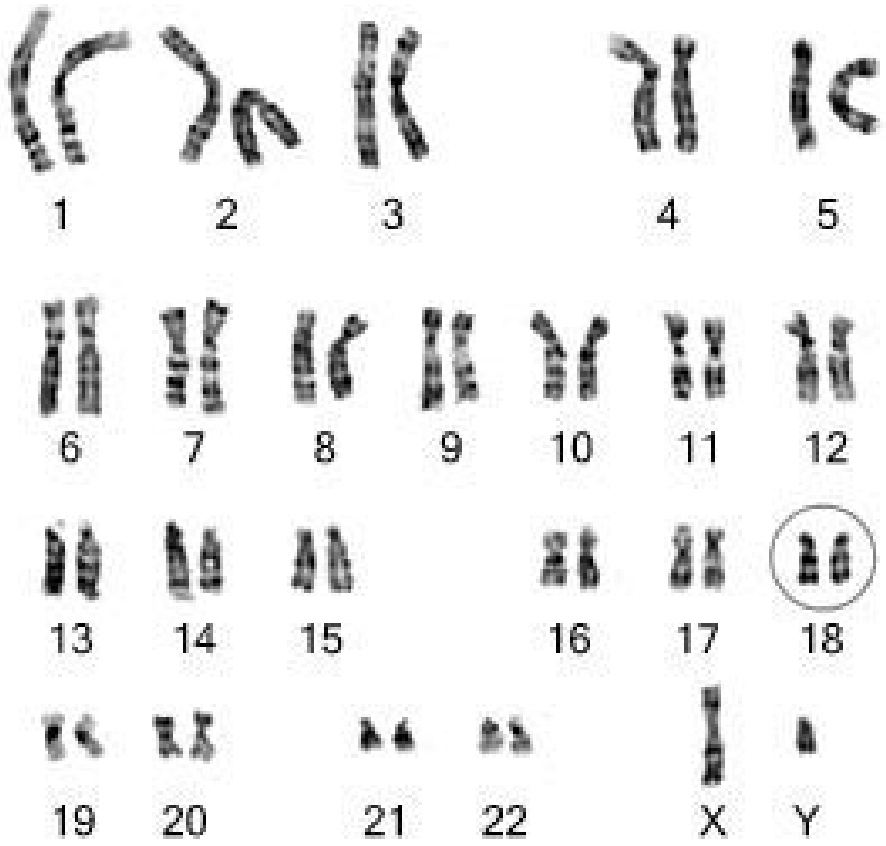
Bone marrow biopsy



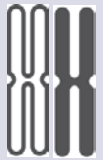
Bone marrow aspiration in patient with MDS

Scott Murphy, http://photo.net

Chromosome analysis (Karyotype)



DIAGNOSING MDS - CYTOGENETIC ABNORMALITIES



Cytogenetic features significantly impact prognosis and treatment, and can be used to confirm MDS diagnosis in cases where morphologic changes are subtle[1-4]

~50%

of *de novo* MDS patients have ≥1 cytogenetic abnormality[5]

The majority of chromosomal aberrations in MDS are unbalanced, resulting in the loss or gain of chromosomal material[6]

The loss or gain of chromosomes impacts the production of gene products that are important in MDS-related pathways[7]

MDS, myelodysplastic syndromes.

[1]Greenberg P, et al. Blood. 1997;89(6):2079-2088. [2]Greenberg P, et al. Blood. 2012;120(12):2454-2465. [3]Fenaux P, et al. Blood. 2011;118:3765-3776. [4]Expert opinion. [5]Haase D, et al. Blood. 2007;110:4385-4395. [6]Ogawa S. Blood. 2019;133:1049-1059. [7]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19.

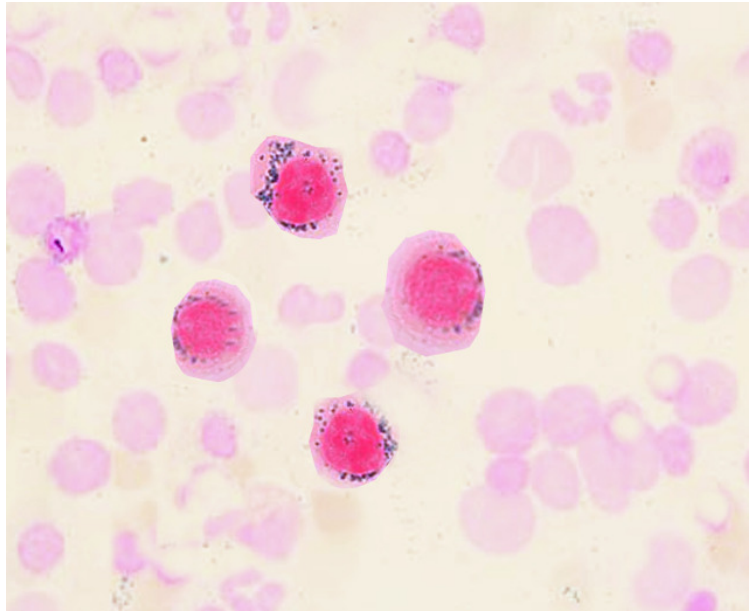
2016 WHO Classification

Myelodyplastic Syndromes:

- Myelodysplastic syndrome with single lineage dysplasia
- Myelodysplastic syndrome and multilineage dysplasia
- Myelodysplastic syndrome with ringed sideroblasts
  - Single lineage dysplasia
  - Multilineage dysplasia
- Myelodysplastic syndrome with excess blasts
  - MDS-Excess blasts-1 (5-9%)
  - MDS Excess blasts-2 (10-19%)
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome unclassifiable

Myelodysplastic/myeloproliferative neoplasms:

- Chronic myelomonocytic leukemia
- Others

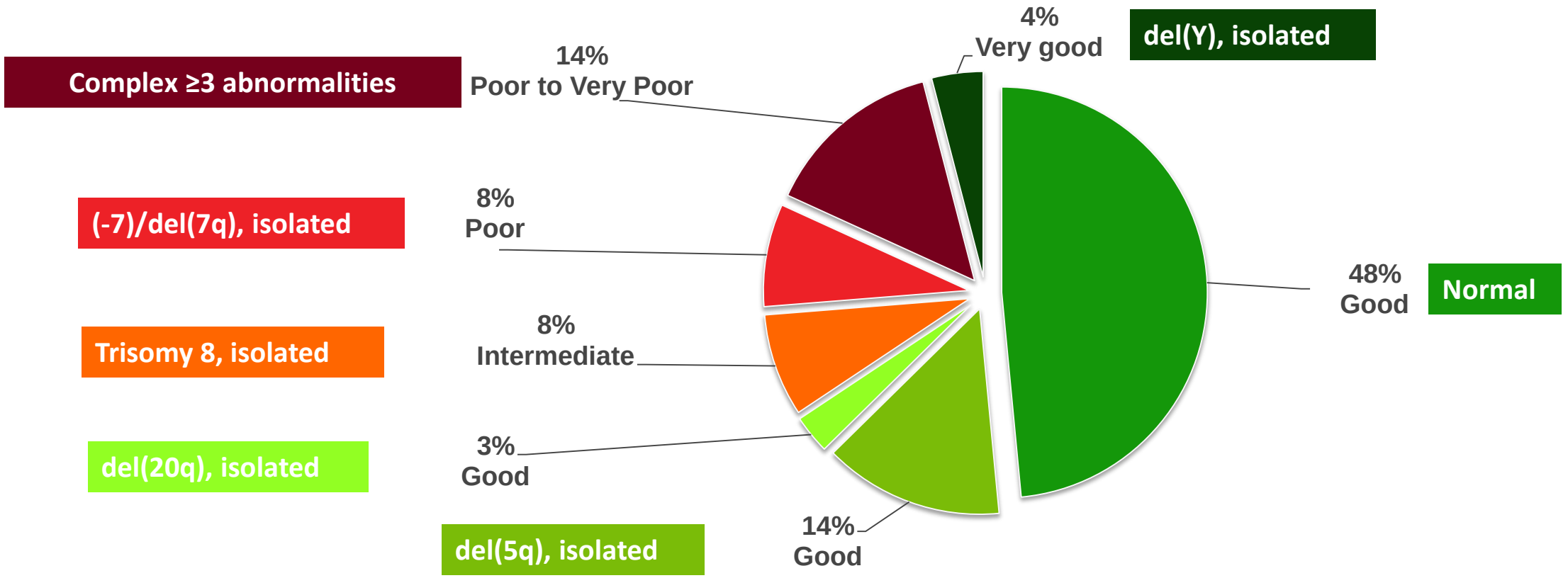


Ringed sideroblasts

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2017.

MOST COMMON CYTOGENETIC ABNORMALITIES

Incidence and Prognosis of Cytogenetic Abnormalities in MDS*[1,2]



*Primarily in de novo MDS (93.3% primary vs. 6.7% secondary).
MDS, myelodysplastic syndromes.
[1]Haase D, et al. Blood. 2007;110:4385-4395. [2]Sperling AS, et al. Nature Reviews Cancer. 2017;17:5-19.

Clinical features that affect prognosis of MDS

- Blast count in the bone marrow
- Cytogenetics risk group
- Degree of low red cells, platelets and neutrophils

- Other features:
  - Secondary MDS (after previous chemo or radiation)
  - Molecular risk factors
  - Fibrosis in the marrow biopsy
  - Transfusion dependency

IPSS-R

Revised International Prognostic Scoring System

Parameter	Categories and Associated Scores				
Cytogenetics	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow Blasts	≤2%	>2 - <5%	5 - 10%	>10%	
	0	1	2	3	
Hemoglobin (g/L)	≥100	80 - <100	<80		
	0	1	1.5		
Absolute neutrophil count (x 10^9/L)	≥0.8	<0.8			
	0	0.5			
Platelet count (x 10^9/L)	≥100	50 - 100	<50		
	0	0.5	1		

Very good = del(11q)
Good = Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate = del(7q), 8, 19, i(17q), any other single or double independent clones
Poor = inv(3)/t(3q)/del(3q), double including 7/del(7q), complex: 3 abnormalities
Very poor = Complex: 3 abnormalities

Link to online R-IPSS calculator: https://www.mds-foundation.org/advanced-calculator/

Greenberg P, Tuechler H, Schanz J, et al. **Blood. 2012;120(12):2454**

IPSS-R Clinical Outcomes

Risk Category	Risk Score	Median Survival	Time for 25% to Progress to AML
Very Low	1.5	8.8 years	Not Reached
Low	1.5-3	5.3 years	10.8 years
Intermediate	3-4.5	3.0 years	3.2 years
High	4.5-6	1.6 years	1.4 years
Very high	6	0.8 years	0.73 years

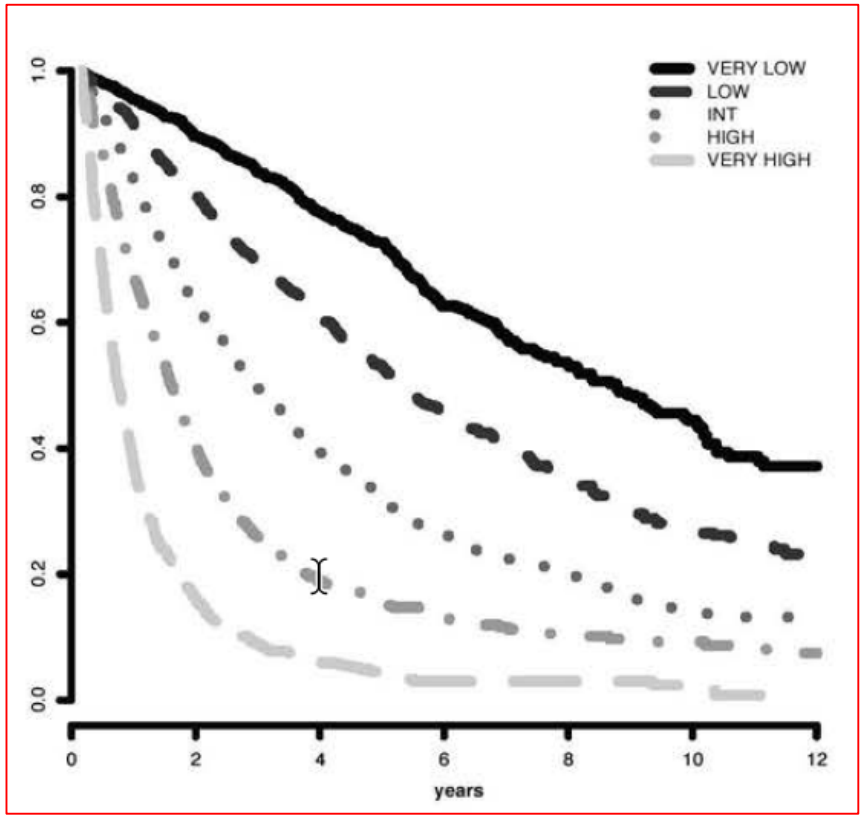
IPSS-R to be used at the time of diagnosis only. It is not applicable for therapy-related MDS. Outcomes are relevant in the absence of therapy.

Greenberg P, Tuechler H, Schanz J, et al**. Blood. 2012;120(12):2454**

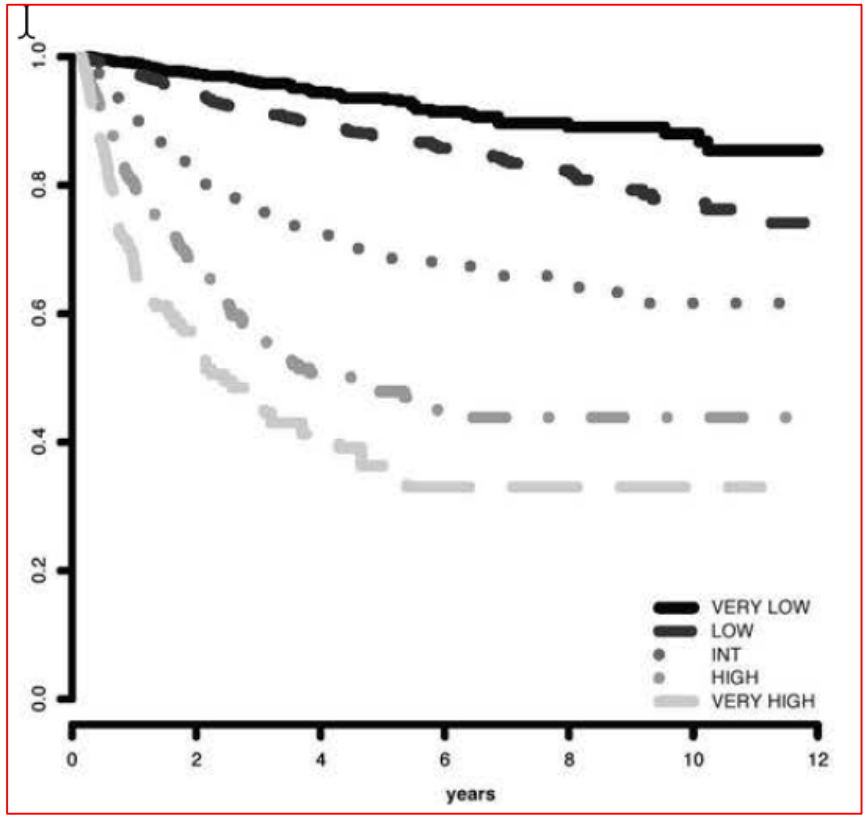
Survival and AML Progression: IPSS-R[1]

Survival and AML Progression

Survival based on IPSS-R prognostic risk-based categories



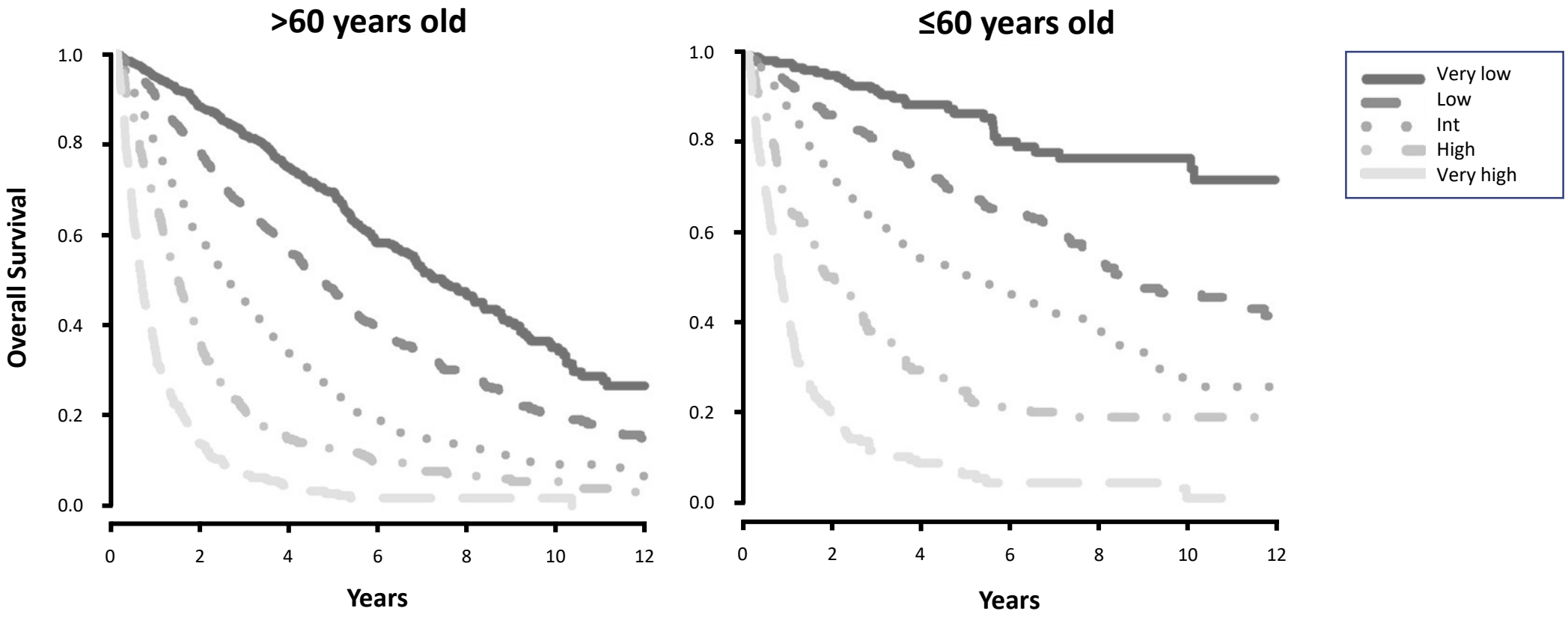
AML evolution based on IPSS-R prognostic risk-based categories



1. Revised International Prognostic Scoring System for Myelodysplastic Syndromes, Peter L. Greenberg et al, BLOOD, 20 SEPTEMBER 2012 ·VOLUME 120, NUMBER 12

OVERALL SURVIVAL ACCORDING TO IPSS-R SCORE

Overall Survival According to IPSS-R Score in Patients with MDS Aged >60 Years and ≤60 Years[1]

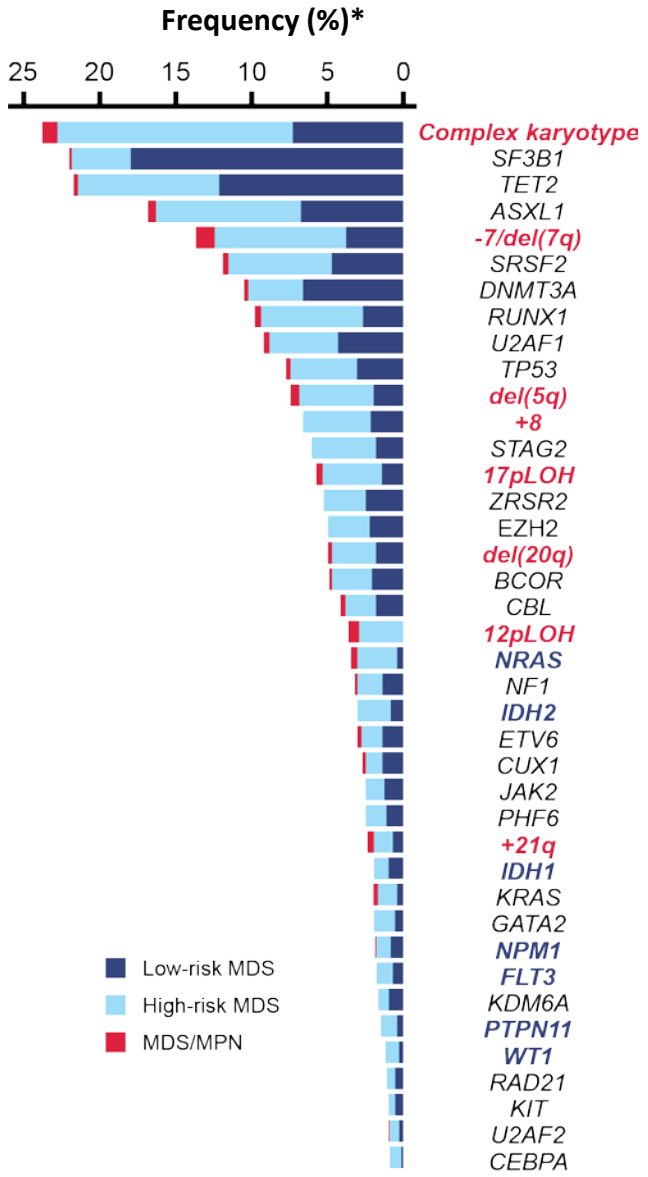


IPSS-R, International Prognostic Scoring System – Revised; MDS, myelodysplastic syndromes.

[1]Greenberg P, et al. Blood. 2012;120(12):2454-2465.

DRIVER ALTERATIONS IN MDS

- >30 driver genes involved in the pathogenesis of MDS have been identified
- A typical MDS patient has a median of 2 or 3 driver mutations
- High-risk MDS tends to show higher numbers of driver mutations than lower-risk MDS



*Frequencies of major driver mutations and CNAs are plotted, combining data from 7 publications
AML, acute myeloid leukemia; CNA, chromosomal and copy-number abnormalities; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms
Ogawa S. Blood. 2019;133(10):1049-1059

MDS is Heterogeneous

- DNA damage and associated evolution of clonal cytogenetic abnormalities
  - Frequent abnormalities in DNA methylation and epigenetics

Signalling	Epigenetic	mRNA Splicing	Transcription	Cohesin genes	DNA damage
Jak2 CBL NRAS PTPN11 BRAF GNAS	TET2 DNMT3A IDH1/2 EZH2 ASXL1	SF3B1 SRSF2 U2AF1/2 ZRSR2	RUNX1 ETV6 BCOR CEBPA GATA2	STAG2 SMC1A SMC3 RAD21	P53

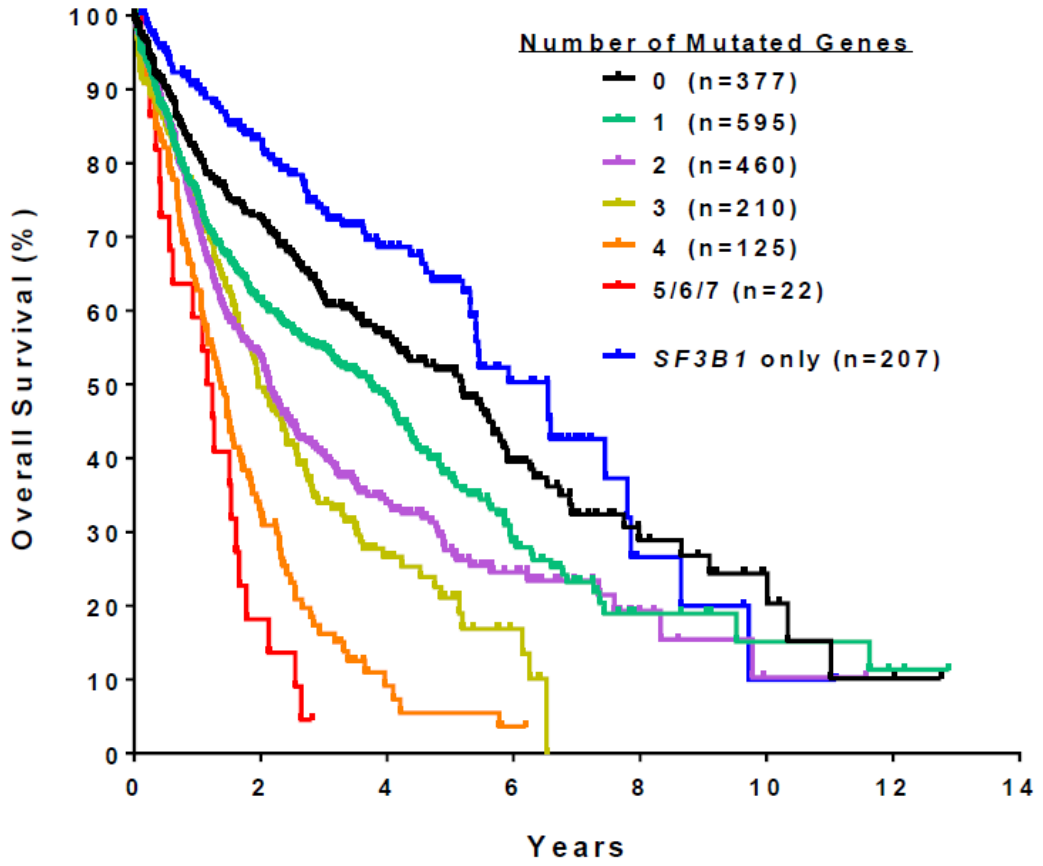
MDS chromosomal abnormalities & Gene mutations[1]

Overall Survival based on number of mutations[1]

17 genes sequenced in 1996 patients with OS data

ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

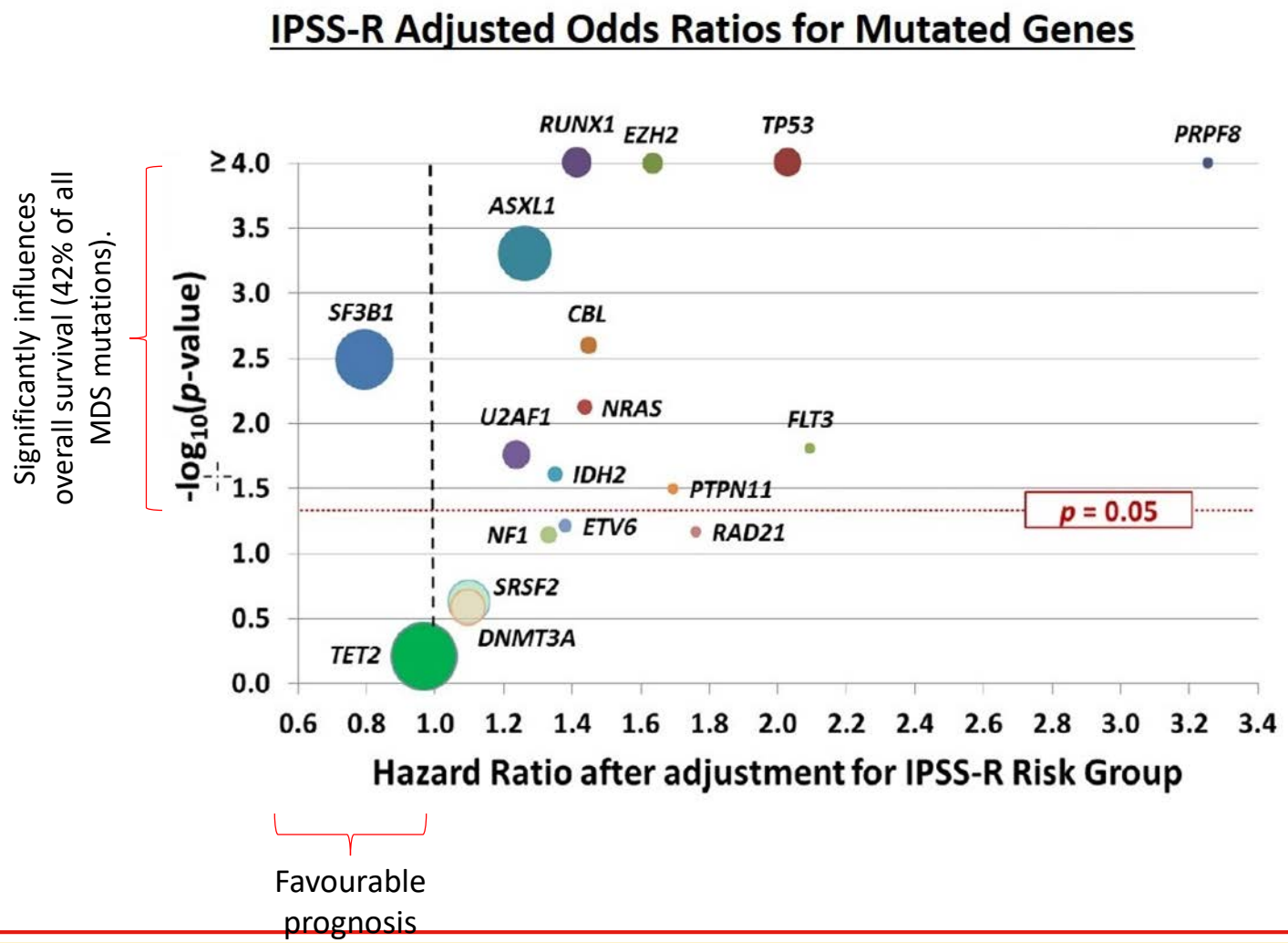
SF3B1



1. Integrating Molecular Findings into the Diagnosis and Prognosis of MDS, Rafael Bejar, Biological and Clinical Advances in MDS, San Diego, CA, December 2nd, 2016; Link: https://www.mds-foundation.org/wp-content/uploads/2016/12/Bejar-IntegratingMolecularFindings.pdf; Accessed on 22nd Dec, 2020

Some gene mutations are good prognosis and others are poor prognosis

IPSS-R Adjusted Odds Ratios for Mutated Genes[1]

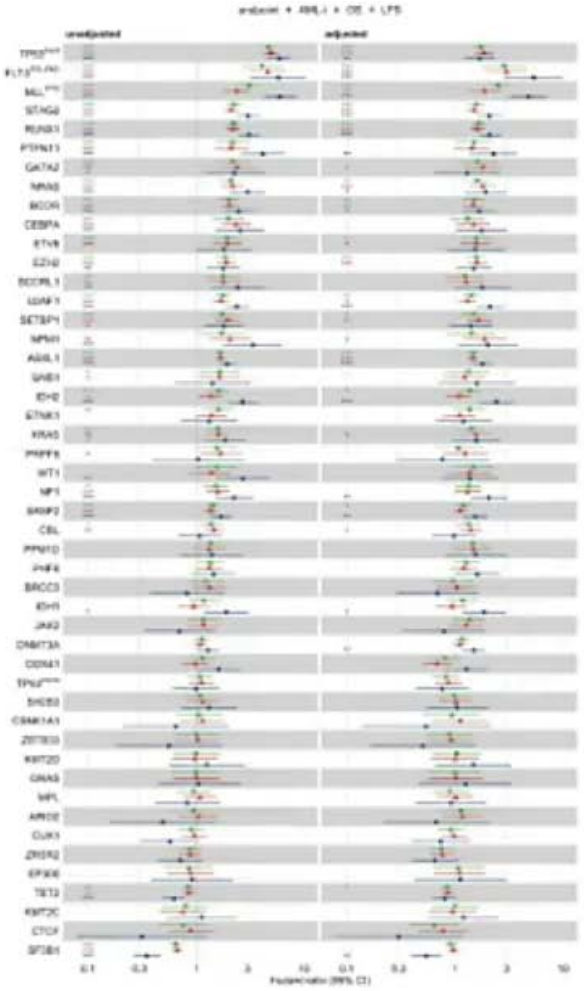


Legend:

- Size of the circle correlates to the frequency of the mutation.
- Dotted red line separates out mutations that significantly influence overall survival (42% of all MDS mutations).
- Mutations to the left of the dashed black line have a favourable prognosis while mutations to the right have an unfavourable prognosis).

1. Integrating Molecular Findings into the Diagnosis and Prognosis of MDS, Rafael Bejar, Biological and Clinical Advances in MDS, San Diego, CA, December 2nd, 2016; Link: https://www.mds-foundation.org/wp-content/uploads/2016/12/Bejar-IntegratingMolecularFindings.pdf; Accessed on 22nd Dec, 2020

Molecular IPSS score (IPSS-M) for MDS



Association between gene mutations and clinical endpoints

Leukemia free survival (LFS)

Overall survival (OS)

AML transformation (AML-t)

Adjusting for age, sex, MDS type (primary vs. therapy-related), and IPSS-R raw score, 14, 16 and 15 genes were significantly associated with adverse outcomes for the three endpoints, respectively.

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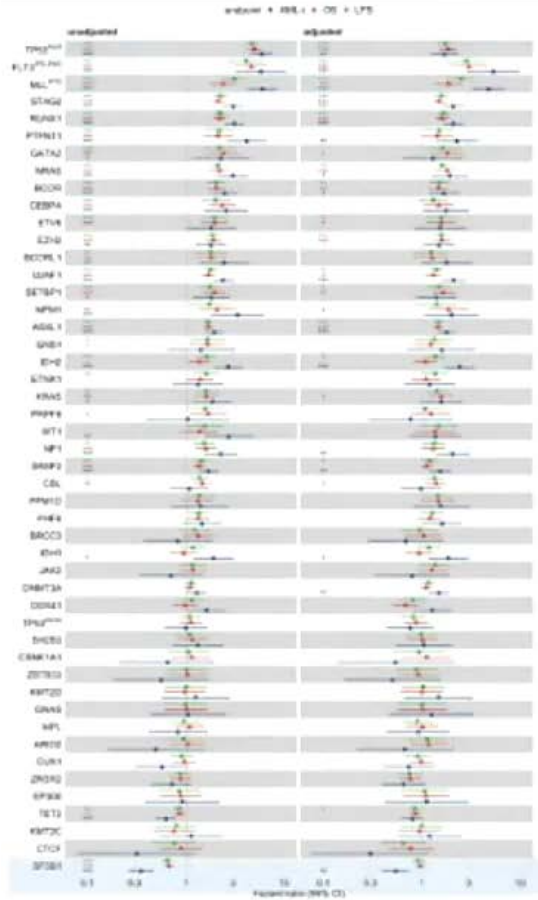


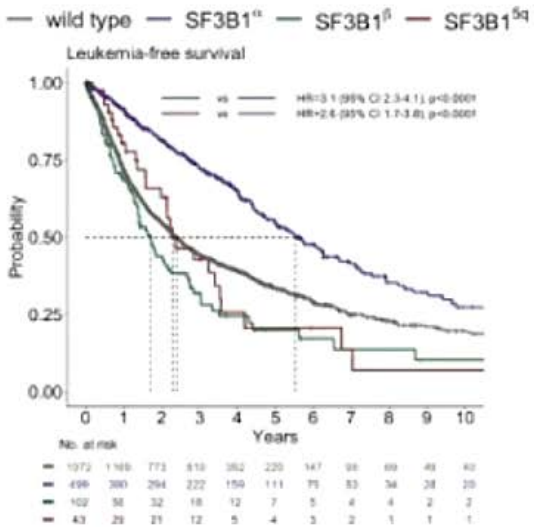
***SF3B1* mutations were associated with favorable outcomes.**

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.

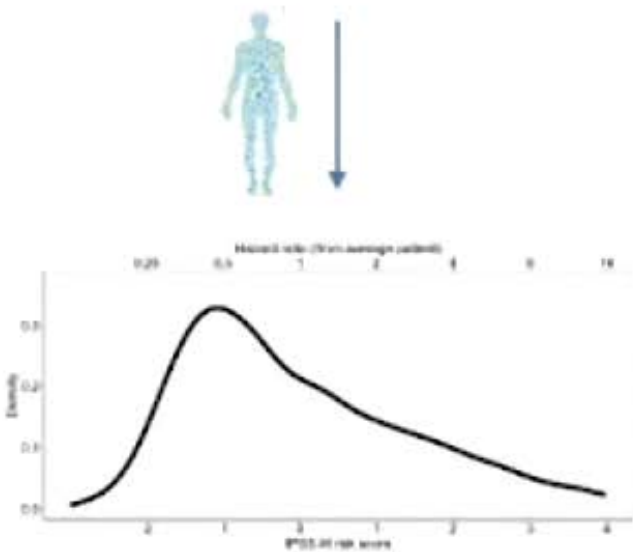


Malcovati et al. Blood 2011;2015;2021
Meggendorfer et al. Haematologica 2017

ASH 2021 abstract 61

Category	Variable	Multivariable model: hazard ratio[a] (95% CI)	Weight w	Scaling s^{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[4]	1.33 (1.21 - 1.47)	0.287	1.389
gene main effects 17 variables, 16 genes	*TP53*[mult]	3.27 (2.38 - 4.48)	1.19	0.0710
	BCL7[TTD]	2.22 (1.49 - 3.32)	0.798	0.0247
	FLT3[ITD+TKD]	2.22 (1.11 - 4.45)	0.798	0.0108
	SF3B1[K/N]	1.68 (1.03 - 2.66)	0.504	0.0169
	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	0.0568
	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	0.181
	ASXL1	1.24 (1.02 - 1.51)	0.213	0.252
	KRAS	1.22 (0.84 - 1.77)	0.202	0.0271
	SF3B1[P]	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals[3] 1 variable, 15 genes	min(**Nras**,2) Possible values are 0,1 or 2	1.26 (1.12 - 1.42)	0.231	0.368

$$\text{score} = \frac{1}{\log 2} \sum_{\text{variables } j} w_j (x_j - x_j^{\text{mean}})$$



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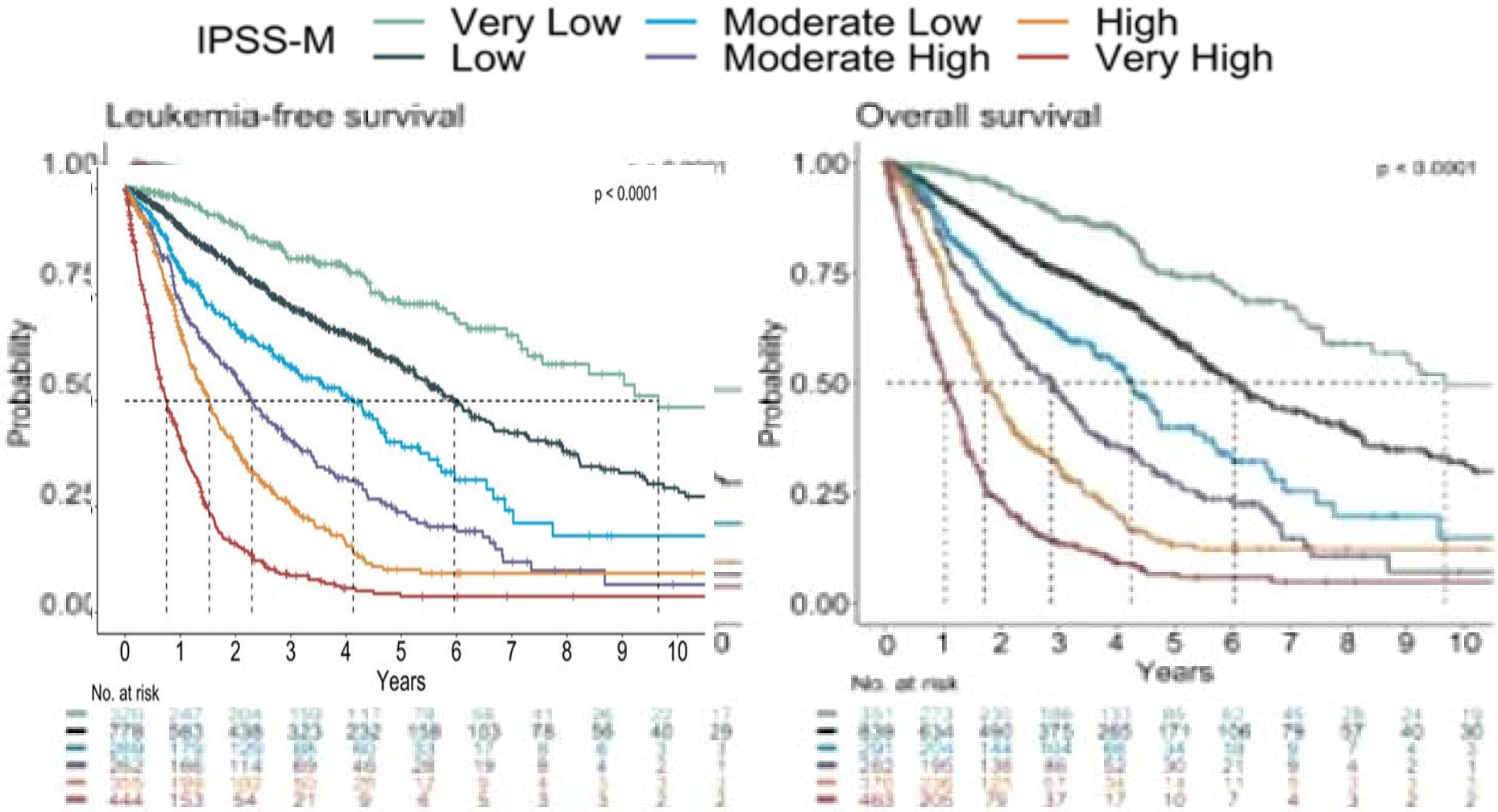

Prognostic separation of the IPSS-M risk categories

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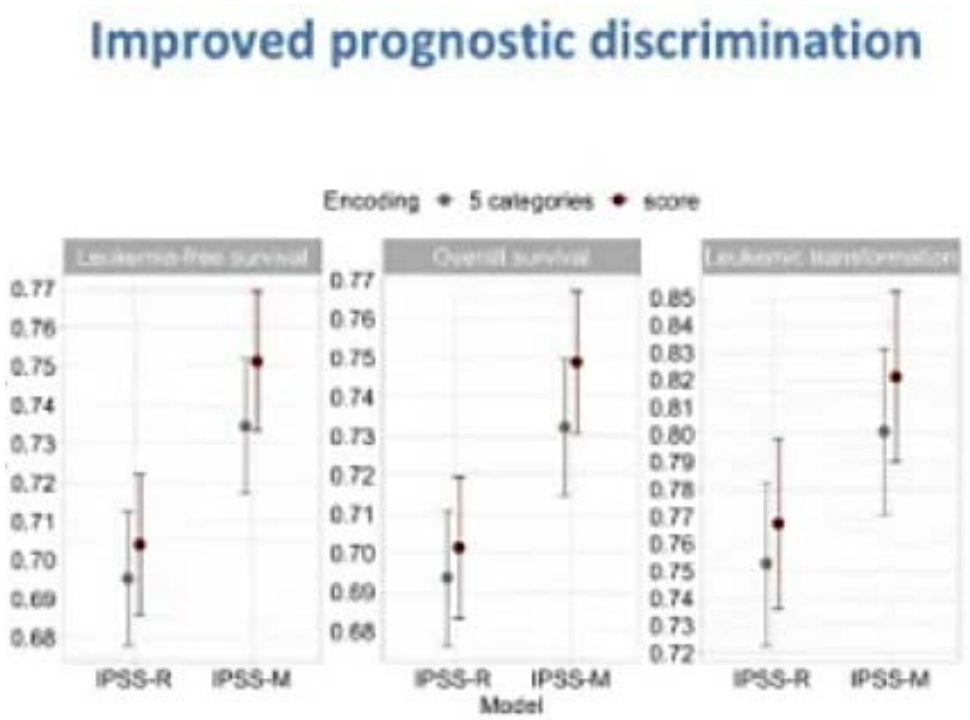
Better prediction of outcomes with incorporation of molecular mutations and clinical factors



Web calculator that helps look at mutations and computational status and incorporate these with clinical features to improve prognostication

Approximately 46% of 1,223 patients were reclassified to a different risk group

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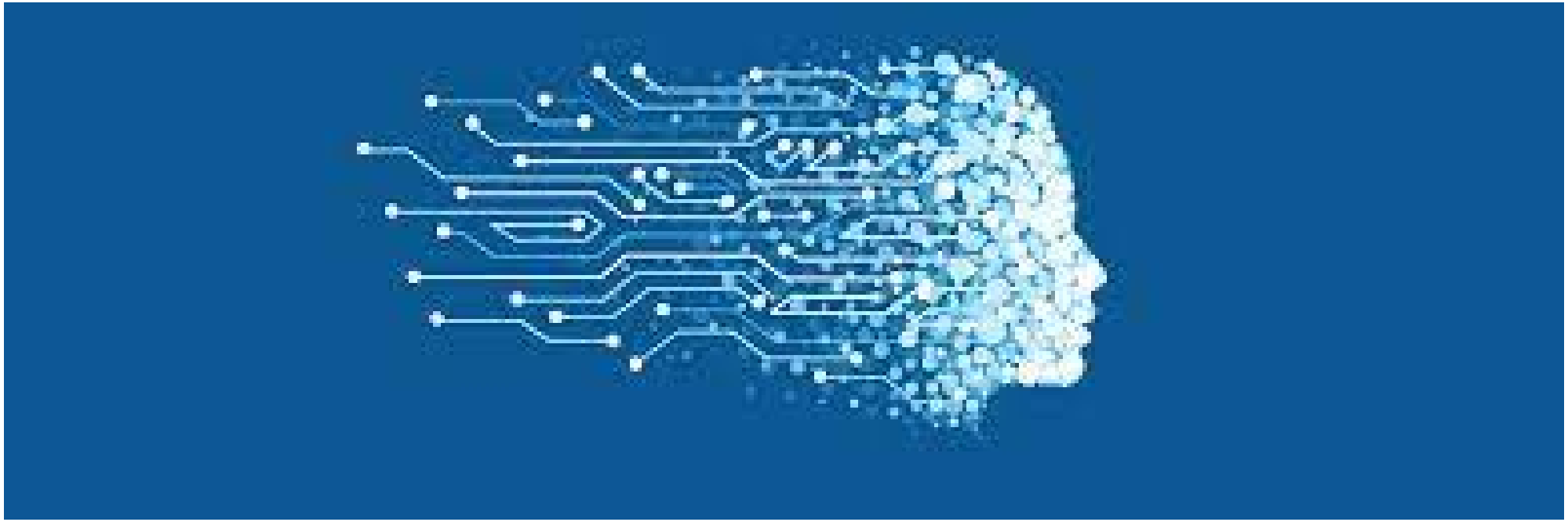
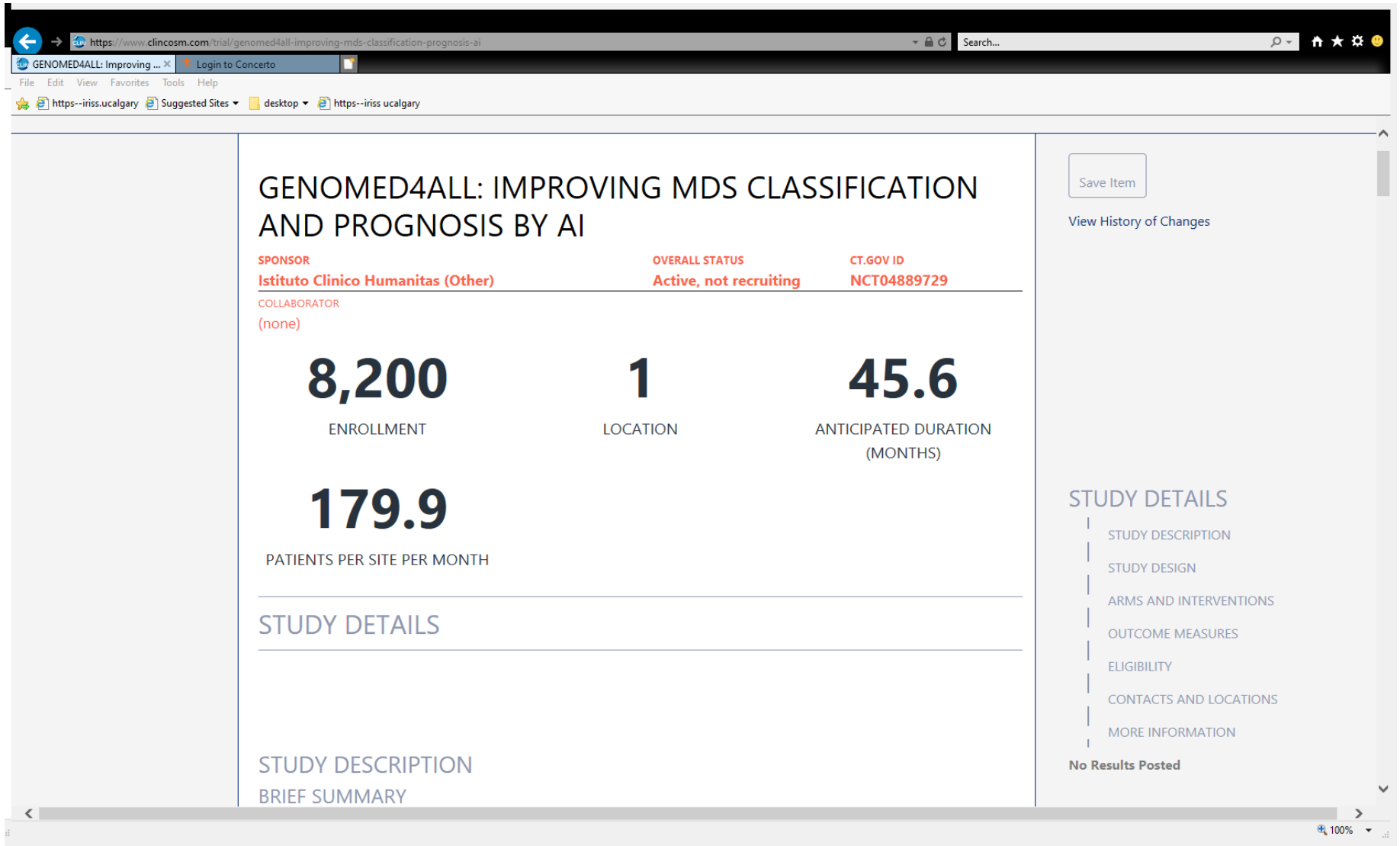
Machine Learning may help incorporate MDS molecular risk factors into prognostic scores




https://www.clincosm.com/trial/genomed4all-improving-mds-classification-prognosis-ai
Search...
GENOMED4ALL: Improving ...
Login to Concerto
File Edit View Favorites Tools Help
https--iriss.ucalgary
Suggested Sites
desktop
https--iriss ucalgary
GENOMED4ALL: IMPROVING MDS CLASSIFICATION AND PROGNOSIS BY AI
SPONSOR
Istituto Clinico Humanitas (Other)
OVERALL STATUS
Active, not recruiting
CT.GOV ID
NCT04889729
COLLABORATOR
(none)
8,200
ENROLLMENT
1
LOCATION
45.6
ANTICIPATED DURATION (MONTHS)
179.9
PATIENTS PER SITE PER MONTH
STUDY DETAILS
STUDY DESCRIPTION
BRIEF SUMMARY
Save Item
View History of Changes
STUDY DETAILS
STUDY DESCRIPTION
STUDY DESIGN
ARMS AND INTERVENTIONS
OUTCOME MEASURES
ELIGIBILITY
CONTACTS AND LOCATIONS
MORE INFORMATION
No Results Posted
100%

How do we use this information to guide care?

Goals of Therapy

Goals of therapy[1]

Priorities in Low-Risk MDS

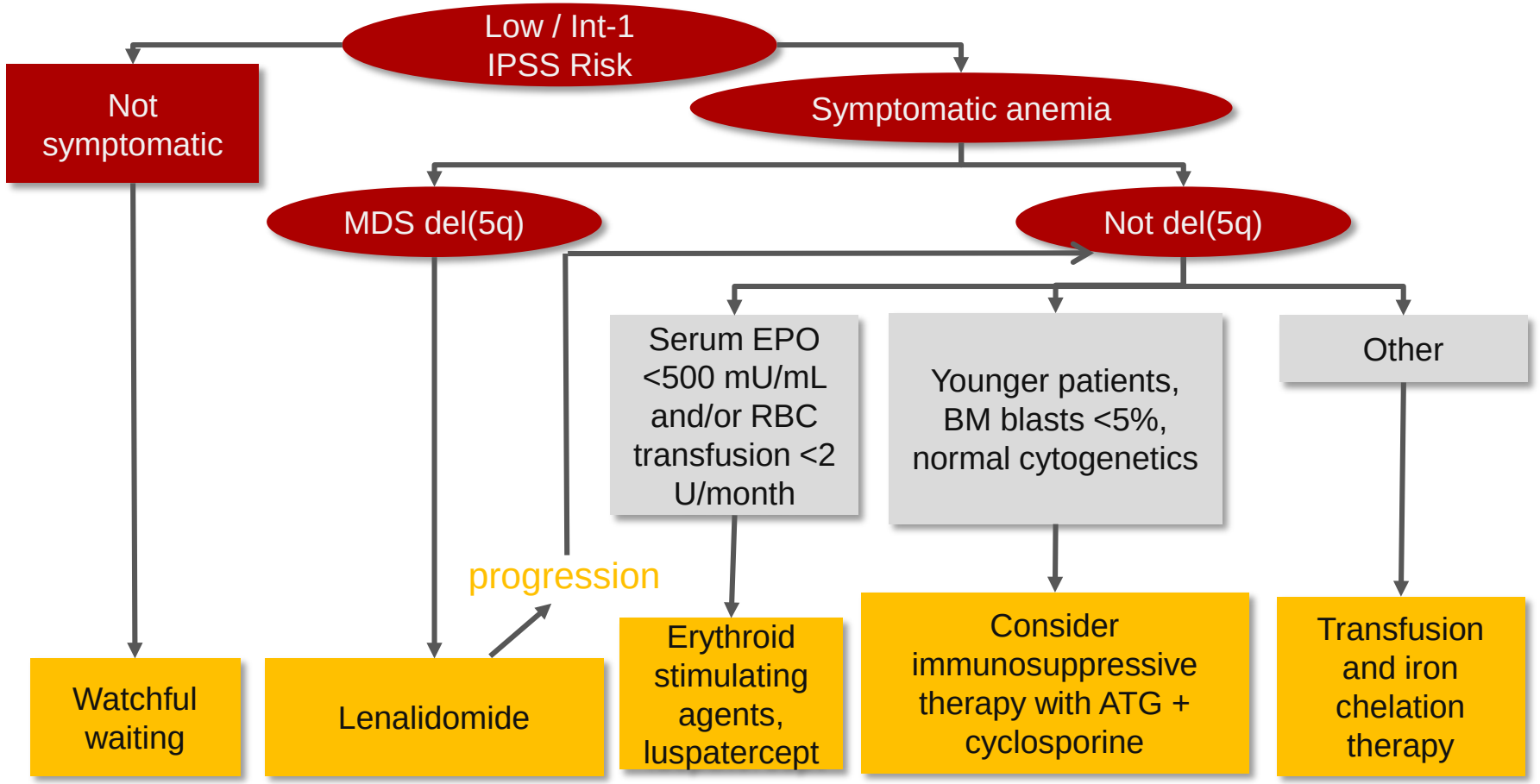
1. Improvement of cytopenias
   Less transfusions
   Less iron overload
2. Tolerability of a given treatment
   Quality of Life
3. Delay disease progression
   Improve survival
4. Cure

Priorities in High-Risk MDS

1. Delay disease progression
   Improve survival
   Cure
2. Reduction of disease burden
   Improvement of cytopenias
   Less transfusions
3. Tolerability of a given treatment
4. Quality of Life

1. Treatment of MDS, Uwe Platzbecker, Blood. 2019 Mar 7;133(10):1096-1107

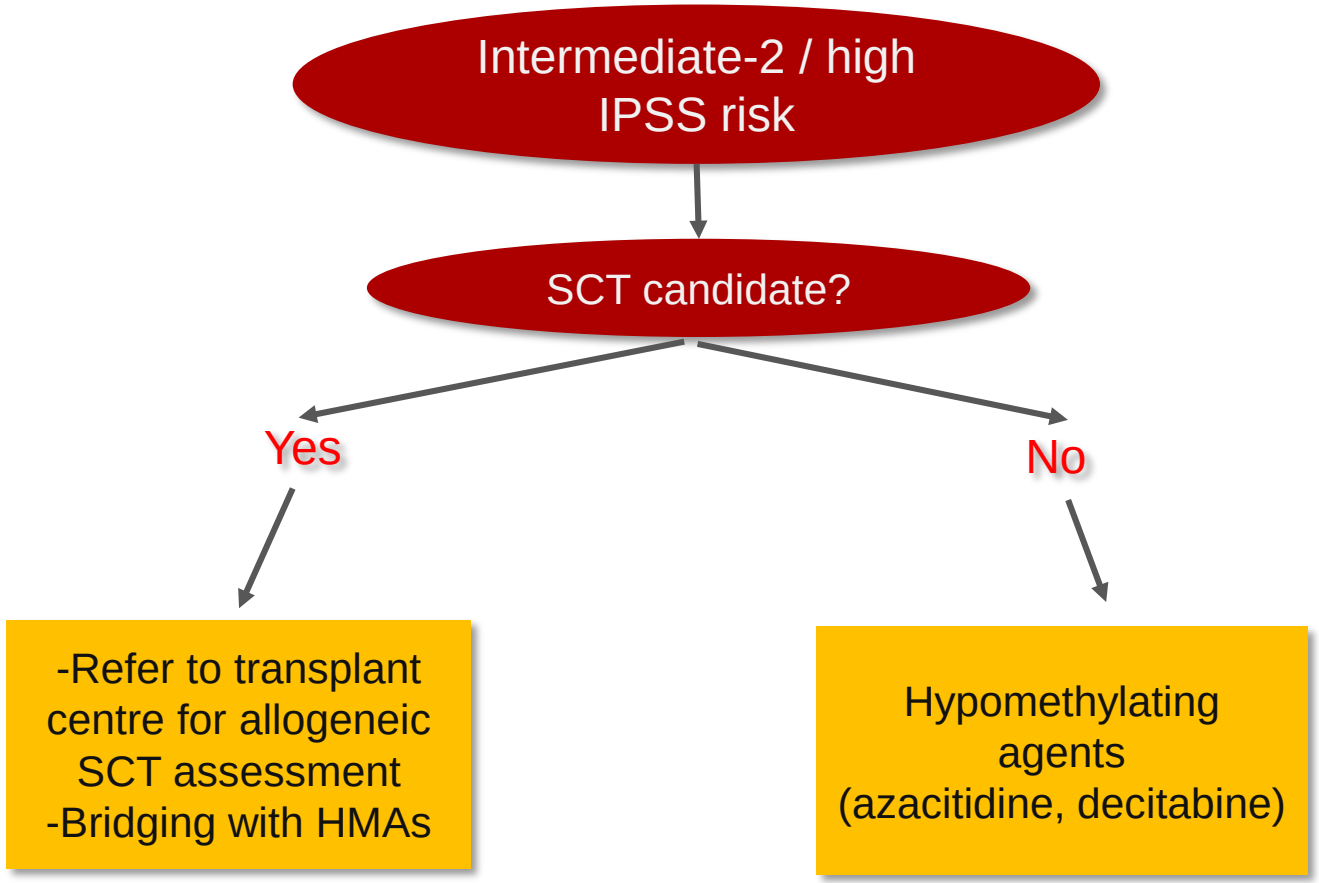
Recommendations for patients with low / intermediate-1 IPSS risk



ATG, anti-thymocyte globulin. BM, bone marrow. EPO, erythropoietin. G-CSF, granulocyte colony-stimulating factor. IPSS, International Prognostic Scoring System. RBC, red blood cell

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).

Recommendations for patients with intermediate-2 / high IPSS risk



SCT, stem cell transplant.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).

Between a rock and a hard place

Transplantation is currently the only curative therapy for myelodysplastic syndromes

Median age at diagnosis is 65-70
Toxicity of transplantation can be prohibitive

Questions?