

# **MDS in 2026: IPSS-M, Clonal Hematopoiesis, and Biological Classification**

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**McCredie Professor of Medicine**

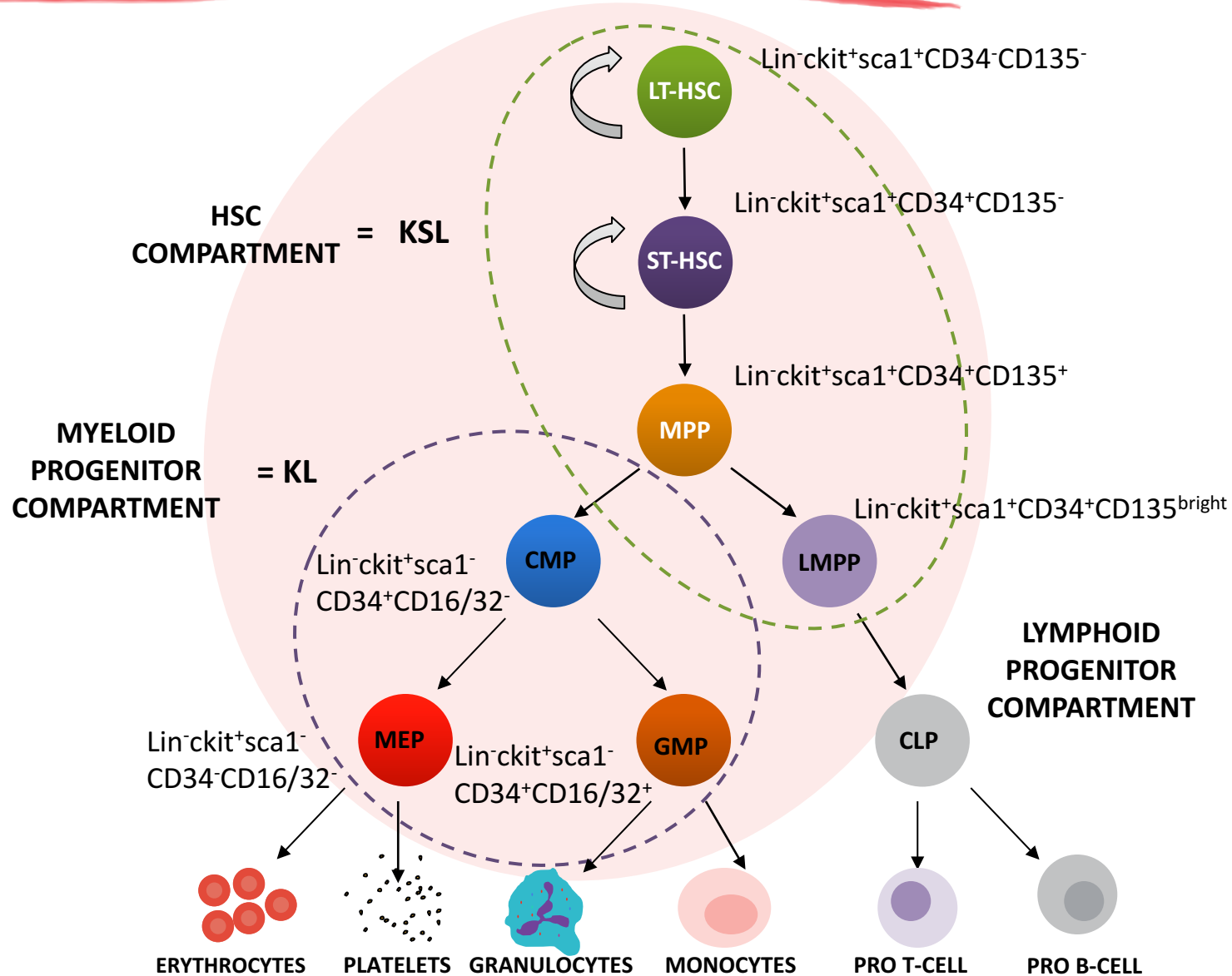
**Chair, ad interim, Department of Leukemia**

**Chief Section of MDS**

**University of Texas MD Anderson Cancer Center**

**SOHO Brazil/SINTOMA 2026**

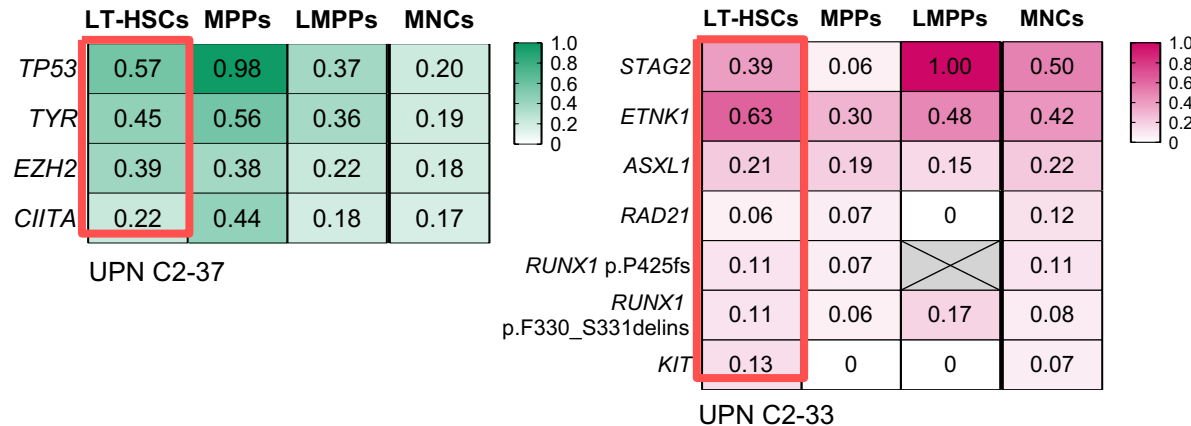
# Adult murine hematopoiesis



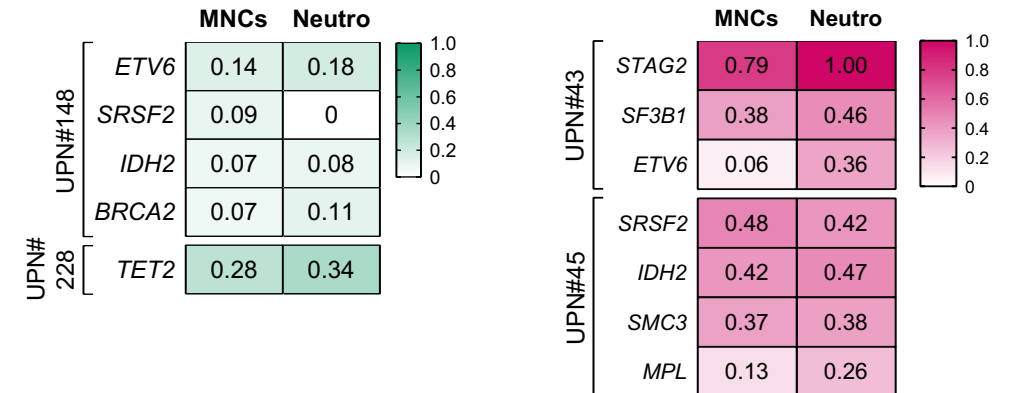
# MDS HSCs Are Almost All Mutated

- >90% of HSCs are mutated (n=46 patients)
- **Should we target mutant HSCs in patients with cytopenias?**
- **Abnormal HSPC frequencies persist** throughout HMA therapy independently of response
- **Persistent tumor burden** found in terminally differentiated neutrophils from patients with hematological response

Representative mutational profiles in HSCs and BM MNCs (VAF)



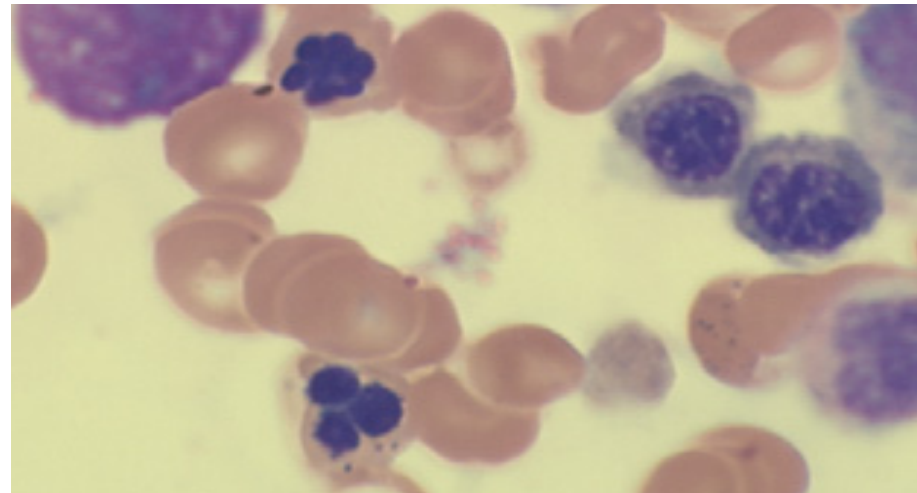
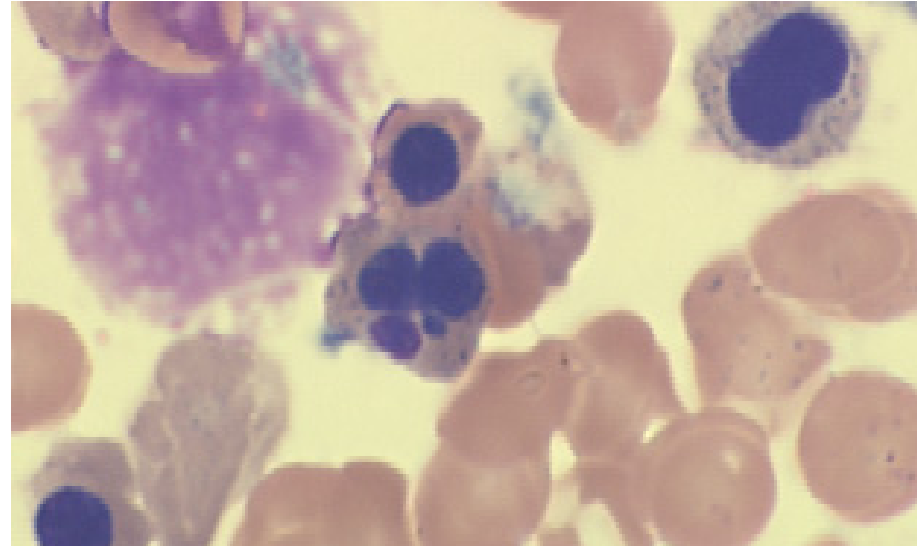
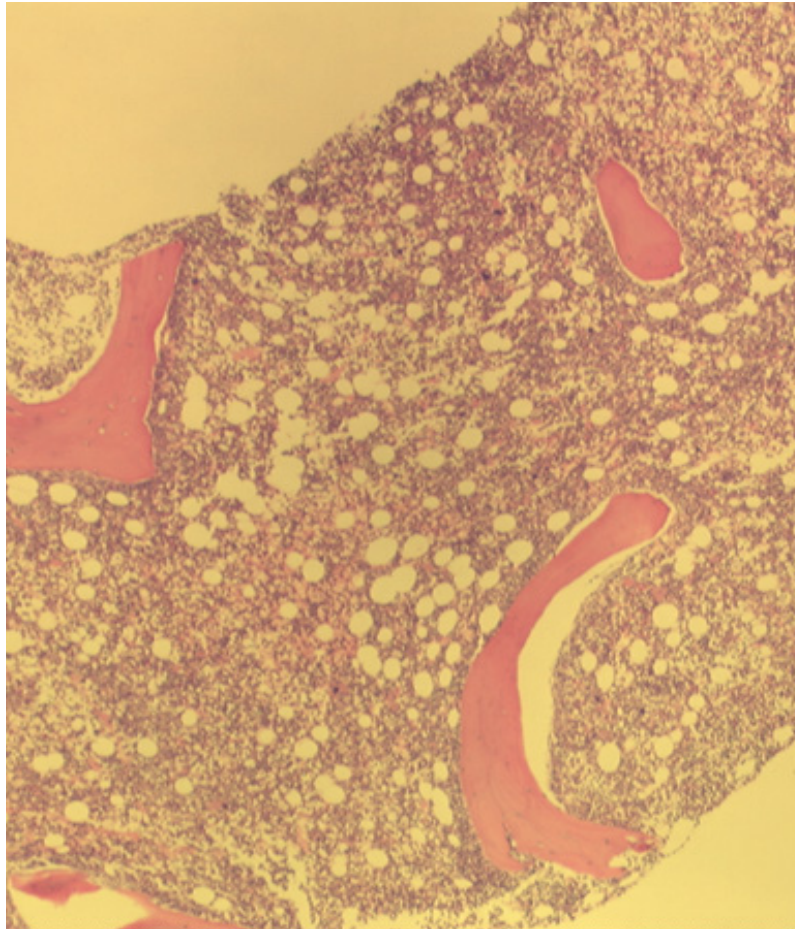
Allele frequencies (VAF) of somatic mutations in patients with hematologic response



**MDS HSCs are all mutated and HMA therapy induces differentiation of leukemic cells**

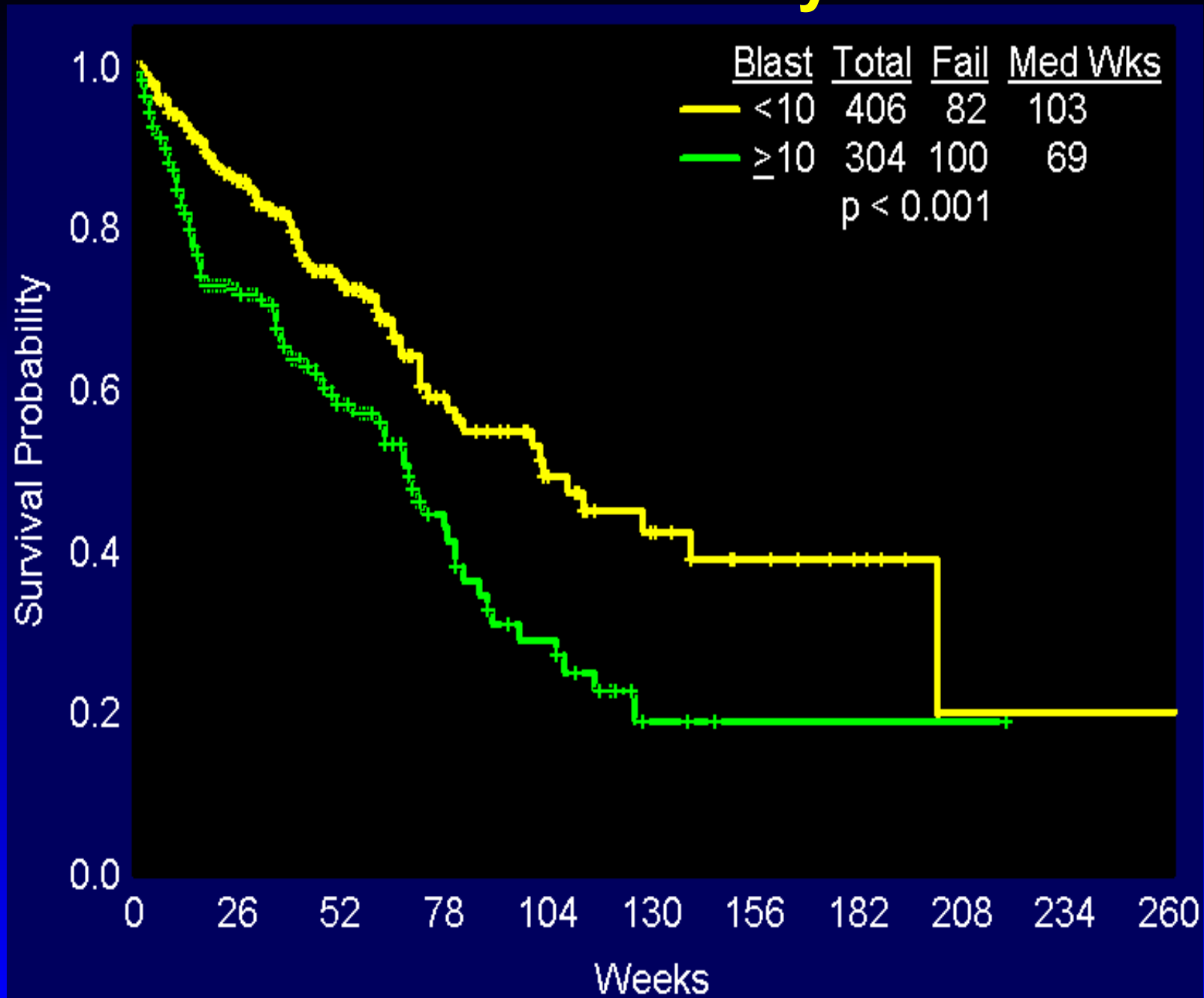
# Diagnosis of MDS is (WAS) based on morphology

CAM 2026 Chicago



Courtesy of Dr. Carlos Bueso-Ramos

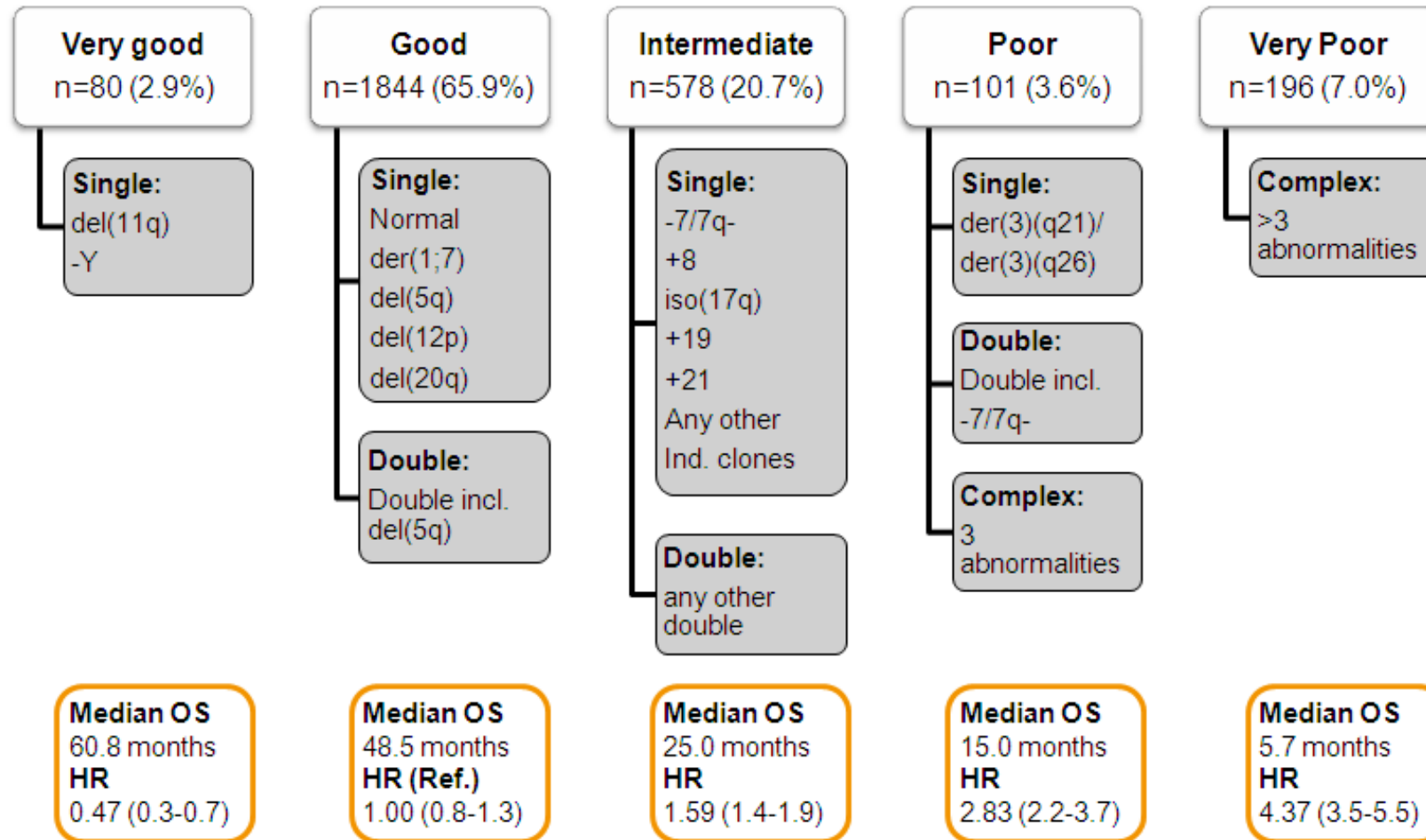
# 1999-2003: Survival by # Blasts



# Prognostic models

- **IPSS**
- **WPSS**
- **Global MDACC model**
- **MDACC lower risk model**
- **Impact of comorbidities**
- **Revised IPSS**

# Cytogenetic Scoring System in MDS



# Revised IPSS

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	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	—	—	—	—	—

# High-resolution Structural Variant profiling in MDS

101 consecutive newly diagnosed MDS

Standard work-up

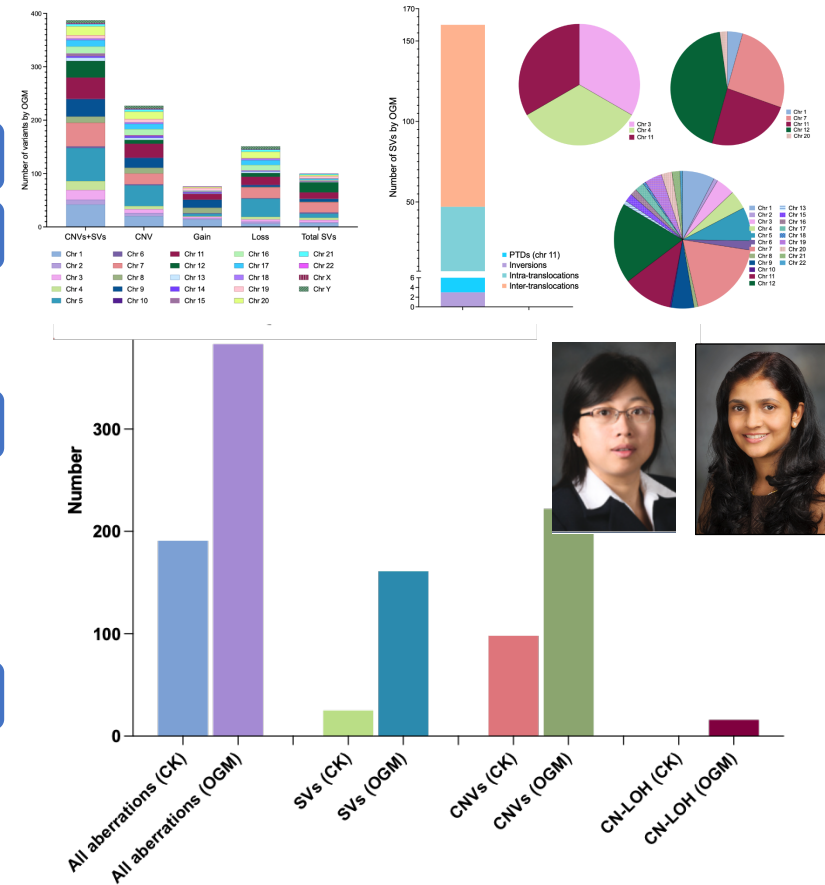
- 81-gene panel NGS
- Conventional karyotyping +/- FISH
- Optical Genome Mapping (Saphyr, Bionano)

383 clinically significant variants by OGM

- Copy Number Variants
- Structural Variants
  - Inversions
  - Inter and intra-chromosomal translocations
  - Partial tandem duplications

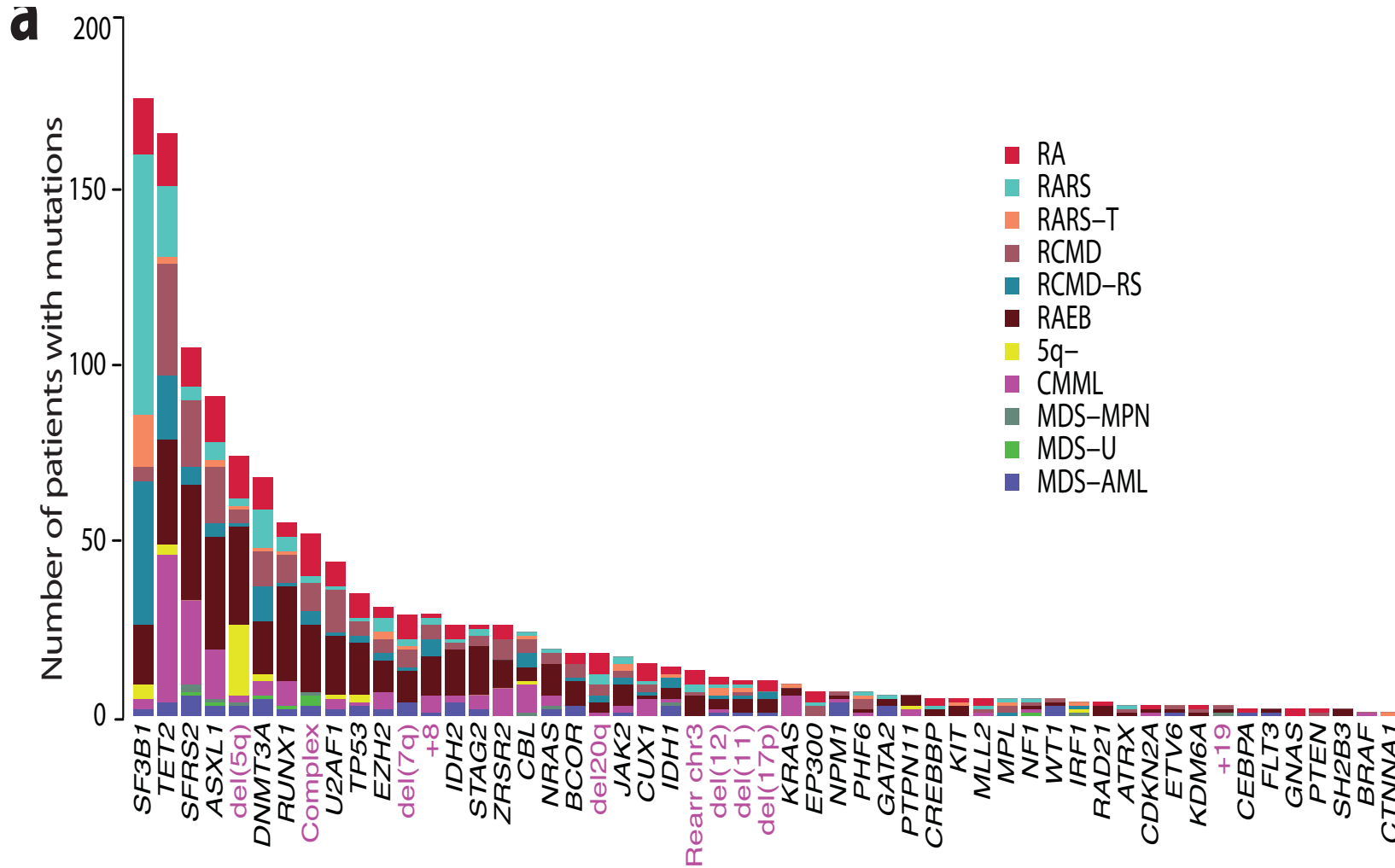
224 of 383 (51%) were NOT detected by traditional karyotyping

- Seen across 34% of patients



Hui Yang et al Leukemia 22

# Genomics of MDS



# Impact of number of mutations in survival in MDS

Adverse Factor		HR	P value	Assigned Score
IPSS-R	Intermediate	1.45	0.45	0.5
	High/Very high	4.66	<0.001	1.5
<i>TP53</i> mutation		3.12	0.011	1
≥ 3 mutations		2.51	0.005	1

Montalban-Bravo et al. Oncotarget 2018

# Molecular International Prognostic Scoring System for myelodysplastic syndromes

**Elsa Bernard, PhD**

Research Associate

Computational Oncology | Papaemmanuil Lab | Memorial Sloan Kettering Cancer Center

 @Elsa2Bernard



ASH 21, NEJM evidence

# The IPSS-M model

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

Category	Variable	Multivariable model: hazard ratio <sup>§</sup> (95% CI)	Weight w	Scaling $x^{\text{mean}}$
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
	$\gamma_{\text{res}} \min(\text{Platelets}, 250)$ , in $\times 10^9/L$	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 <sup>§</sup>	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects 17 variables, 16 genes	<i>TP53</i> <sup>mut</sup>	3.27 (2.38 - 4.48)	1.18	0.0710
	<i>MLL</i> <sup>PTD</sup>	2.22 (1.49 - 3.32)	0.798	0.0247
	<i>FLT3</i> <sup>TD+TKD</sup>	2.22 (1.11 - 4.45)	0.798	0.0108
	<i>SF3B1</i> <sup>sq</sup>	1.66 (1.03 - 2.66)	0.504	0.0166
	<i>NPM1</i>	1.54 (0.78 - 3.02)	0.430	0.0112
	<i>RUNX1</i>	1.53 (1.23 - 1.89)	0.423	0.126
	<i>NRAS</i>	1.52 (1.05 - 2.20)	0.417	0.0362
	<i>ETV6</i>	1.48 (0.98 - 2.23)	0.391	0.0216
	<i>IDH2</i>	1.46 (1.05 - 2.02)	0.379	0.0429
	<i>CBL</i>	1.34 (0.99 - 1.82)	0.295	0.0473
	<i>EZH2</i>	1.31 (0.98 - 1.75)	0.270	0.0588
	<i>U2AF1</i>	1.28 (1.01 - 1.61)	0.247	0.0866
	<i>SRSF2</i>	1.27 (1.03 - 1.56)	0.239	0.158
	<i>DNMT3A</i>	1.25 (1.02 - 1.53)	0.221	0.161
	<i>ASXL1</i>	1.24 (1.02 - 1.51)	0.213	0.252
<i>KRAS</i>	1.22 (0.84 - 1.77)	0.202	0.0271	
<i>SF3B1</i> <sup>nr</sup>	0.92 (0.74 - 1.16)	-0.0794	0.186	
gene residuals <sup>§</sup> 1 variable, 15 genes	$\min(\text{Nres}, 2)$ Possible values are 0, 1 or 2	1.26 (1.12 - 1.42)	0.231	0.388

Continuous clinical parameters  
Marrow blasts, platelets, hemoglobin

IPSS-R cytogenetic categories

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

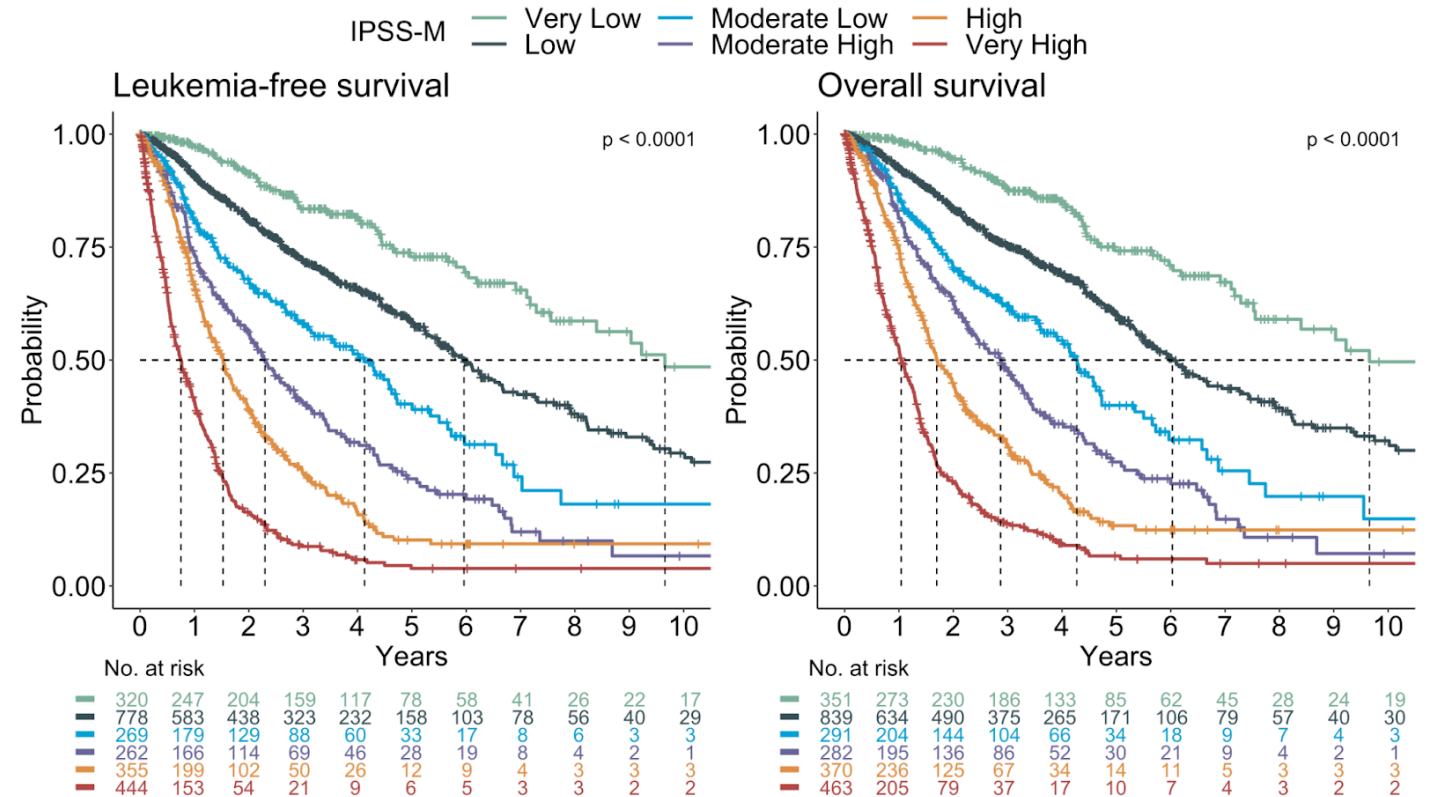
1 genetic variable from 15 residual genes<sup>^</sup>  
Number of mutated genes (0, 1 or 2)

<sup>^</sup>residual genes: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, *WT1*

# The IPSS-M risk categories

## A six-category risk schema

IPSS-M	Very Low VL	Low L	Moderate Low ML	Moderate High MH	High H	Very High VH
Patients, % (n=2,701)	14% (381)	33% (889)	11% (302)	11% (291)	14% (379)	17% (469)
Risk score	≤ -1.5	> -1.5 to -0.5	> -0.5 to 0	> 0 to 0.5	> 0.5 to 1.5	> 1.5
Hazard ratio <sup>a</sup> (95% CI)	0.51 (0.39 - 0.67)	1.0 reference	1.5 (1.2 - 1.8)	2.5 (2.1 - 3.1)	3.7 (3.1 - 4.4)	7.1 (6.0 - 8.3)
Median LFS, yrs 25-75% LFS range, yrs	9.7 5.0 - 17.4	5.9 2.6 - 12.0	4.5 1.6 - 6.9	2.3 0.91 - 4.7	1.5 0.80 - 2.8	0.76 0.33 - 1.5
Median OS, yrs 25-75% OS range, yrs	10.6 5.1 - 17.4	6.0 3.0 - 12.8	4.6 2.0 - 7.4	2.8 1.2 - 5.5	1.7 1.0 - 3.4	1.0 0.5 - 1.8
AML-t by 1 yr, % 2 yrs 4 yrs	0.0 1.2 2.8	1.7 3.4 5.1	4.9 8.8 11.4	9.5 14.0 18.9	14.3 21.2 29.2	28.2 38.6 42.8
Death w/o AML by 1 yr, % 2 yrs 4 yrs	2.2 7.0 15.9	8.5 16.2 29.5	12.0 19.8 33.6	18.0 31.1 51.1	19.3 39.8 54.2	30.6 45.6 51.3

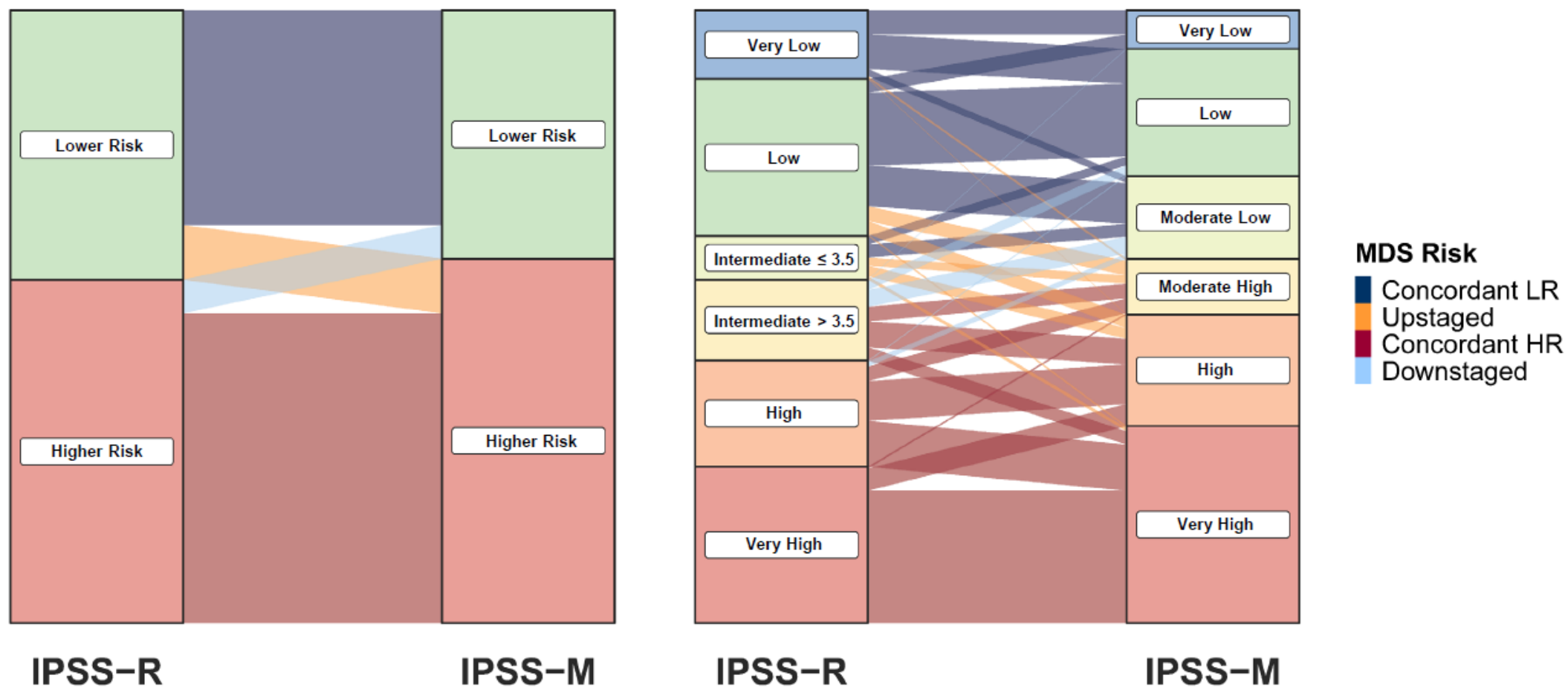


**Very Low | Low | Moderate Low | Moderate High | High | Very High**  
**Prognostic separation of the IPSS-M risk categories**

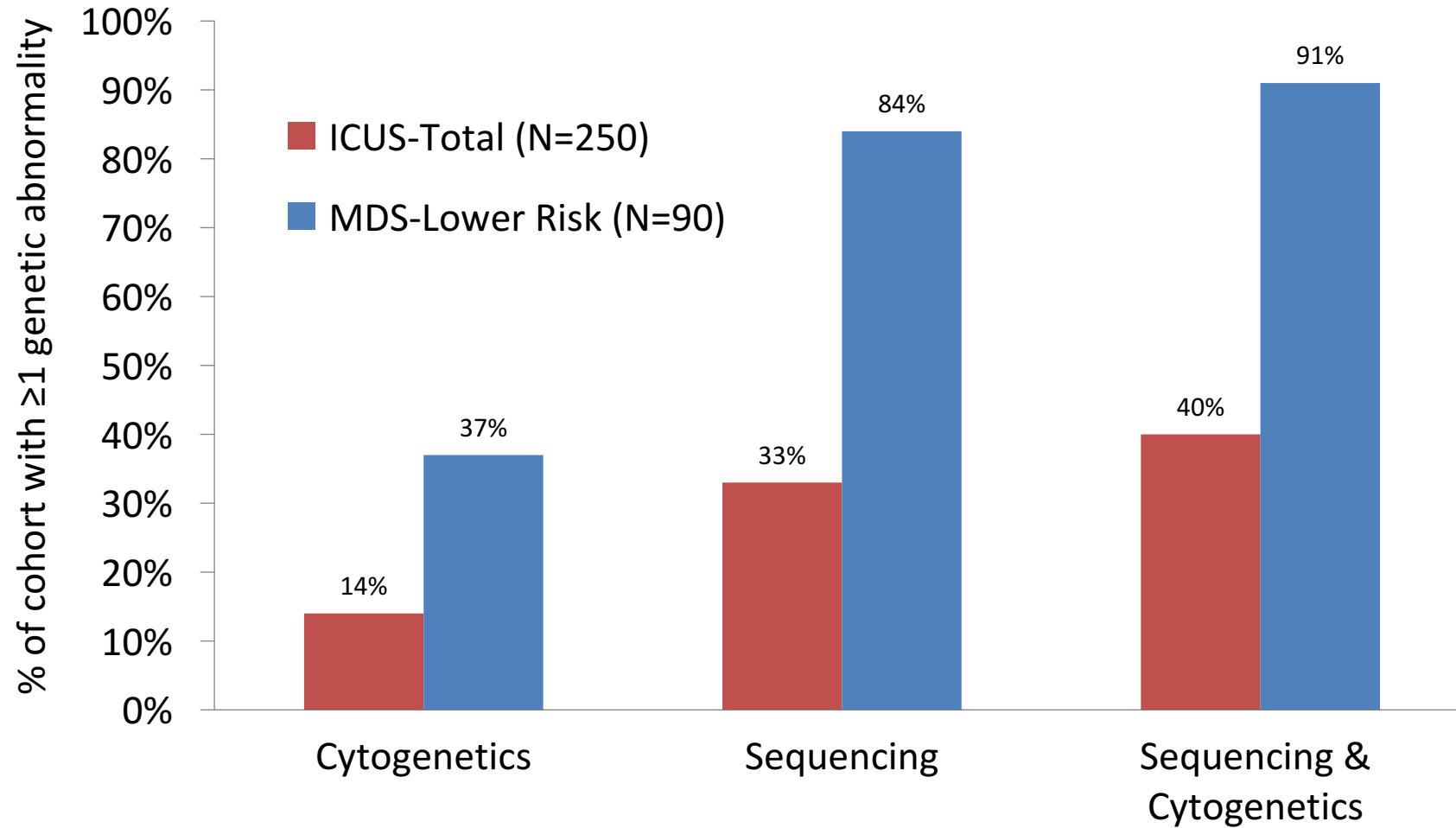
# IPSS-R vs IPSS-M

N=1054

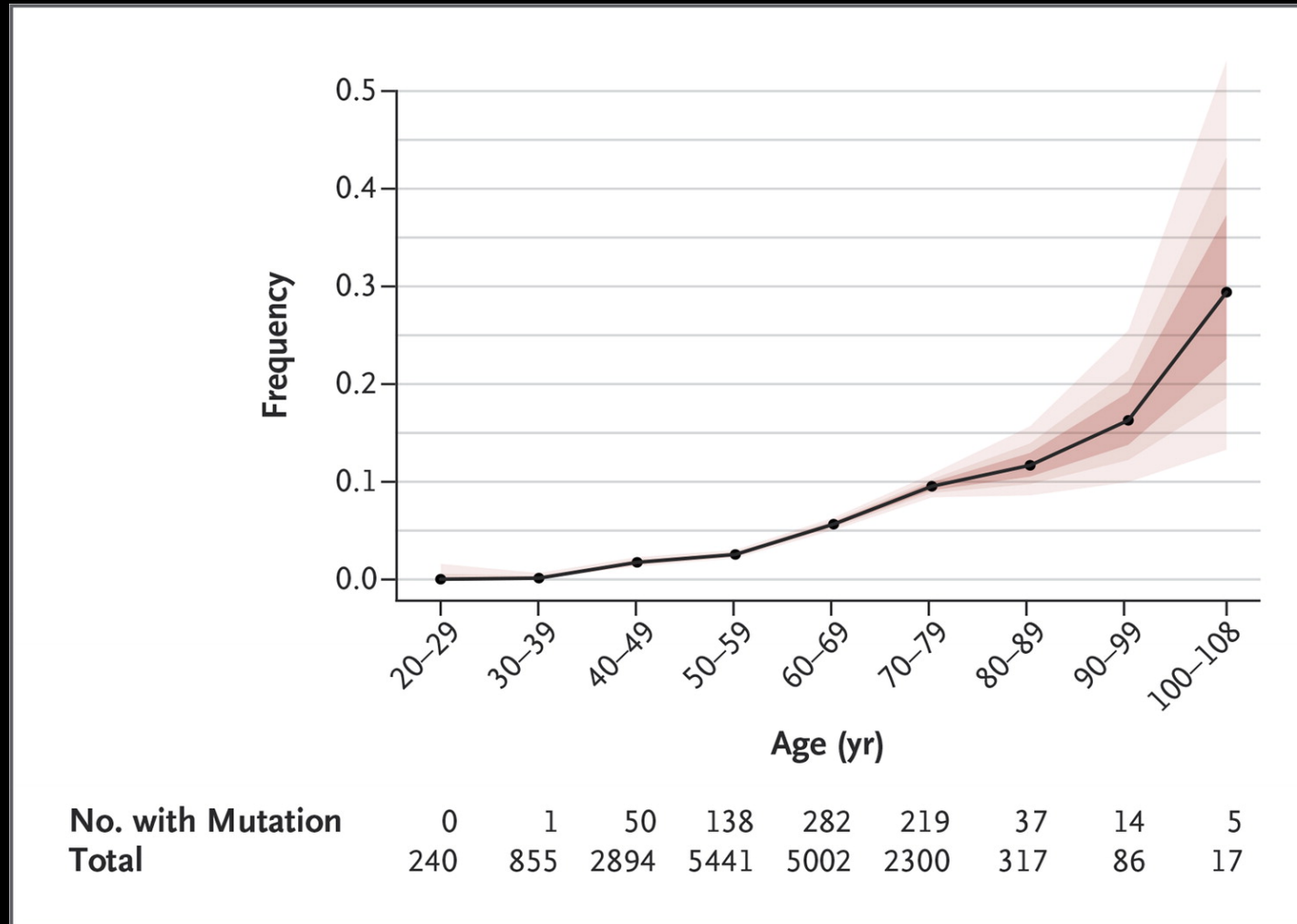
365 (35%) concordant LR, 533 (51%) concordant HR, 94 (9%) upstaged, 58 (6%) downstaged.



# Frequency of Genetic Abnormalities in ICUS vs MDS



# Prevalence of Somatic Mutations, According to Age



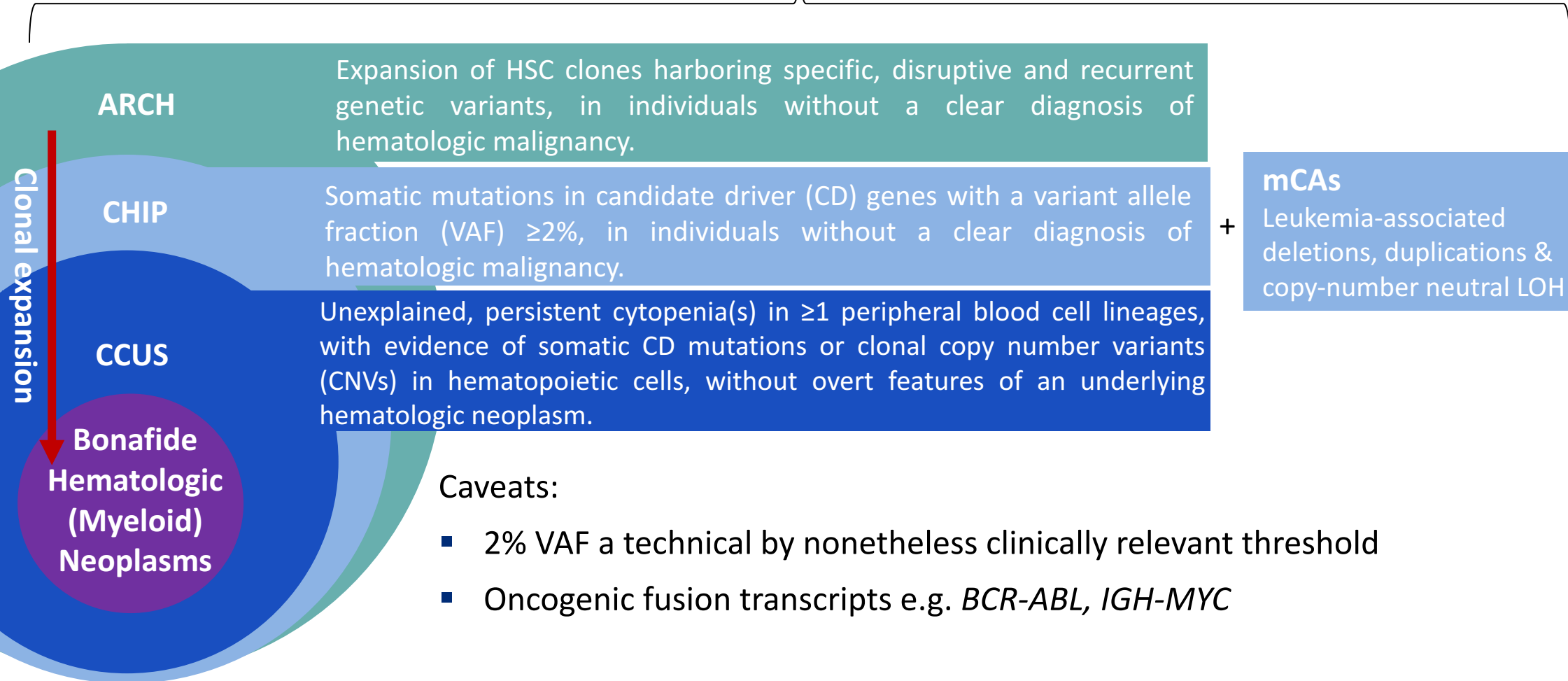
Jaiswal S et al. N Engl J Med 2014;371:2488-2498.



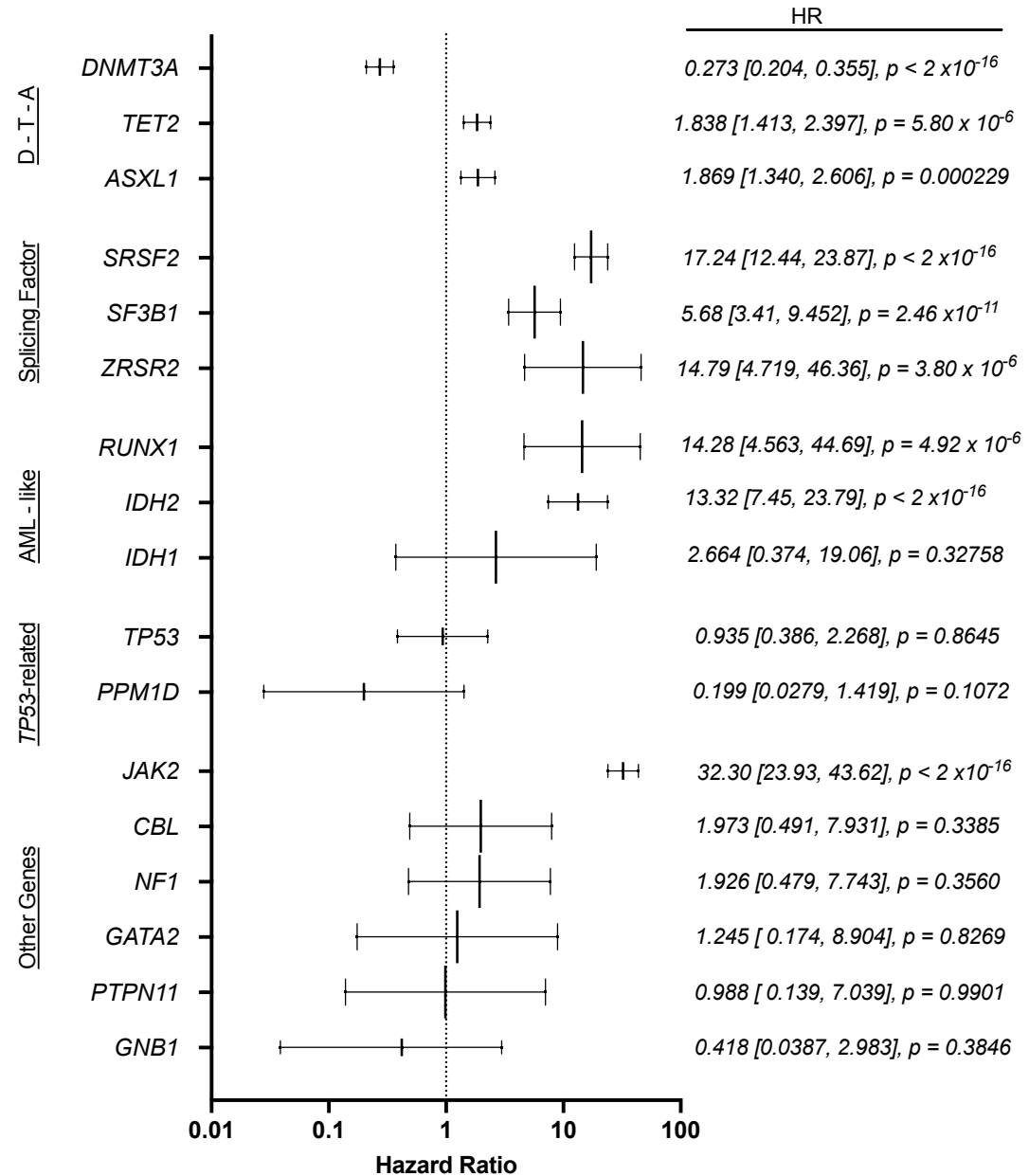
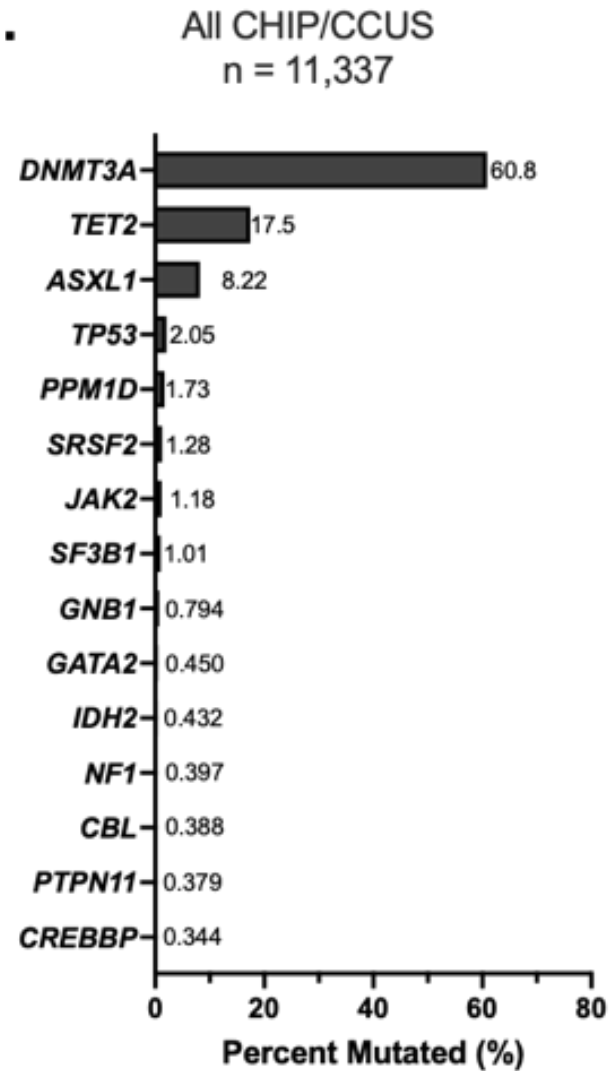
The NEW ENGLAND  
JOURNAL of MEDICINE

# CHIP/CCUS: Key Definitions

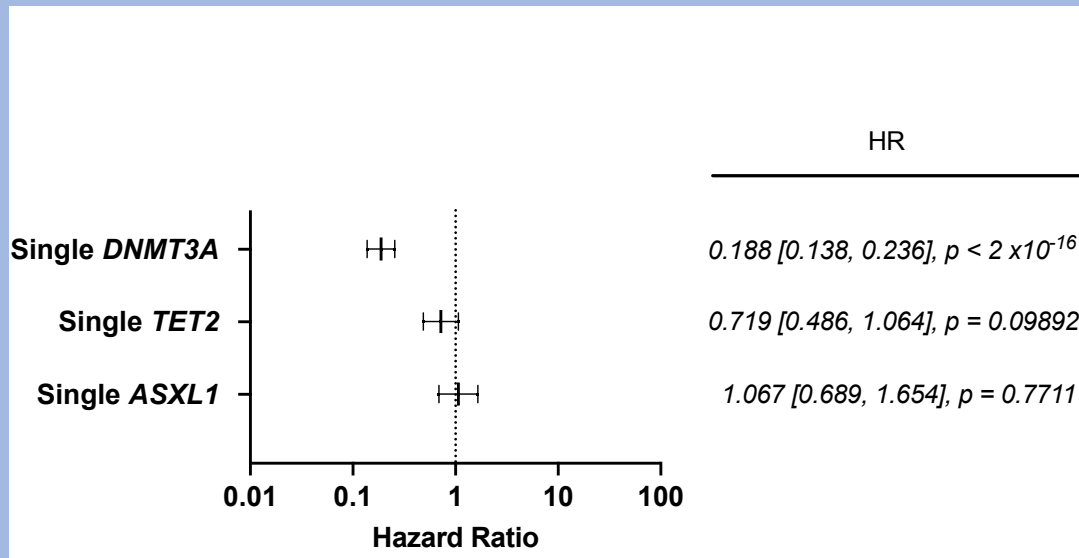
## Clonal hematopoiesis (CH)



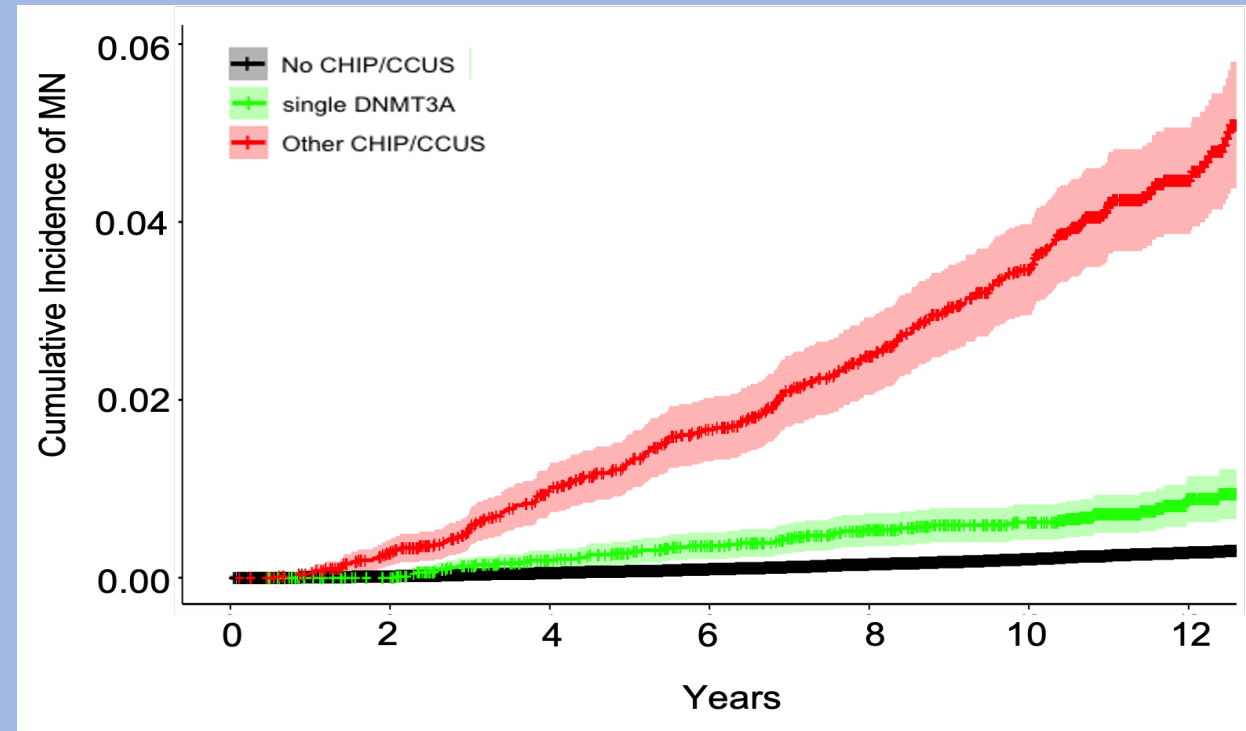
# Risk of incident MN is genotype specific in CHIP/CCUS



# DNMT3A mutations have the lowest risk of progression to MN



Weeks et al. ASH 22



# Clonal Hematopoiesis Risk Score (CHRS)

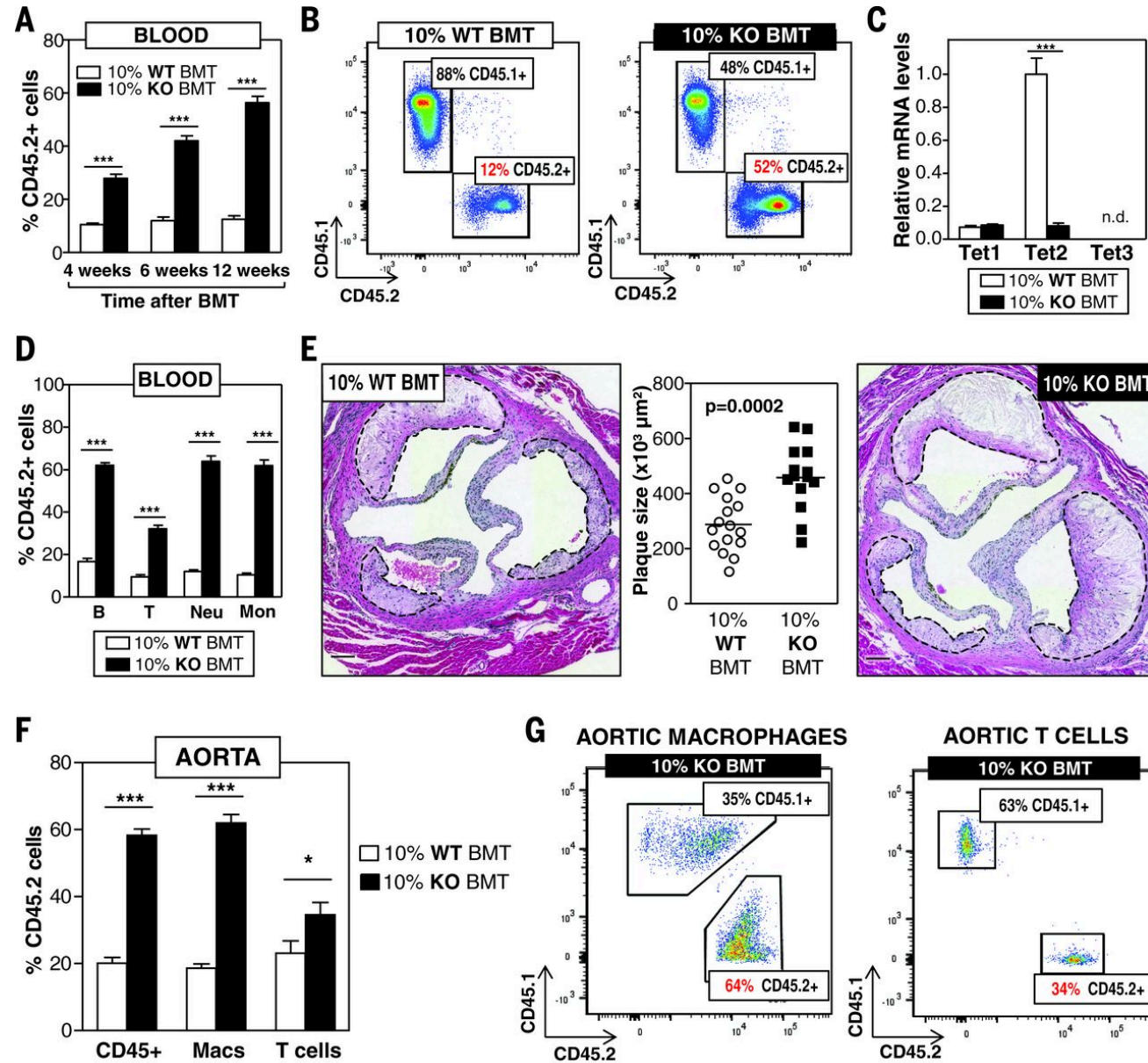
Prognostic Variable	0.5	1	1.5	2	2.5
Single <i>DNMT3A</i>	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–	< 65y	≥ 65y	–	–

High-risk mutations:

- Splicing factors (*SF3B1*, *SRSF2*, *ZRSR2*)
- AML-like mutations (*RUNX1*, *IDH1/2*, *FLT3*)
- *JAK2*
- *TP53* – empiric addition

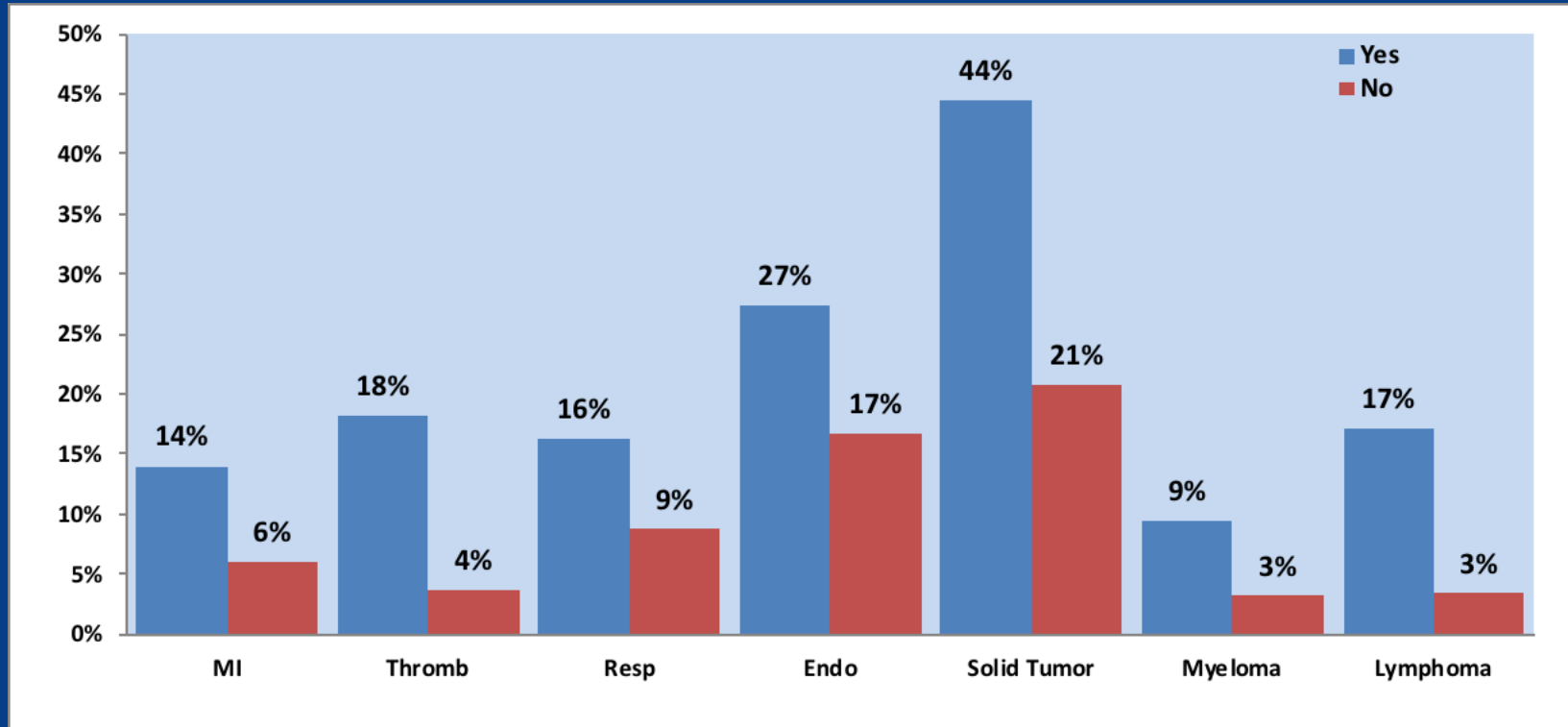
Risk Groups Defined by Clonal Hematopoiesis Risk Score (CHRS)					
Risk Groups	Score	N, per category	Incident MN (N, %)	5-Year CI for MN	10- Year CI for MN
High	≥ 12.5	123	67 (54.5%)	24.4 ± 4.12%	52.2 ± 4.96%
Intermediate	10 – 12	1196	112 (9.36%)	2.76 ± 0.482%	7.83 ± 0.807%
Low	≤ 9.5	10018	90 (0.90%)	0.232 ± 0.0484%	0.669 ± 0.0827%
No CHIP/CCUS	NA	182406	495 (0.27%)	0.0740 ± 0.00640%	0.210 ± 0.0108%

# Clonal Hematopoiesis and Atherosclerosis



# CHIP mutations and comorbidities in MDS.

## Comorbidities by mutations



- *DNMT3A* was associated with a higher frequency of prior history of myocardial infarction (MI) (OR= 2.62; 95% CI 1.095-6.246; p=0.03)
- *JAK2* was associated with a higher frequency of prior history of veno-occlusive disease (OR= 6.48; 95% CI 1.375-30.477; p=0.02)
- *TP53* mutation was highly associated with history of prior malignancy



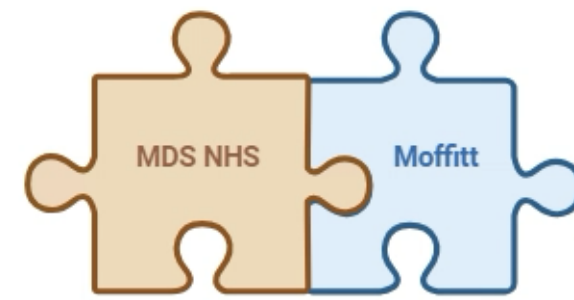
American Society of Hematology  
Helping hematologists conquer blood diseases worldwide

# High-Risk CCUS is Clinically Indistinguishable from Low-Risk Myelodysplastic Syndromes/Neoplasms

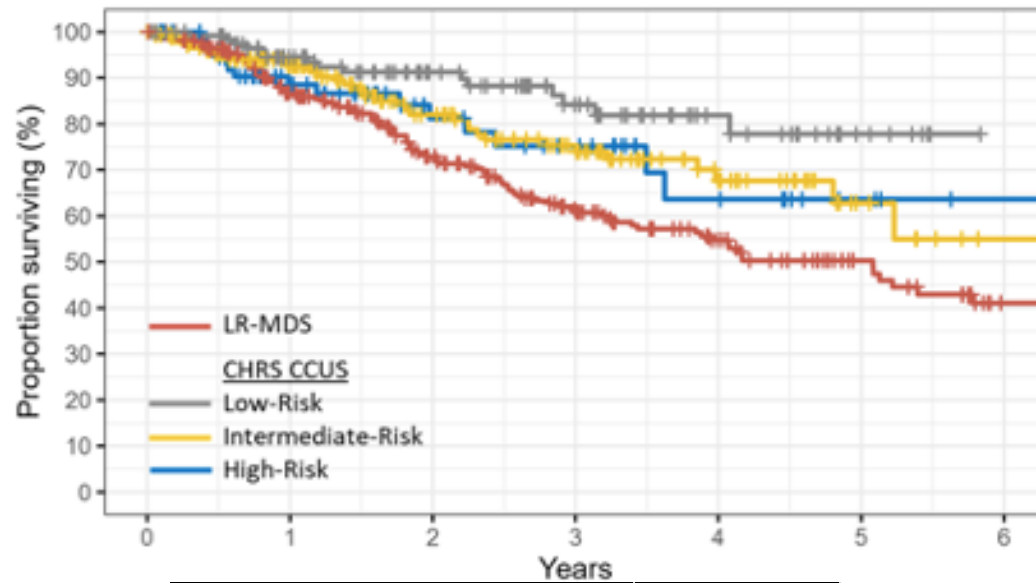
**Zhuoer Xie, MD, MS, Zena Komrokji, Michael Otterstatter, PhD, Ling Zhang, MD, Lynn C. Moscinski, MD, Najla H. Al Ali, David A Sallman, MD, Jeffrey Lancet, MD, Amy E. DeZern, MD, MHS, Mikkael A. Sekeres, MD, Rami S. Komrokji, MD, Nancy K Gillis, PhD and Eric Padron, MD**

Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The Emmes Company, LLC, Rockville, MD; Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; Sylvester Cancer Center, University of Miami Health System, Miami, FL

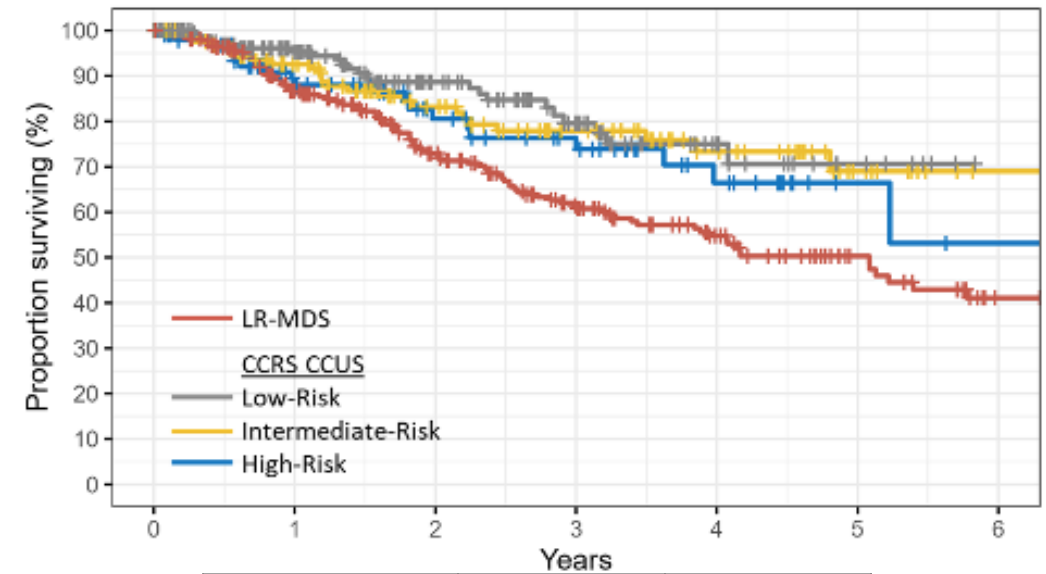
# Overall Survival



- OS: LR-MDS vs CCUS by CHRS and CCRS risk category



	CHRS CCUS vs LR-MDS	
CCUS Risk Category	HR	P-value
Low-Risk	0.35 (0.20-0.60)	< 0.001
Intermediate-Risk	0.63 (0.43-0.92)	0.017
High-Risk	0.65 (0.38-1.12)	0.119



	CCRS CCUS vs LR-MDS	
CCUS Risk Category	HR	P-value
Low-Risk	0.45 (0.29-0.71)	< 0.001
Intermediate-Risk	0.53 (0.34-0.82)	0.004
High-Risk	0.64 (0.40-1.03)	0.068



## Clonal Hematopoiesis/Leukemia Prevention Clinic Objectives

### Referral to CH Clinic

- cfDNA or concurrent PB sequencing in solid tumor patients
- Incidental findings in patients with other non-myeloid malignancies or during germline testing
- Cytopenias warranting referral to benign hematology or leukemia clinic

### Natural History Study

Improve understanding of CH and determinates of clonal progression via longitudinal PB and BM sampling

Sample banking protocol PA19-1345 for CH/MDS/CMML



### Mitigation of Comorbidities

Screen for and offer appropriate care for associated extra-hematologic consequences

Cardiovascular and rheumatologic screening

Health maintenance cancer screening

Vaccinations

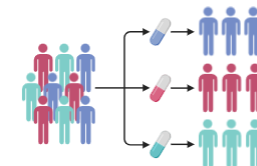
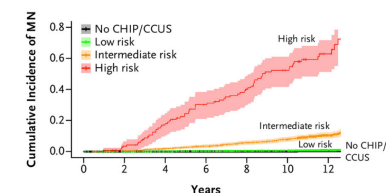


### Leukemia Prevention

Identify and intervene upon high-risk CH states to prevent transformation to hematologic malignancies

Leukemia transformation risk determination

Clinical trial screening and enrollment

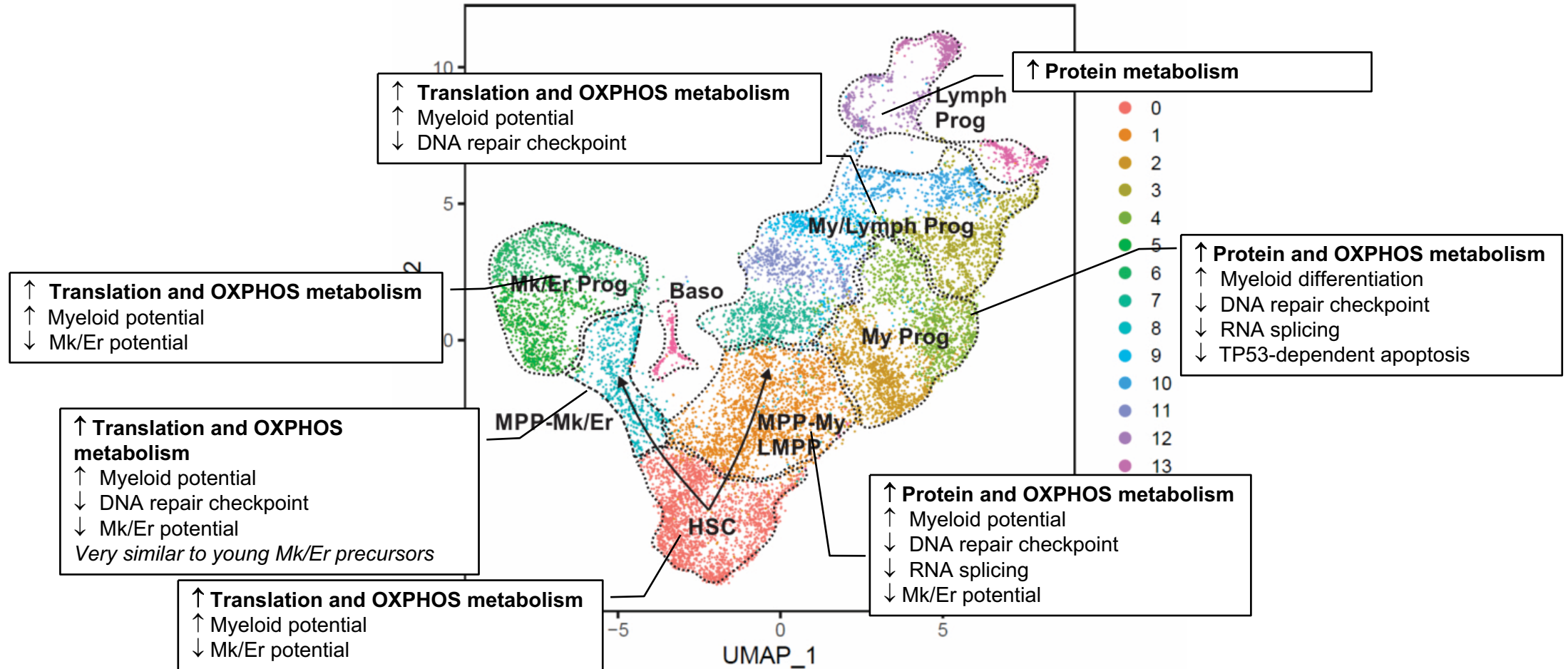


# Clinical Trials in CHIP/CCUS

Agent	Conditions	Included Mutations	Cytopenia Definition	Goal Enrollment	Active Malignancy Allowed	Primary Endpoint	Length of Therapy	NCT Number
<b>Enasidenib</b>	CCUS	<i>IDH2</i>	Hgb < 10, ANC < 1.8, plt < 100	15-20	6+ mos, no tx	HI (IWG 2006)	18 mos	NCT05102370
<b>Ivosidenib</b>	CCUS	<i>IDH1</i>	Hgb < 10, ANC < 1.8, plt < 100	15-20	6+ mos, no tx	HI (IWG 2006)	5 yrs	NCT05030441
<b>Olutasidenib</b>	CCUS, LR-MDS/CMML	<i>IDH1</i>	WHO criteria	15	Yes	HI (IWG 2018)	18 mos	NCT06566742
<b>Decitabine/cedazuridine</b>	CCUS (CHRS high-risk)	Any myeloid mutation	WHO criteria	138	Yes if 6+ mos no chemoRT or PARPi	Safety and feasibility	12 mos	NCT06802146
<b>Atorvastatin or rosuvastatin</b>	CCUS, LR-MDS	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	16	2+ yrs, no tx	Δ hs-CRP	12 mos	NCT05483010
<b>Luspatercept</b>	CCUS	Any myeloid mutation	Hgb < 10, ANC < 0.75, plt < 50	50	Yes if no tx	HI (IWG 2018)	Indefinite	NCT06788691
<b>Canakinumab</b>	CCUS [vs placebo]	Splicing mutations at any VAF, <i>TP53</i> at VAF > 0.05, DTA and/or other CH-associated mutations in combination or at VAF > 0.1	Hgb < 11, 0.5 < ANC < 1.8, 50 < plt < 150	110	Yes if no tx	Time to MN transformation	2 yrs	NCT05641831
	CCUS, LR-MDS	Any myeloid mutation	WHO criteria	70	2+ yrs	HI (IWG 2006), safety	Indefinite	NCT04239157
<b>Curcumin</b>	CCUS, LR-MDS, MPN [vs placebo]	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	30	Yes if no tx except hormonal/growth factors	Δ IL-1β, IL-6, IL-18, TGFβ, TNFα levels; QoL	12 mos	NCT06063486
	CCUS [IV]	<i>TET2</i>	Hgb < 10, ANC < 1.0, plt < 100	Terminated at 10/55	Yes if no tx except hormonal	HI (IWG 2018)	3 mos	NCT03418038
<b>Ascorbic Acid</b>	CCUS, LR-MDS, CMML-0/1 [PO, vs placebo]	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	109	5+ yrs	Δ VAF and median number of mutations	12 mos	NCT03682029
<b>Metformin</b>	CCUS, LR-MDS	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	40	Yes if 6+ mos no tx	Safety and feasibility	12 mos	NCT04741945
<b>DFV890</b>	CCUS (CHRS high-risk), LR-MDS/CMML	Any myeloid mutation	Hgb < 11, ANC < LLN, plt < 150	105	Yes if 12+ mos no tx	Safety and tolerability	Indefinite	NCT05552469
<b>DFV890 + MAS825</b>	CHIP + h/o MI	<i>DNMT3A</i> or <i>TET2</i>	No cytopenia allowed	31	No	Δ IL-6, IL-18 levels	3 mos	NCT06097663

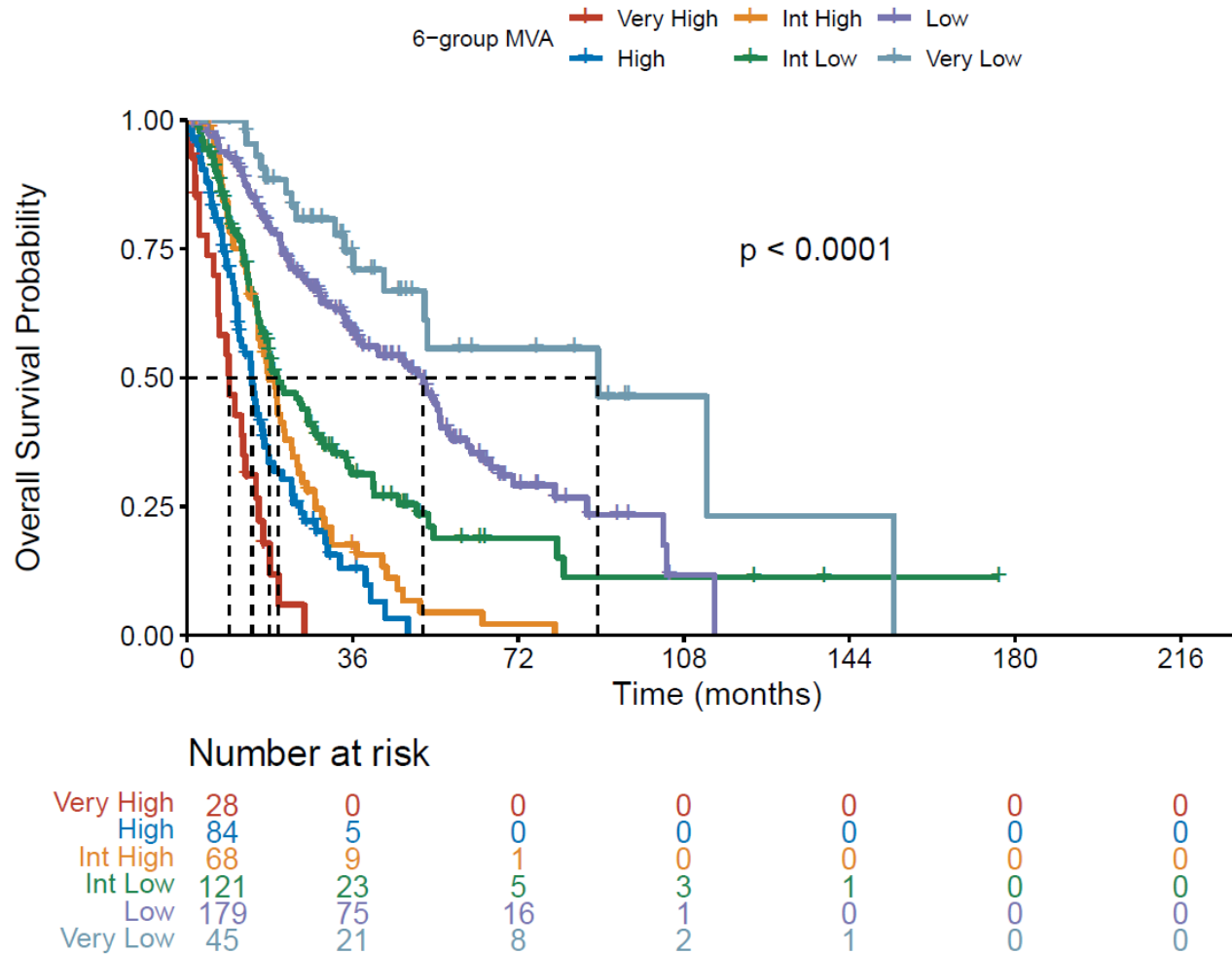
# CHIP/CCUS induces Expression Changes in HSPC

- Changes in **HSPC** expression profile: CHIP vs normal aging



**Conclusion:** Metabolic activation across all HSPC populations in CHIP

# HMA-Treated MDS: MDS-HOPE (Validation)



**VALIDATION COHORT (n=551)**  
Patients in original IPSS-M cohort who eventually receive HMA

## Comparison of Models by Akaike Information Criterion

Risk stratification model	No. of parameters	AICc	Change in AICc
6-group multivariable	5	3508.71	0
5-group multivariable	4	3513.73	5.03
IPSS-M	5	3531.23	22.52
IPSS-R	4	3552.97	44.26

# MDS-HOPE Web Application

The screenshot displays the MDS-HOPE web application interface. The top header includes the MD Anderson Cancer Center logo, the application name "MDS-HOPE", and a version string "PID: 1166, Version: V1.1.0, Last Update: 01/20/2026".

**REQUIRED INPUT DATA**

- Bone Marrow Blasts:** Percentage (Enter value: e.g. 10 (0-30))
- Hemoglobin:** g/dL (Enter value: e.g. 6 (4-20))
- Platelet Count:** 1e9/L (Enter value: e.g. 300 (0-2000))
- Absolute Neutrophil Count:** 1e9/L (Enter value: e.g. 8 (0-100))
- Age:** Years (Enter value: e.g. 85 (18-120))
- Gene Mutation:** TP53 (Selected: N/S, Other options: No, Single-hit, Multi-hit)

**Patient Summary Panel**

Bone Marrow Blasts: N/A	Hemoglobin: N/A	Platelet Count: N/A	Absolute Neutrophil Count: N/A	Age: N/A
Number of clones: N/A	Number of Abnormalities: N/A	Cytogenetics Category: N/A	Complex Karyotype: N/A	

**Overall Distribution**

Five violin plots showing the distribution of input variables: Bone Marrow Blasts, Hemoglobin, Platelet, Absolute Neutrophil Count, and Age. Each plot includes a box plot overlay.

**Stratification Result Panel**

MDS-HOPE Score: N/A	IPSS-R Score: N/A
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<https://biostatistics.mdanderson.org/shinyapps/MDS-HOPE/>

## 1. HMA-Treated Patients

**AIM:** to assess the applicability of IPSS-M in HMA-treated patients with MDS and develop a multivariate model for this patient population

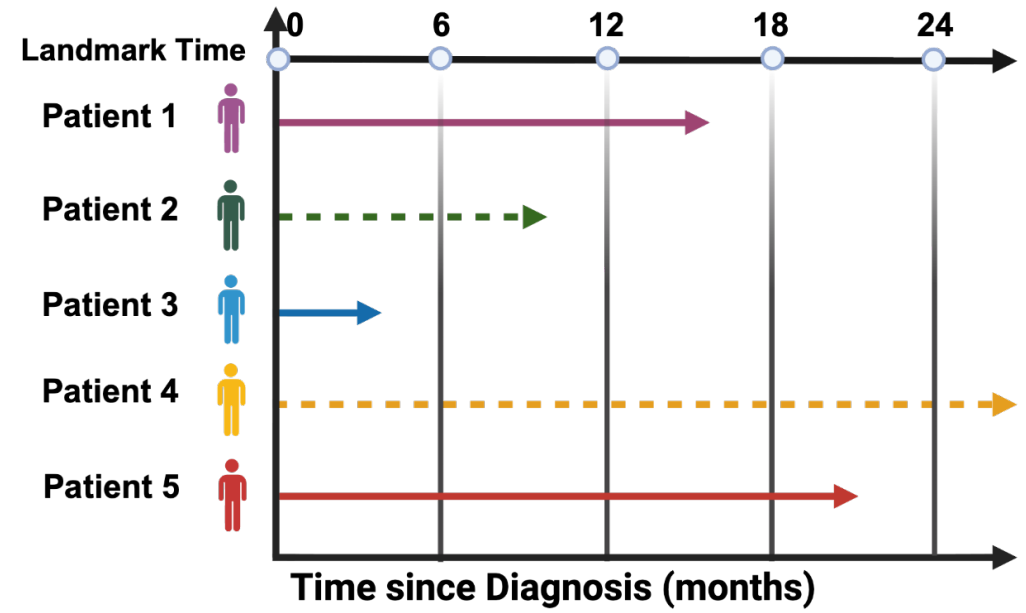
## 2. Incorporation of Timepoints Other Than Baseline

**AIM:** to create a dynamic survival prediction model that captures disease evolution and patient-specific trajectories over time

- **Goal:** Predicts survival time of MDS patients using longitudinal data, which helps in personalized treatment planning and risk stratification
- **Data:** Combined longitudinal clinical, gene mutation and cytogenetics data. Dynamic covariates updated at multiple landmark times (e.g., 6, 12, 18 months, etc.)
- **Model:** Employed Landmarking SuperLearner, an ensemble of machine learning models tailored to time-specific survival prediction. Base learners include Cox, gradient boosting, random survival forests, etc.
- **Highlight:** Provides individualized survival curves at desired prediction time point, adapting to new clinical information. Improves predictive accuracy by leveraging multiple learners and time-updated data

# DPSS: Methods

## Landmarking Model



**Patients Included**

LM 0 Model: Pt 1, 2, 3, 4, 5  
 LM 6 Model: Pt 1, 2, 4, 5  
 LM 12 Model: Pt 1, 4, 5  
 LM 18 Model: Pt 4, 5  
 LM 24 Model: Pt 4

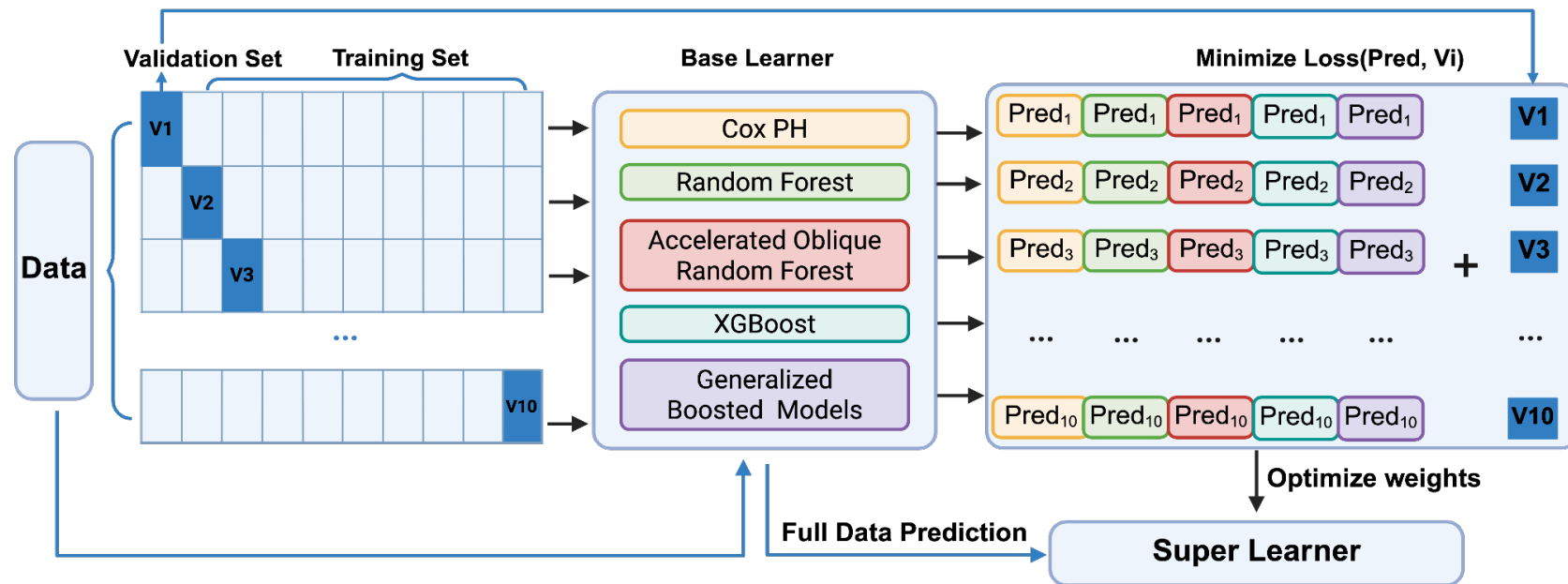
## Longitudinal Data

Enrollment (Mo)	0	2	4	6	8	10	12
Hemoglobin	○						△
Bone Marrow Blasts	○			☆			
Platelet	○		☆			△	
Gene Mutation	○	☆					△
Cytogenetics	○						



# DPSS: Methods

## SuperLearner Framework



Model	Description
<b>Cox Proportional Hazard model (COX)</b>	<ul style="list-style-type: none"> <li>The <b>most common</b> statistical model used</li> <li>Relates the survival time to one or more predictor variables like linear regression</li> </ul>
<b>Random Forest (RSF)</b>	<ul style="list-style-type: none"> <li>An <b>ensemble bagging</b> method that constructs multiple <b>decision trees</b></li> <li>Merges their results for more accurate and robust predictions</li> </ul>
<b>Oblique Random Forests (ORSF)</b>	<ul style="list-style-type: none"> <li>A variant of <b>random forests</b>, also based on <b>decision trees</b></li> <li>Allows for more complex decision boundaries by using linear combinations of features at each split</li> </ul>
<b>Generalized Boosted Models (GBM)</b>	<ul style="list-style-type: none"> <li>An <b>ensemble boosting</b> method that builds successive shallow and weak <b>decision trees</b></li> <li>Each tree learning on the errors of the previous ones <b>sequentially</b></li> </ul>
<b>Extreme Gradient Boosting (XGB)</b>	<ul style="list-style-type: none"> <li>An <b>ensemble boosting</b> method based on the <b>gradient boosting</b> framework</li> <li>Utilizing <b>decision trees</b> as base learners and employs <b>regularization techniques</b> to enhance model generalization</li> </ul>

# DPSS: Training and Validation Data

	Training Data	Validation Data
<b>Number of patients</b>	1085	305
<b>Peripheral laboratory values</b>	70/patient	89/patient
<b>BM blasts</b>	5/patient	9/patient
<b>Cytogenetics</b>	4/patient	7/patient
<b>Mutations (<i>ASXL1, BCORL1, CBLC, CREBBP, DNMT3A, EZH2, GFI1, KDM6A, RUNX1, SF3B1, SRSF2, TERT, TET2, TP53, U2AF1</i>)</b>	3/patient	3/patient

Model	# Pts (Train)	# Pts (Validation)
<b>Landmark = 0</b>	878	304
<b>Landmark = 6</b>	600	275
<b>Landmark = 12</b>	462	244
<b>Landmark = 18</b>	353	203
<b>Landmark = 24</b>	251	174

# DPSS Web Application

**MDS-DPSS** PID: 1183, Version: V1.0.0, Last Update: 11/21/2025

### REQUIRED INPUT DATA

#### Time Since Diagnosis

- ✓ Not Selected
- Shorter than 6 Months
- 6 ~ 12 Months
- 12 ~ 18 Months
- 18 ~ 24 Months
- Longer than 24 Months

#### Bone Marrow Blasts

Percentage

#### Hemoglobin

g/dL

#### Platelet Count

1e9/L

### Patient Summary Panel

Bone Marrow Blasts: <b>N/A</b>	Hemoglobin: <b>N/A</b>	Platelet Count: <b>N/A</b>	Absolute Neutrophil Count: <b>N/A</b>	Age: <b>N/A</b>
Number of Clones: <b>N/A</b>	Number of Abnormalities: <b>N/A</b>	Cytogenetics Category: <b>N/A</b>	Complex Karyotype: <b>N/A</b>	

#### Overall Distribution

### Stratification Result Panel

MDS-DPSS Score: <b>N/A</b>	IPSS-R Score: <b>N/A</b>	IPSS-M Score: <b>N/A</b>
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<https://qcsrlpconnect.mdanderson.edu/MDS-DPSS/>

MPN-MDS

US Focus Meeting 2026

# MDS and AML Classification Coming Together in 2026

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Sanam Loghavi, MD  
MD Anderson Cancer Center

# What is the CAM?

Classification Advancement Meeting — Background & Purpose

## The Problem (2022)

- WHO5 and International Consensus Classification (ICC) published as two separate systems
- Divergent disease names, criteria, and thresholds caused global confusion
- Clinical trials and patient care impacted by classification dissonance

## The Solution (2024)

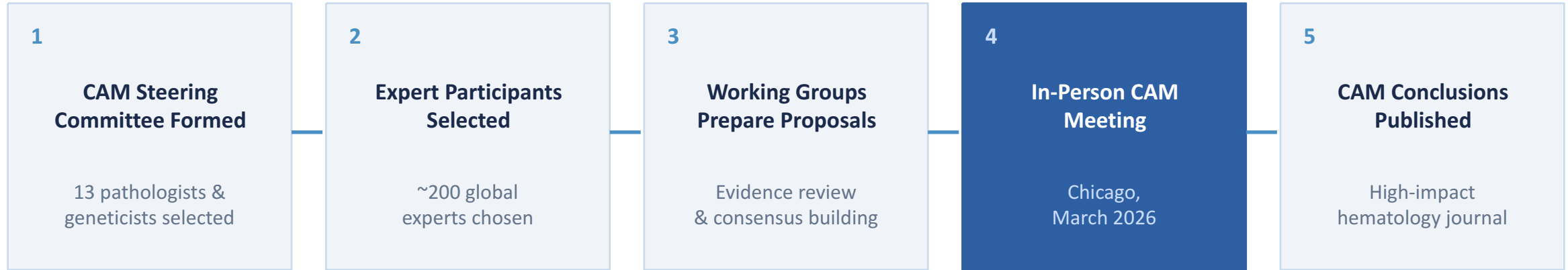
- SH and EA4HP presidents convened with WHO Classification of Tumours leadership
- Memorandum of understanding signed November 2024
- Goal: converge on WHO 6th Edition as the single definitive classification

## The CAM Process

- ~200 expert pathologists, clinicians, and geneticists selected based on recent scientific output
- Disease-specific working groups prepared evidence-based proposals prior to the in-person meeting
- Proposals debated, refined, and voted upon in Chicago, March 2026

# CAM → WHO 6th Edition

How the Classification Advancement Meeting feeds into WHO6



## → 6th Edition WHO Classification of Haematolymphoid Tumours (WHO6)

- WHO6 editorial board independently considers CAM recommendations (nonbinding but given strong weight)
- Final classification balances scientific advances with global applicability and resource equity
- Published in both online and printed Blue Book format — estimated 2026–2027

# Myelodysplastic Syndrome (MDS)

Key Classification Updates — CAM Proposals

## General Aspects

- MDS diagnosis may be made without dysplasia if  $\geq 3$  mutations at VAF  $\geq 10\%$  (at least 1 VAF  $\geq 20\%$ )- gene list in progress
- Flow cytometry accepted alongside morphology for demonstrating dysplasia (validated methods required)
- MDS with 10–19% blasts: majority favored single MDS-EB category (5–19%); removal of ‘MDS/AML’ term

## New Genetic Entities Proposed

- MDS with -7/SETB1 mutation ( $\geq 20\%$  VAF)
- MDS with der(1;7)
- MDS with *TET2+SRSF2* co-mutation ( $\geq 20\%$  VAF)
- MDS with *DDX41* mutation (subgroup of myeloid neoplasms with *DDX41* mutation)
- MDS with *UBTF* tandem duplication (subgroup of myeloid neoplasms with *UBTF* TD)

## Morphology, NOS & Classification Framework

- 30% dysplasia threshold retained for megakaryocytes; 10% for other lineages
- Hypoplastic and fibrotic subtypes: qualifiers to MDS diagnosis, not separate entities
- Myeloid neoplasms with *TP53* mutation: confirmed/probable biallelic and monoallelic subtypes
- MDS NOS: specific lineage involvement documented in the pathology report

# Acute Myeloid Leukemia (AML)

## Key Classification Updates — CAM Proposals

Blast Threshold: AML with recurrent genetic abnormalities requires  $\geq 5\%$  blasts in BM/PB | *BCR::ABL1*, *DDX41*, *UBTF*-TD, AML-MR, and AML NOS require  $\geq 20\%$

### New / Updated Entities

- AML with *MYB::GATA1*; AML with *FUS::ERG*; AML with *MNX1::ETV6*
- AMKL with HOX rearrangement; AMKL with *GATA1* mutation (non-DS)
- AML with *CBFB-GDXY* mutation; AML with *NPM1* rearrangement
- AML with *KAT6A*; AML with *NFIA*; AML with *CBFA2T3::GLIS2*; AML with *NUP98* rearrangement

### AML Myelodysplasia-Related (AML-MR)

- *RUNX1* mutation **omitted** from MR gene mutation list
- MR cytogenetic abnormalities refined: complex karyotype, -5/del(5q), -7/del(7q), i(17q), -17/del(17p)
- Prior MR cytogenetic markers removed: +8, del(20q), -13/del(13q), del(11q), abn(12p)

### Qualifiers, NOS & TP53

- *TP53*: confirmed/probable biallelic (multihit) and monoallelic (single-hit) categories
- Progression from MDS/MDS-MPN, therapy-related, and germline predisposition documented as qualifiers
- AML NOS: monocytic, erythroid, megakaryocytic, and PDC differentiation as modifiers

# Proposed Classification: Structural Overview

## Myeloid Neoplasms with *TP53* mutation

### Myeloid Neoplasm with Confirmed/Probable Biallelic *TP53* alteration (multihit *TP53* alteration)

*Defining: TP53 mutation + evidence of biallelic alteration*

- MDS
- MDS/MPN
- AML
- Blast % and differentiation as qualifiers
- Therapy-related qualifier when applicable

### AML with Monoallelic *TP53* Mutation \*

*Defining: Single TP53 hit, no biallelic alteration evidence*

- ≥20% blasts required
- No evidence of biallelic inactivation/multihit status
- Monoallelic status must be confirmed with **adequate** assessment; "allelic status indeterminate" cases are excluded from this category
- Distinct from AML-MR category
- Inferior outcomes vs. AML-MR without *TP53*

**\*Does not include isolated *TP53/17p* deletion; the significance isolated *TP53* deletion remains unknown**

# TP53 Classification Principles

## Key Concepts for Allelic State Determination

### Global Accessibility

- Criteria must work at centers where comprehensive assessment is unavailable
- Any center can classify a case, but the report must honestly reflect what was and was not measured
- Resource limitations do not justify redefining genetic criteria with non-genetic surrogates

### No False Binary

- Classifiable: genetic criteria met; classification assigned with confidence
- **Indeterminate**: incomplete molecular data: contextual features may 'favor' or be 'consistent with' probable multi-hit status
- Not assessed: No molecular evaluation of *TP53* was performed; case classified using available data

### Modular Architecture

- Genetic criterion: **mutations, deletion, cnLOH, VAF-based LOH inference**
- Assay requirements: minimum depth, LOD, platform class, confirmation policy (to be discussed at length in the companion genetics paper)
- Non-genetic features: complex karyotype, p53 IHC : separately valuable, interpretively informative, not genetically definitional
- Future-compatible: as data mature, modular components can be updated without forcing revision of the entity definition

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