Multidisciplinary Approaches to Cancer Symposium

Myelodysplastic Syndrome: Molecular Markers & Management with Novel Drugs

Molecular Markers in MDS

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City of Hope

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

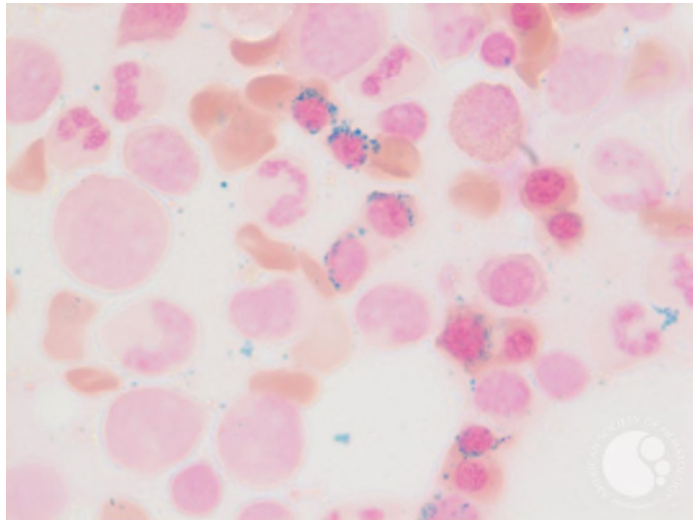
EXEMPTION:

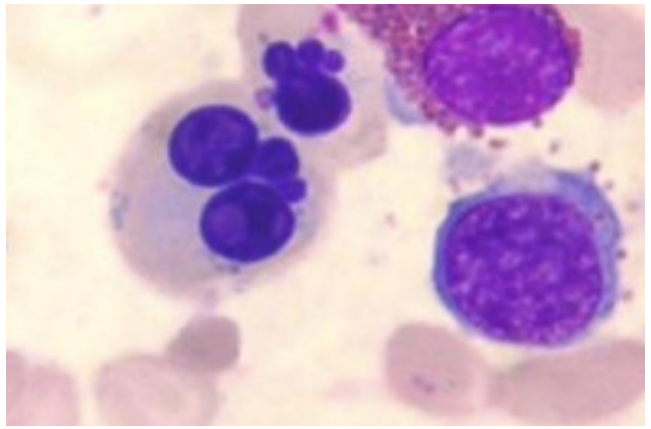
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

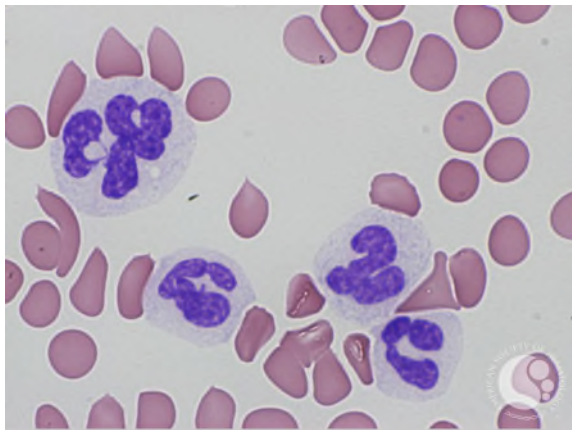
This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

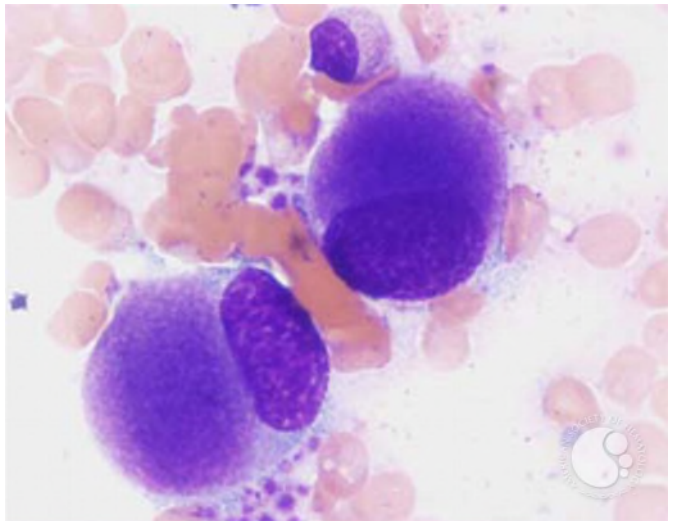
Overview of MDS

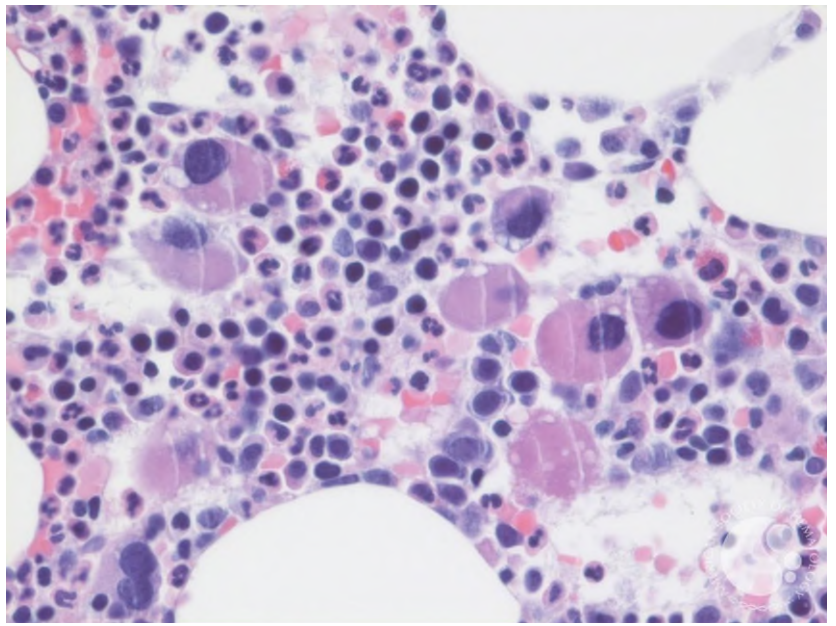
- Ineffective hematopoiesis
- Peripheral blood
- Bone marrow biopsy





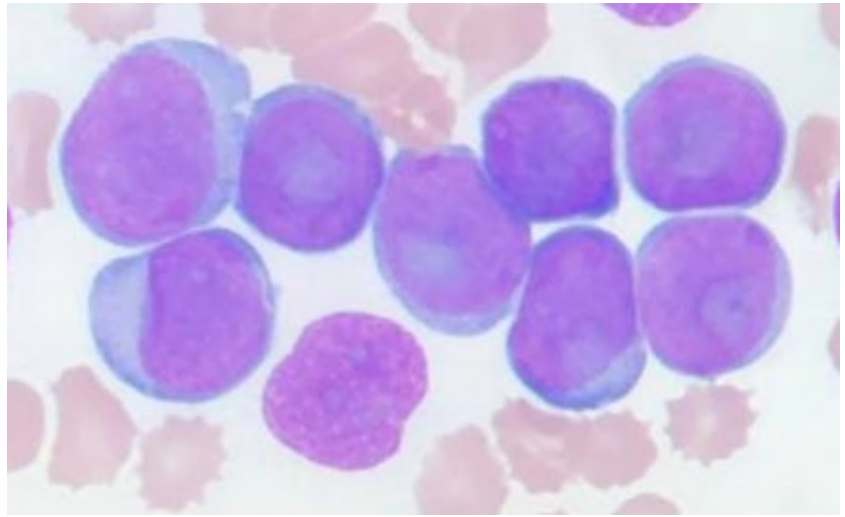


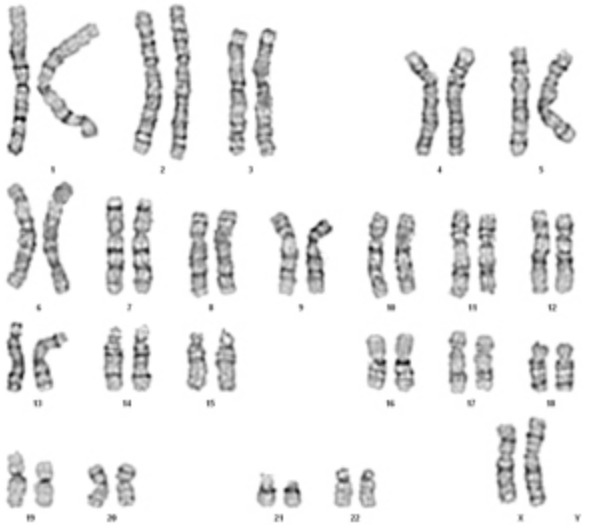


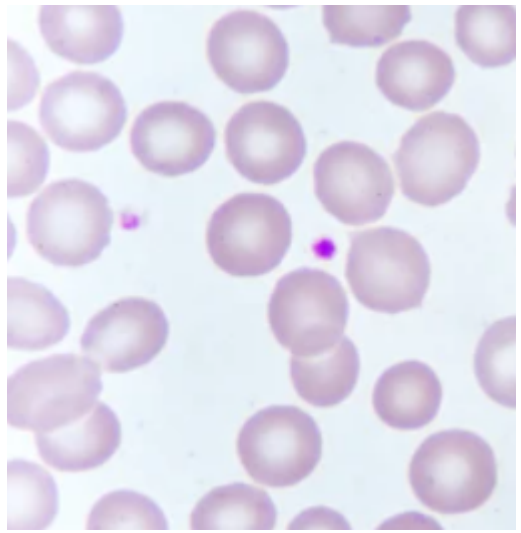


Testing and Prognosis

- Importance of prognostic markers
  - IPSS, IPSS-R, IPSS-M
- Karyotype and FISH analysis
- NGS panel
  - Whole genome sequencing
  - Target sequencing platform

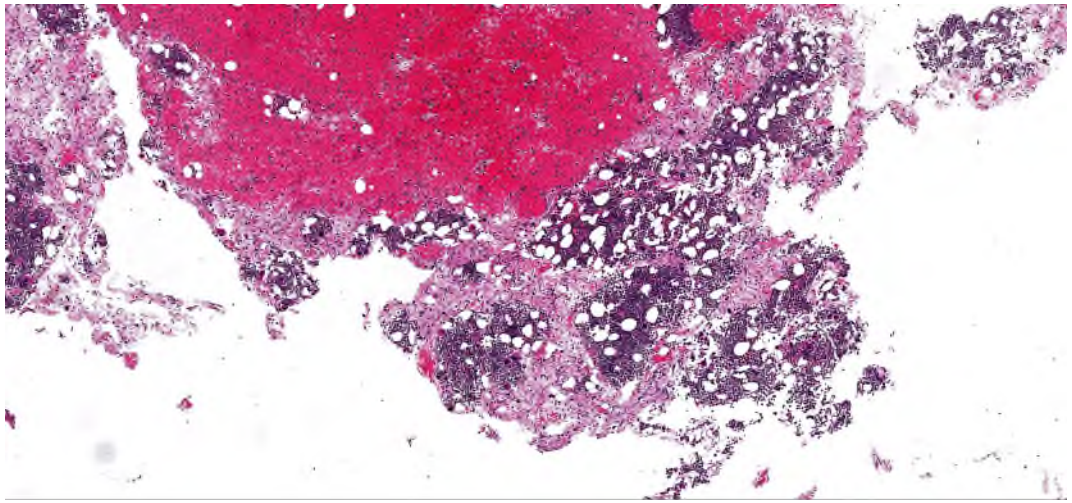


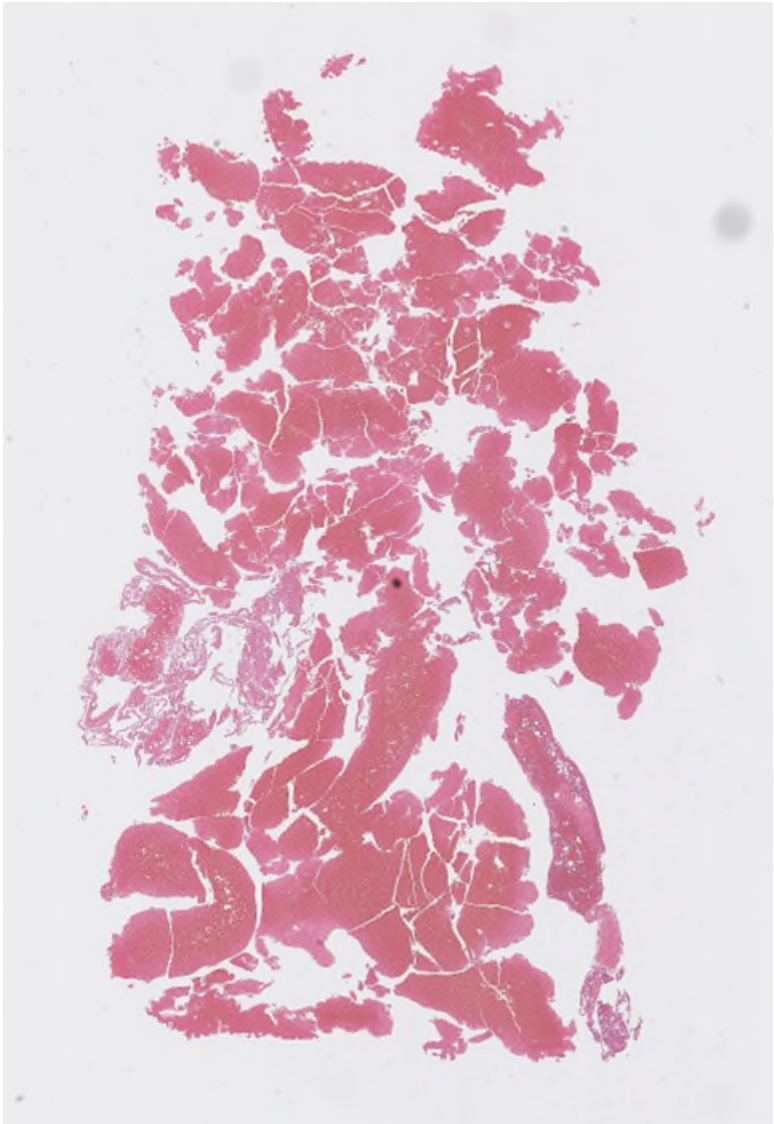




Testing

- Types of samples
  - Bone marrow aspirate or clot sections
    - Limitations: Aparticulate clot
  - Peripheral blood
    - Limitations: Low WBC count



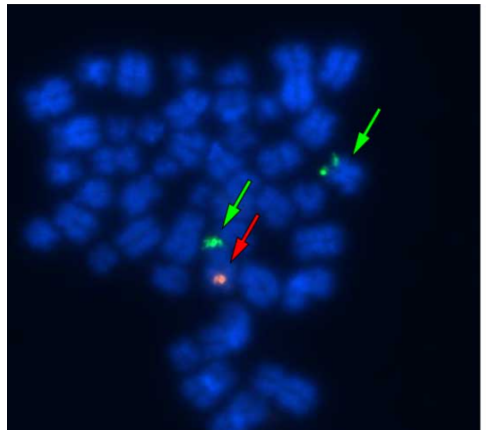


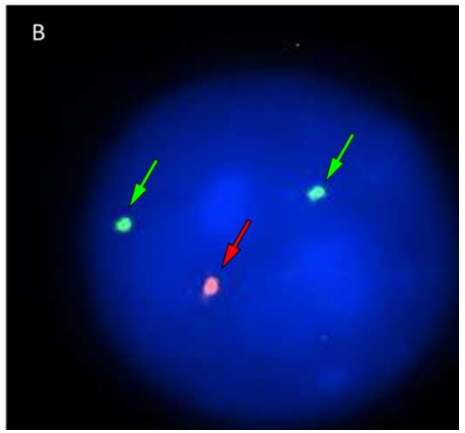
Cytogenetics and FISH

- **Karyotype**
- **FISH analysis**

- Very Good: -Y, del(11q)
- Good: del(5q), 20q deletions
- Intermediate: +8, del(12p), +19
- Poor: monosomy 7, inv(3)
- Very Poor: Complex karyotype (>3)

	Prognostic score value						
	0	0.5	1	1.5	2	3	4
Prognostic category							
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blasts, %	≤ 2		> 2 to < 5		5–10	> 10	
Hgb, g/dL	≥ 10		8 to < 10	< 8			
Platelets, x 10^9/L	≥ 100	50 to < 100	< 50				
ANC, x 10^9/L	≥ 0.8	< 0.8					
Cytogenetic group		**Characteristics**					
Very good		−Y, del(11q)					
Good		Normal, del(5q), del(12p), del(20q), del(5q) + 1 additional abnormality					
Intermediate		del(7q), +8, +19, i(17q), other abnormalities not in other groups					
Poor		−7, inv(3)/t(3q), −7/del(7q) + 1 additional abnormality, complex (3 abnormalities)					
Very poor		Complex (> 3 abnormalities)					





NGS

- Splicing factor mutations: SF3B1, SRSF2, U2AF1, ZRSR2
- DNA methylation: TET2, DNMT3A, IDH1/IDH2, KMT2A/MLL
- Chromatin modification: ASXL1, EZH2
- Tumor suppressor: TP53
- Signaling pathway: STAG2, JAK2, NRAS/KRAS, FLT3

NGS

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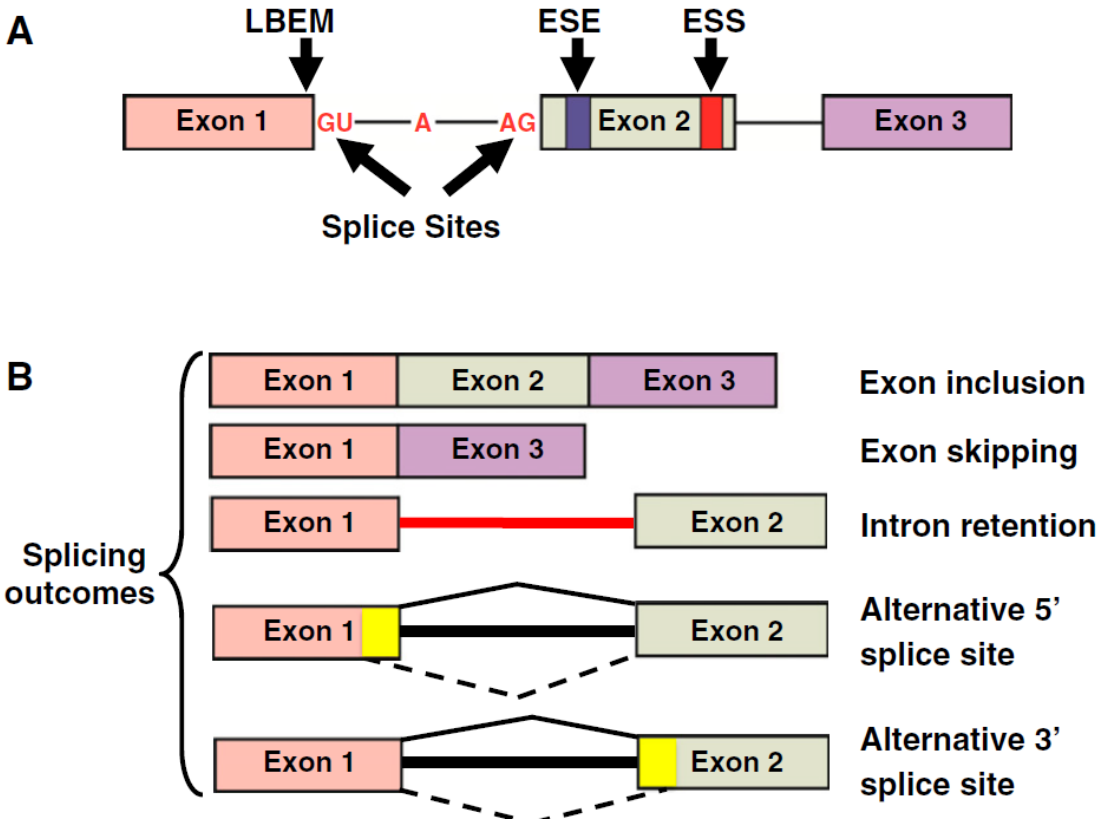
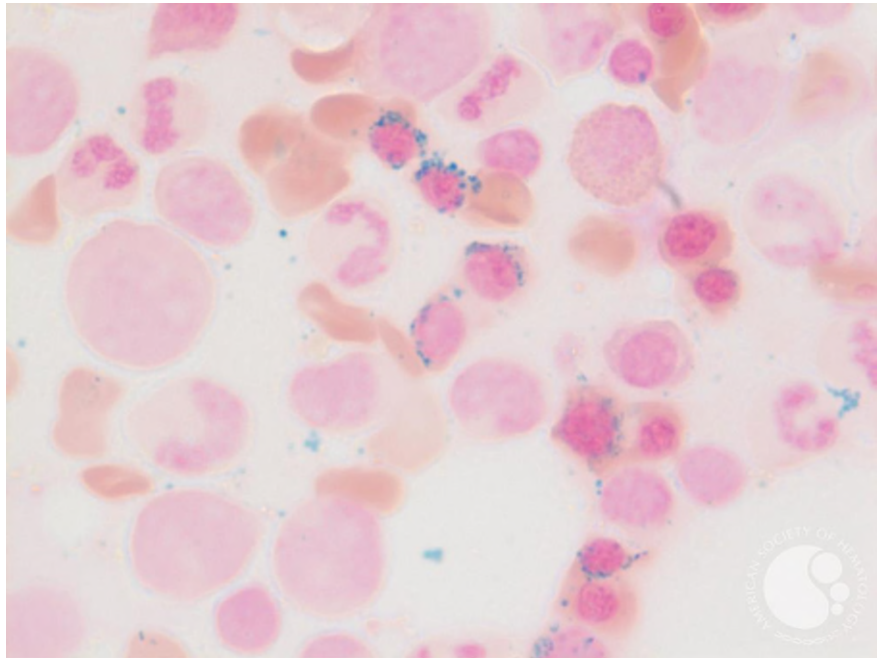
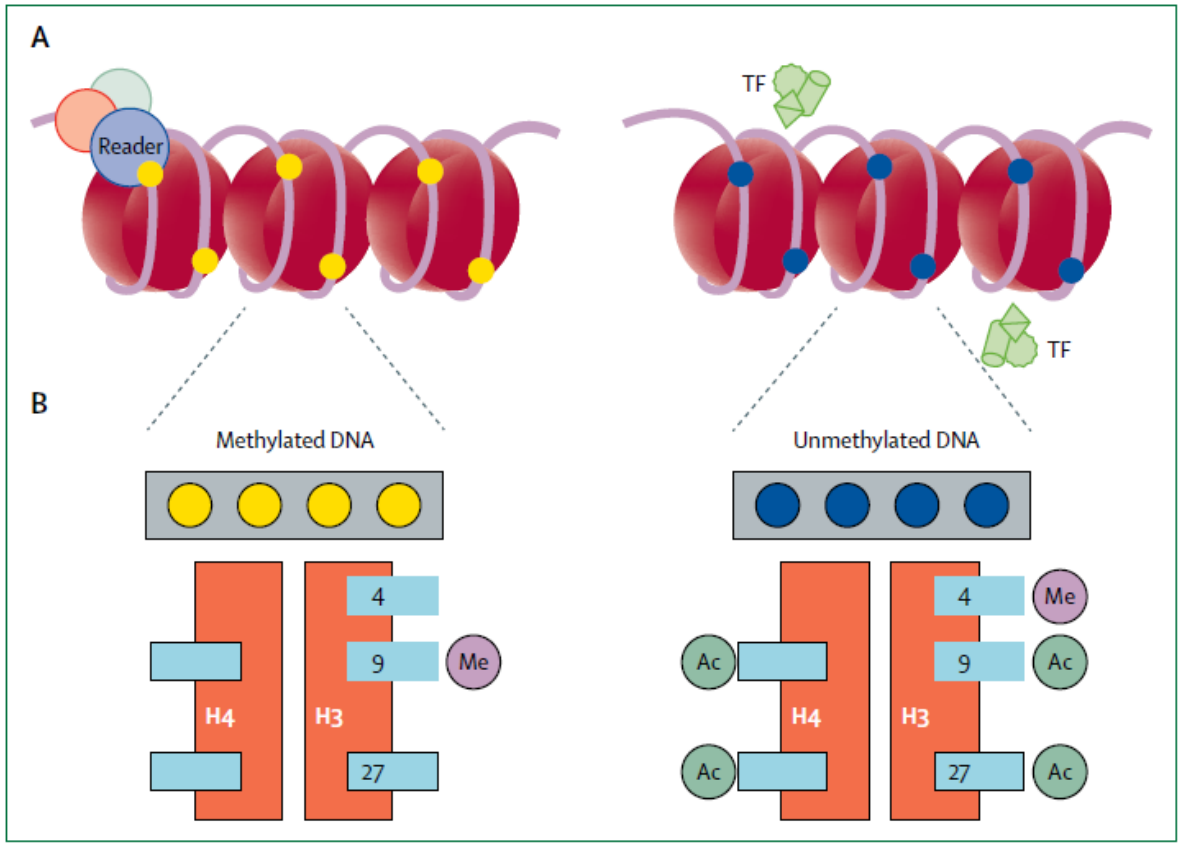




Saez et al, Blood 2017

NGS

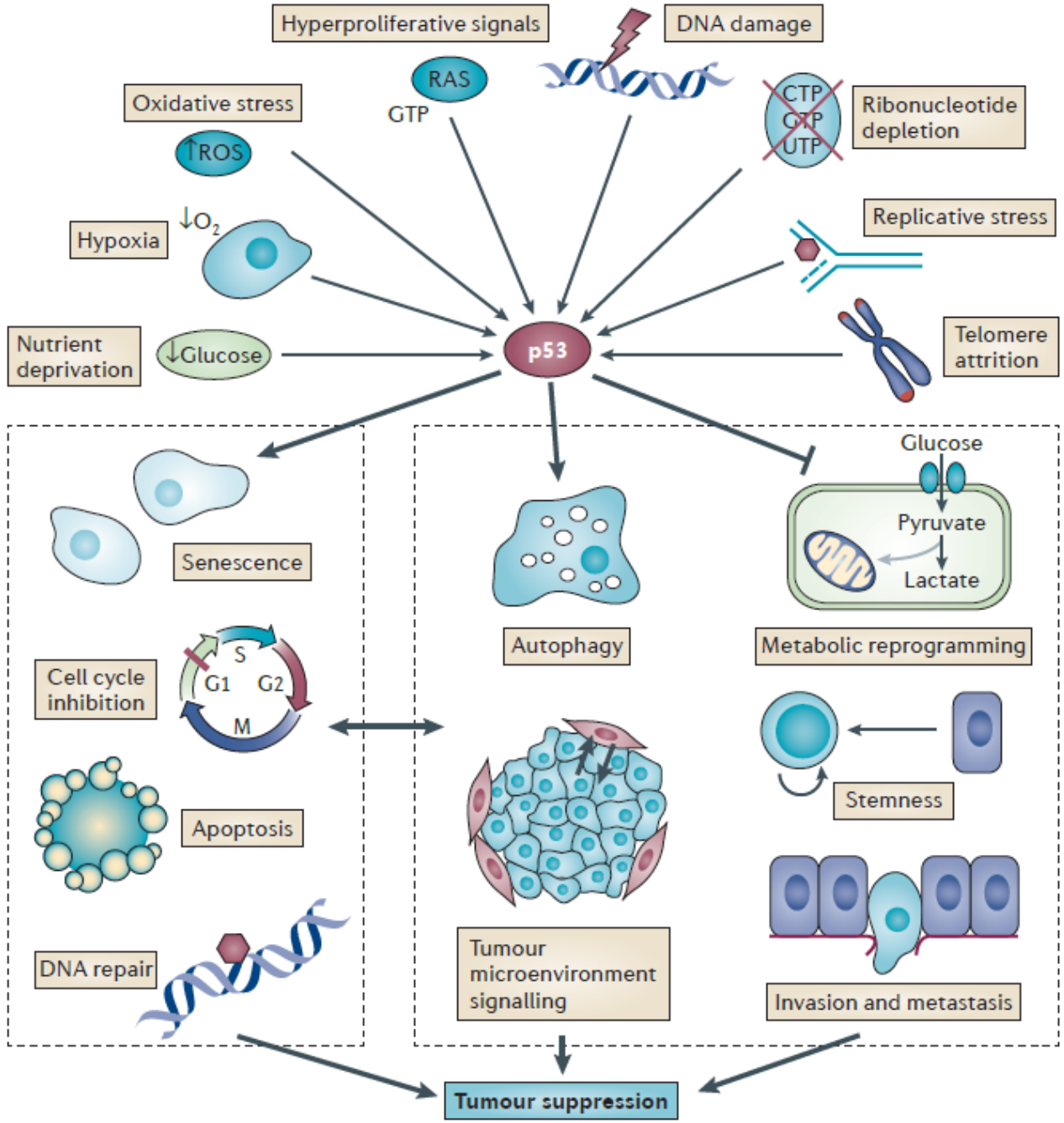
- DNA methylation: TET2, DNMT3A, IDH1/IDH2
- **Histone: KMT2A (Partial Tandem Duplication)**



Dor et al, Lancet 2018
Dai et al, J Mol Dia 2021

NGS

- TP53
  - DNA repair
  - Apoptosis
  - Senescence
  - Angiogenesis
  - Oxidative stress
- Multi-hit TP53
  - Biallelic
  - LOH



Bieging et al, Nat Review 2014

IPSS-M

- Incorporates IPSS-R and genomics
- 2957 patients, validated 754 patients
- 31 genes

- **Adverse**
  - **TP53 (multi-hit)**
  - **MLL/KMT2A PTD**
  - **FLT3 ITD/TKD**
  - **SF3B1 and 5q-**

- **Favorable**
  - **SF3B1 isolated**

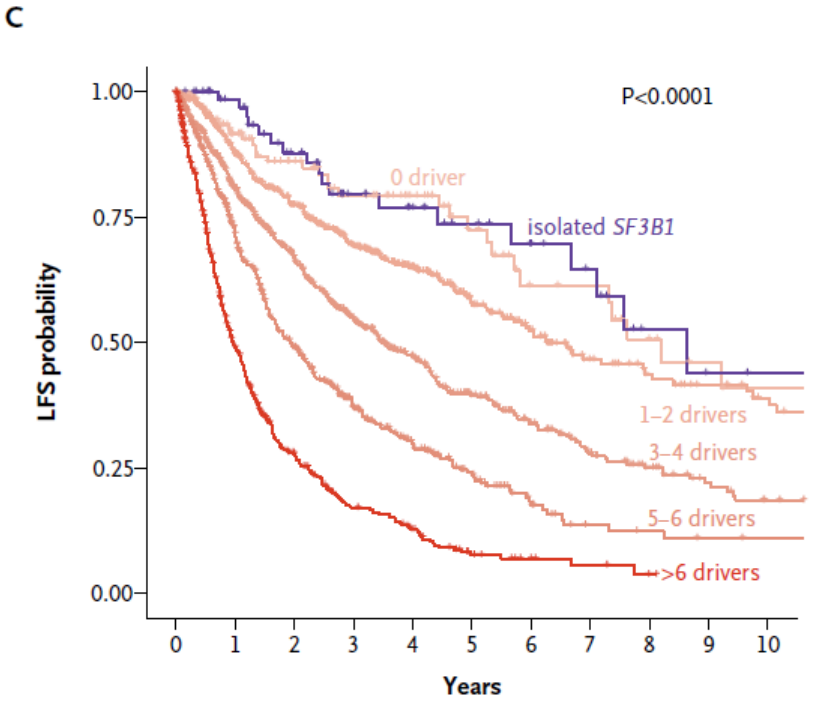
Bernard et al, NEJM Evidence, 2022

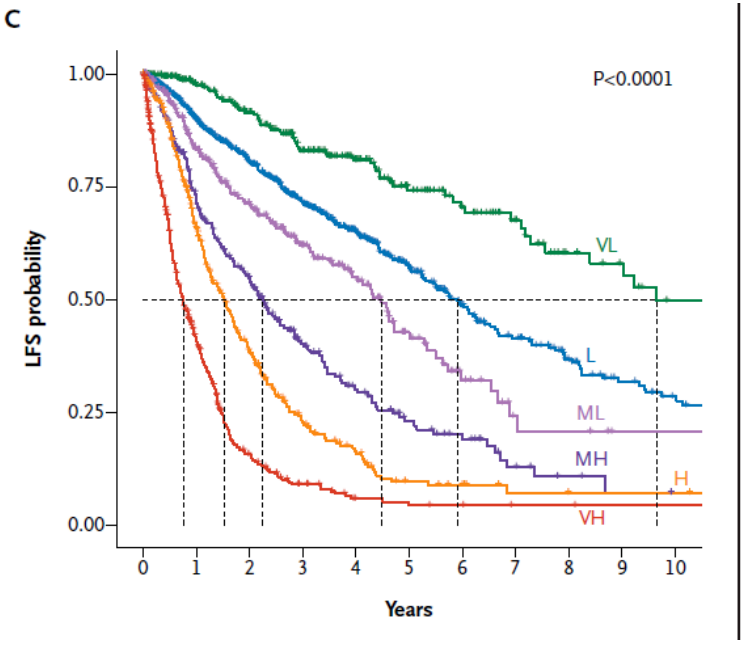
Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

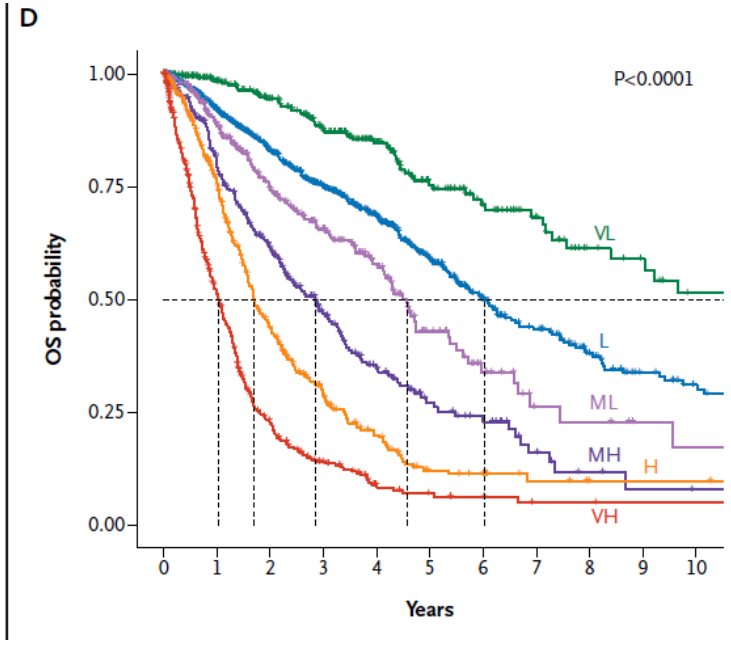
Category and Variable	Adjusted Hazard Ratio (95% CI)†
Clinical	
Bone marrow blasts — %	1.07 (1.05–1.09)
min(Platelets,250) — $x10^9$/l	0.998 (0.997–0.999)
Hemoglobin — g/dl	0.84 (0.81–0.88)
Cytogenetic	
IPSS-R cytogenetic category§	1.33 (1.21–1.47)
Gene main effects (17 variables, 16 genes)¶	
TP53^{multihit}	3.27 (2.38–4.48)
MLL^{PTD}	2.22 (1.49–3.32)
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)
SF3B1^{5q}	1.66 (1.03–2.66)
NPM1	1.54 (0.78–3.02)
RUNX1	1.53 (1.23–1.89)
NRAS	1.52 (1.05–2.20)
ETV6	1.48 (0.98–2.23)
IDH2	1.46 (1.05–2.02)
CBL	1.34 (0.99–1.82)
EZH2	1.31 (0.98–1.75)
U2AF1	1.28 (1.01–1.61)
SRSF2	1.27 (1.03–1.56)
DNMT3A	1.25 (1.02–1.53)
ASXL1	1.24 (1.02–1.51)
KRAS	1.22 (0.84–1.77)
SF3B1$^{\alpha}$	0.92 (0.74 1.16)
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖	
min(Nres,2)	1.26 (1.12–1.42)

IPSS-M

- Improved prognostic determination compared to IPSS-R
- 46% re-stratified
- **Real-World validation** (Sauta et al)
- Open access calculator







Bernard et al, NEJM evidence, 2022
Sauta et al, JCO 2023

Summary

- IPSS-R still important and relevant for prognostication
- Genomics has an important role (e.g. TP53, MLL, FLT3, SF3B1)
- Molecular is more routinely used
- Improves prognostic accuracy
- Tailored therapeutic decisions