

VI Reunión

GESMD

Incorporating Molecular Genetics Into the Care of Patients With MDS

La aplicación clínica de estudios moleculares en SMD

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5 Marzo 2016



UC San Diego

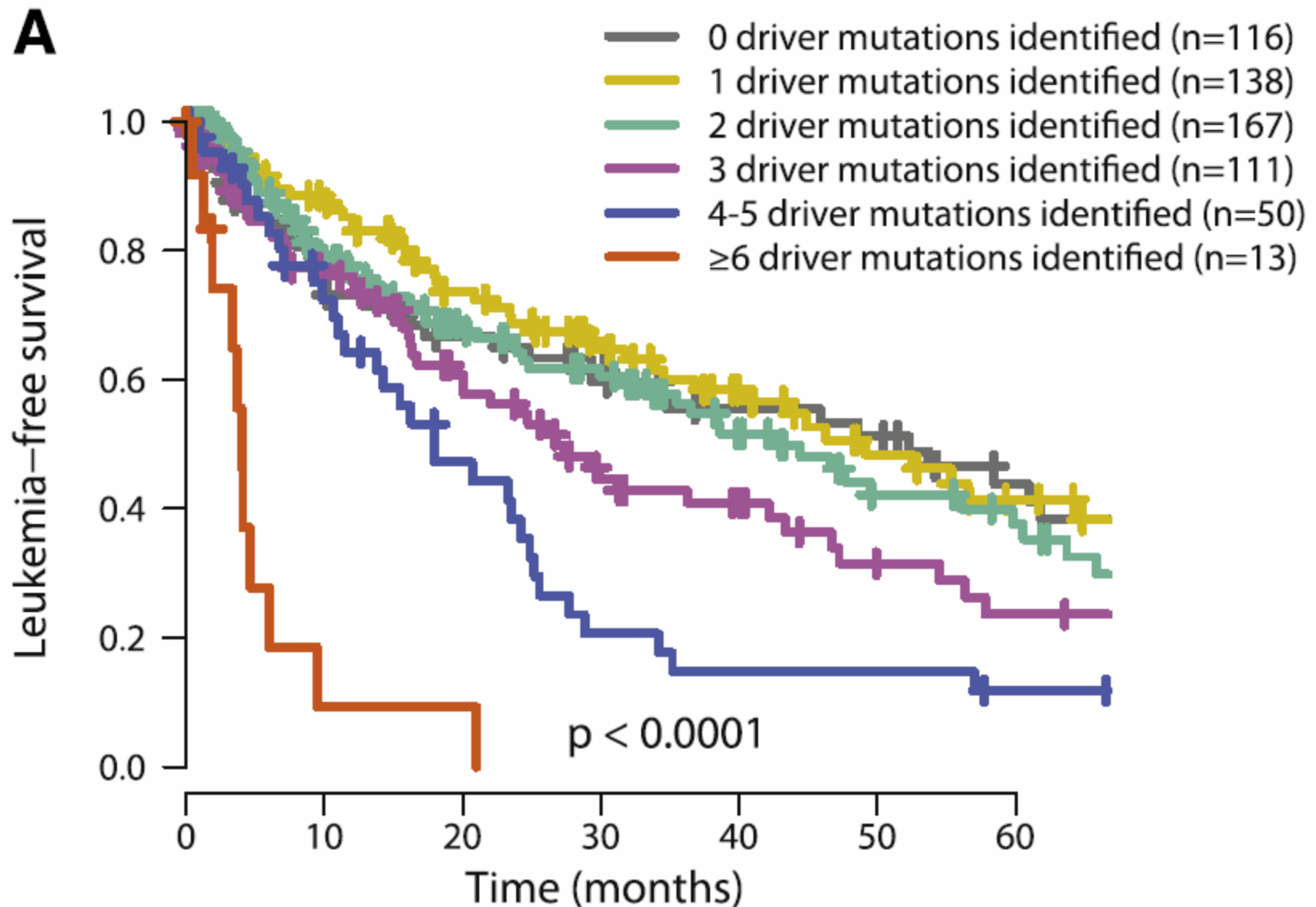
MOORES CANCER CENTER

Overview

- Prognosis – Pronóstico
- Response to Therapy – Respuesta al tratamiento
- Diagnosis – Diagnóstico

Prognosis – Pronóstico

Clonality and Prognosis



Impact of Mutations by IPSS Group

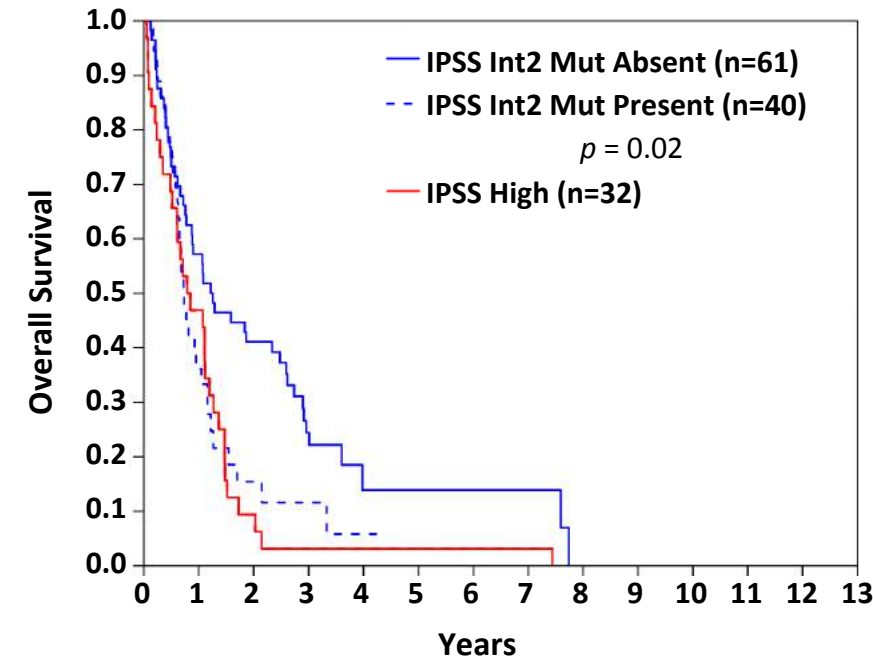
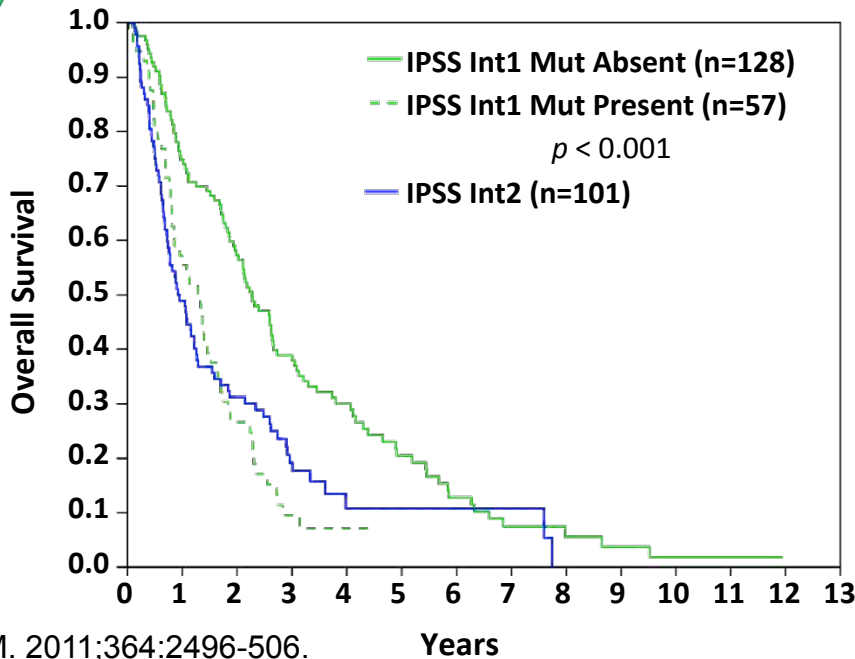
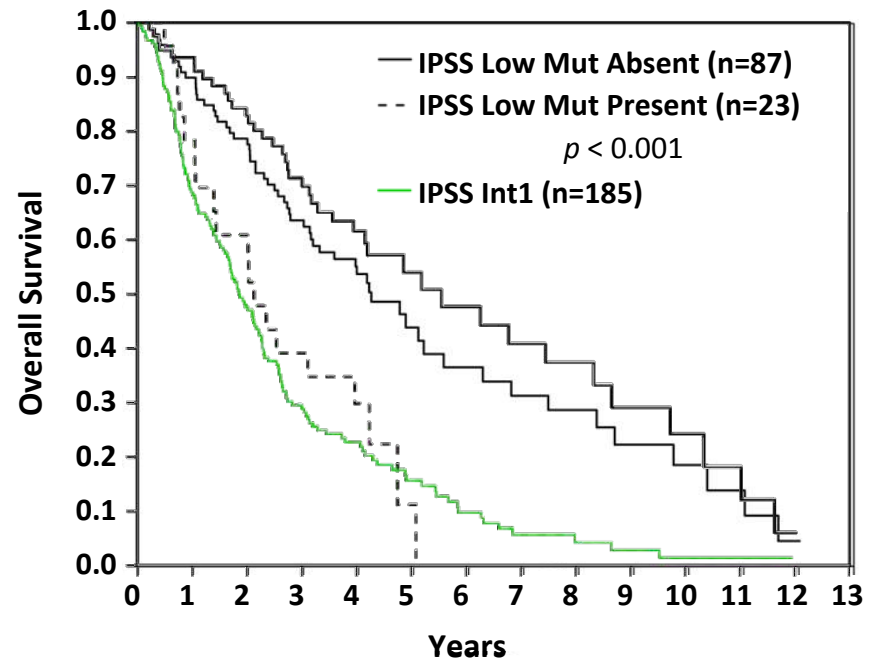
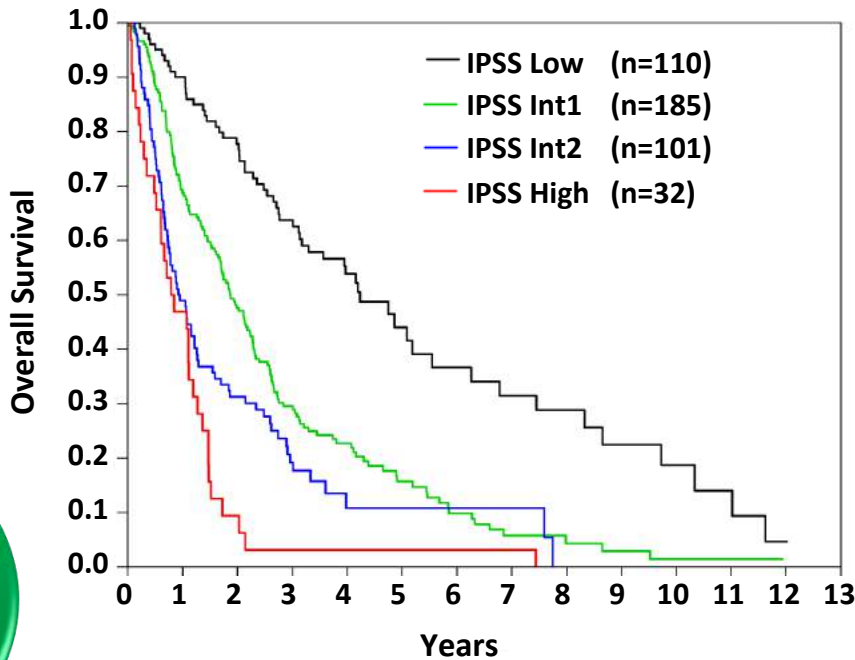
TP53

ETV6

ASXL1

EZH2

RUNX1



Impact of Mutations by IPSS-R Group

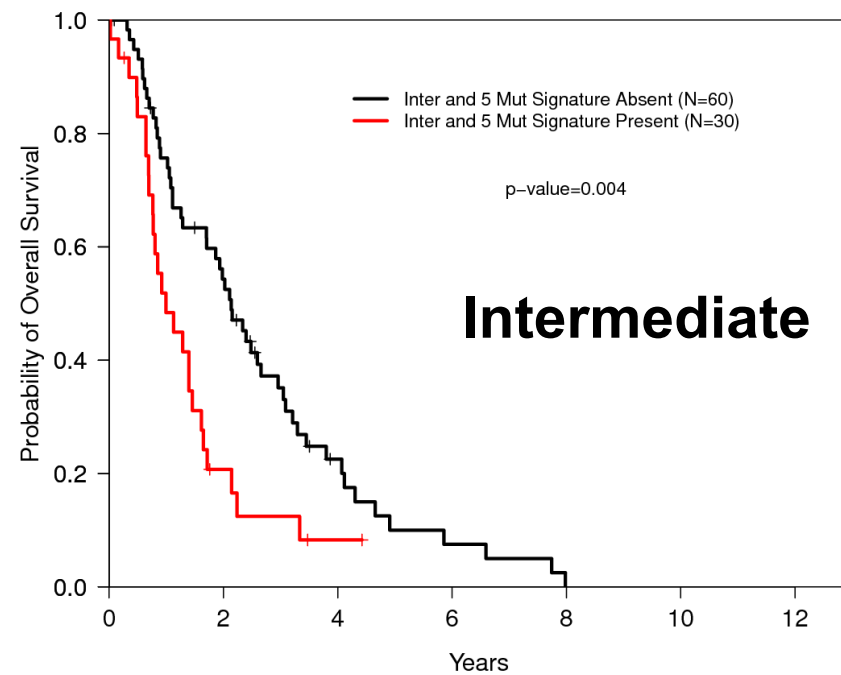
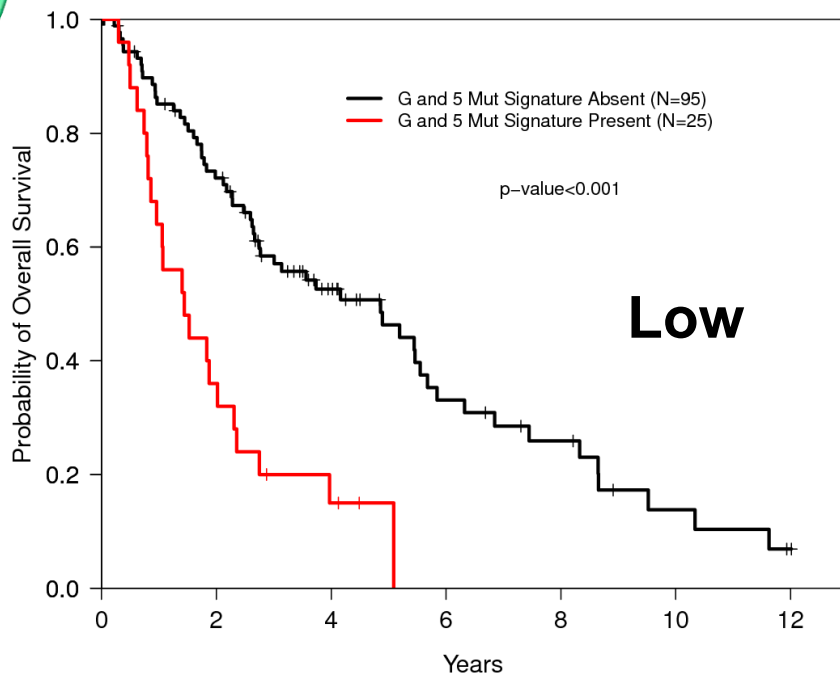
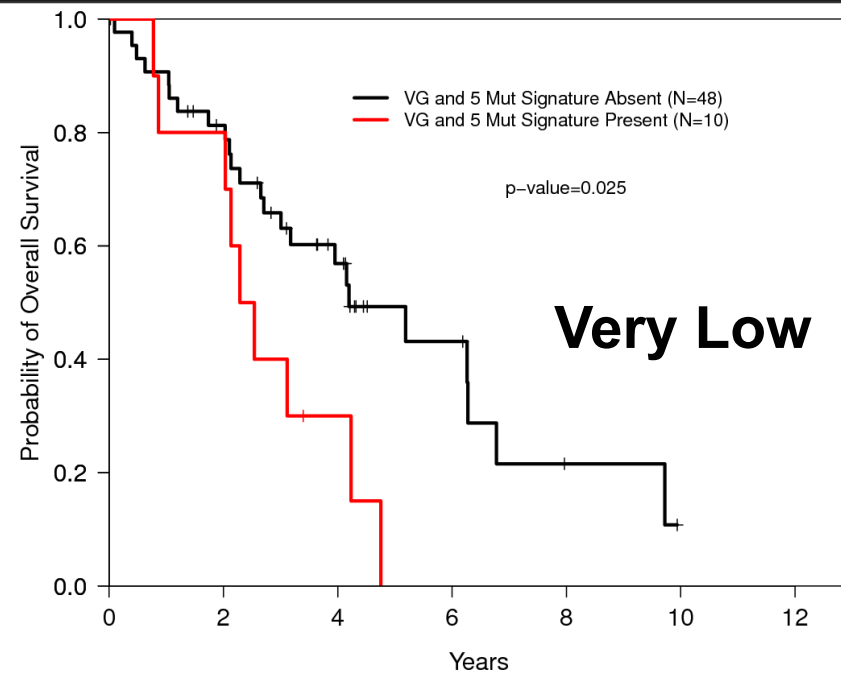
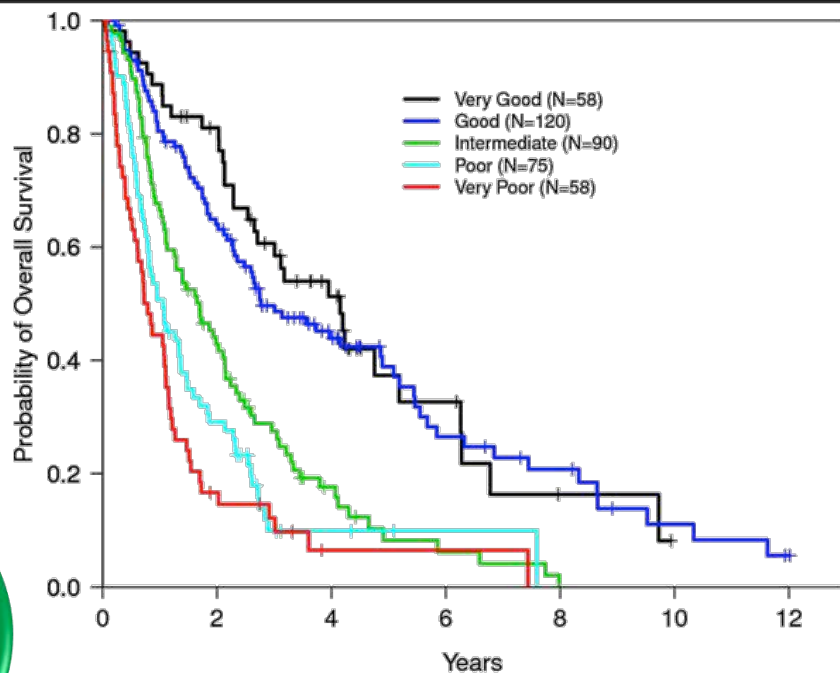
TP53

ETV6

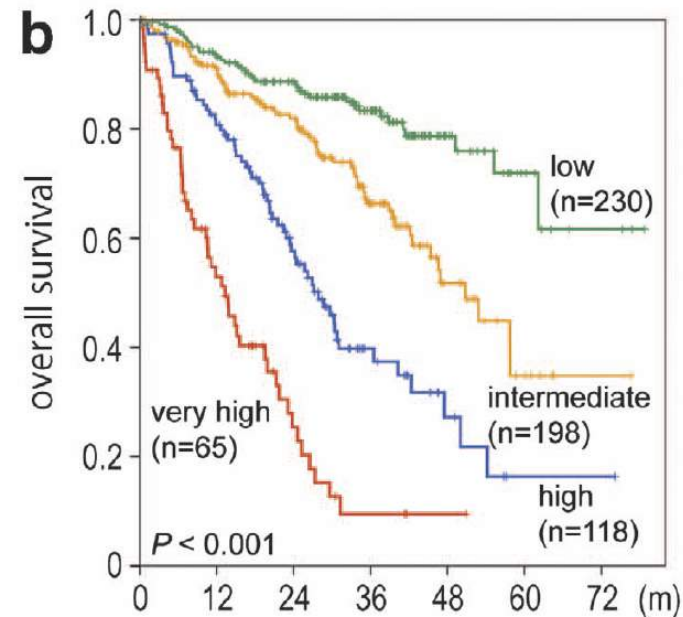
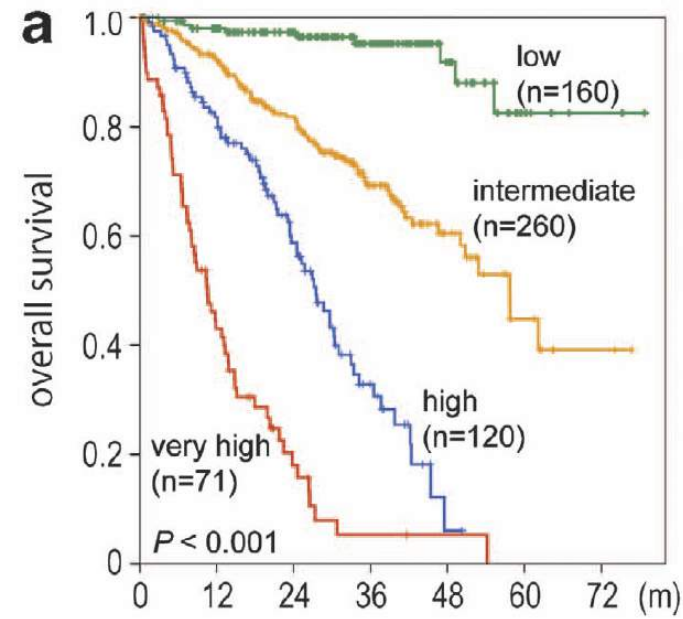
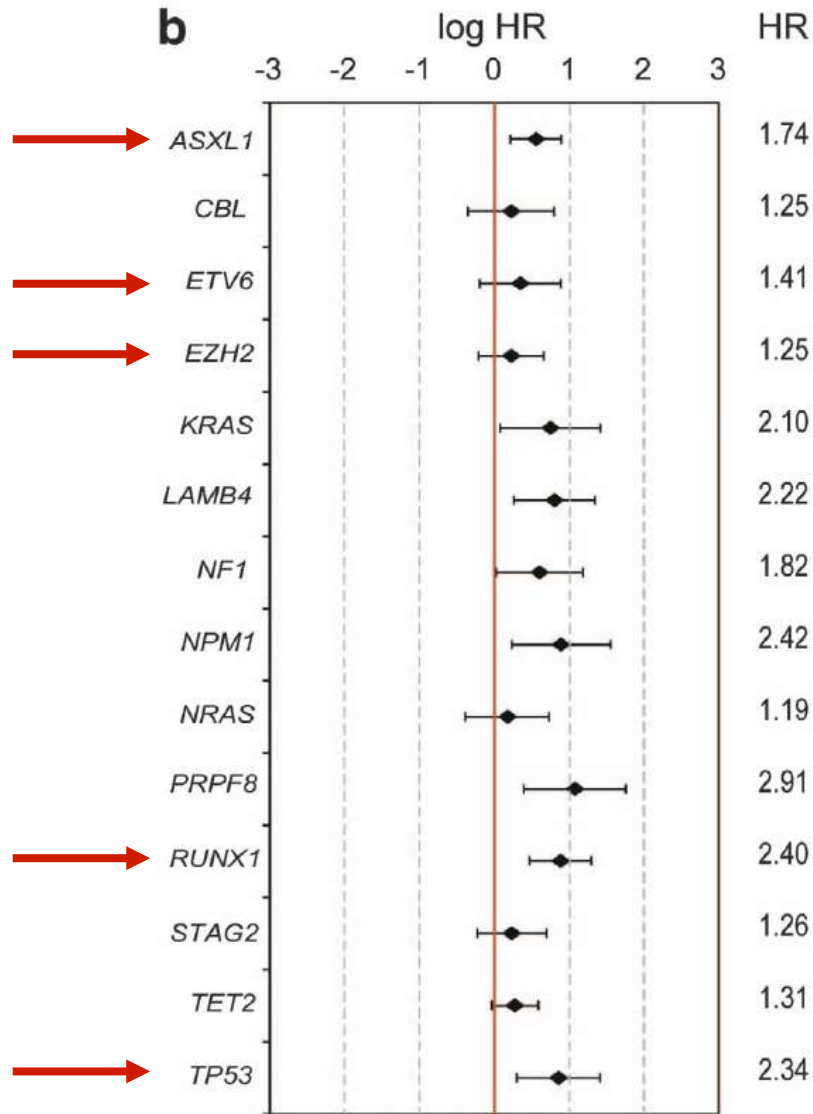
ASXL1

EZH2

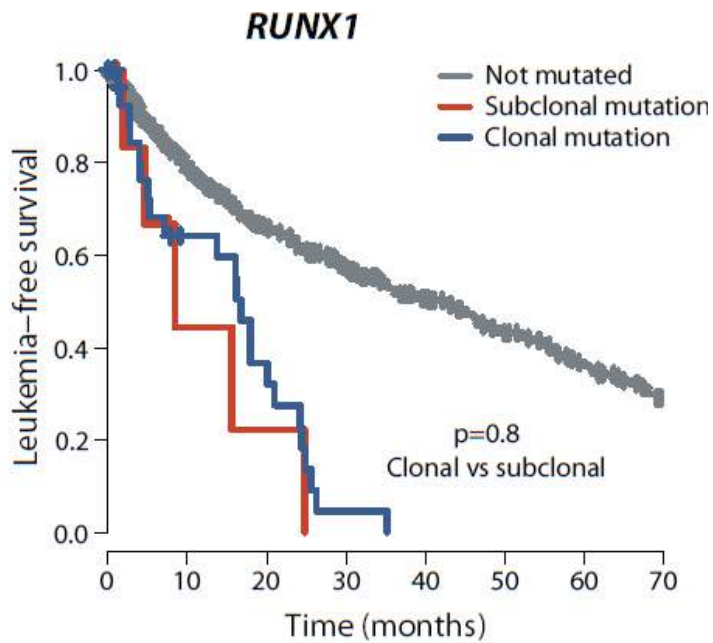
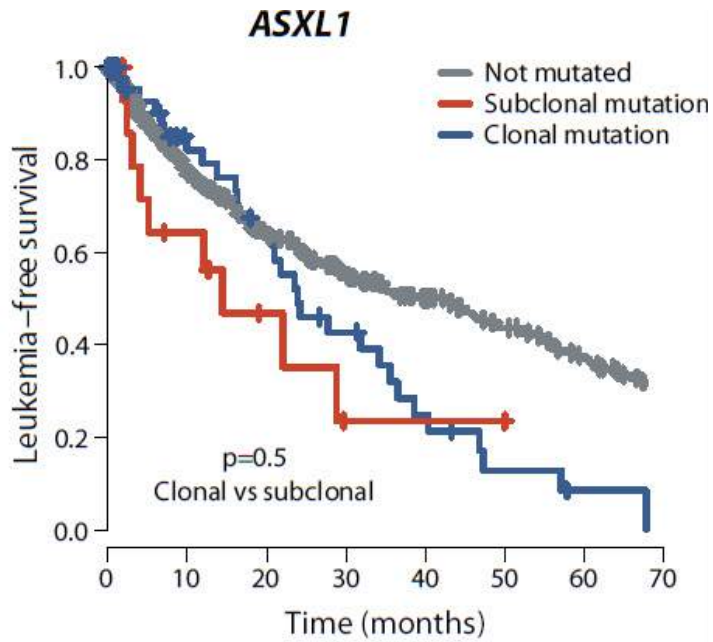
RUNX1



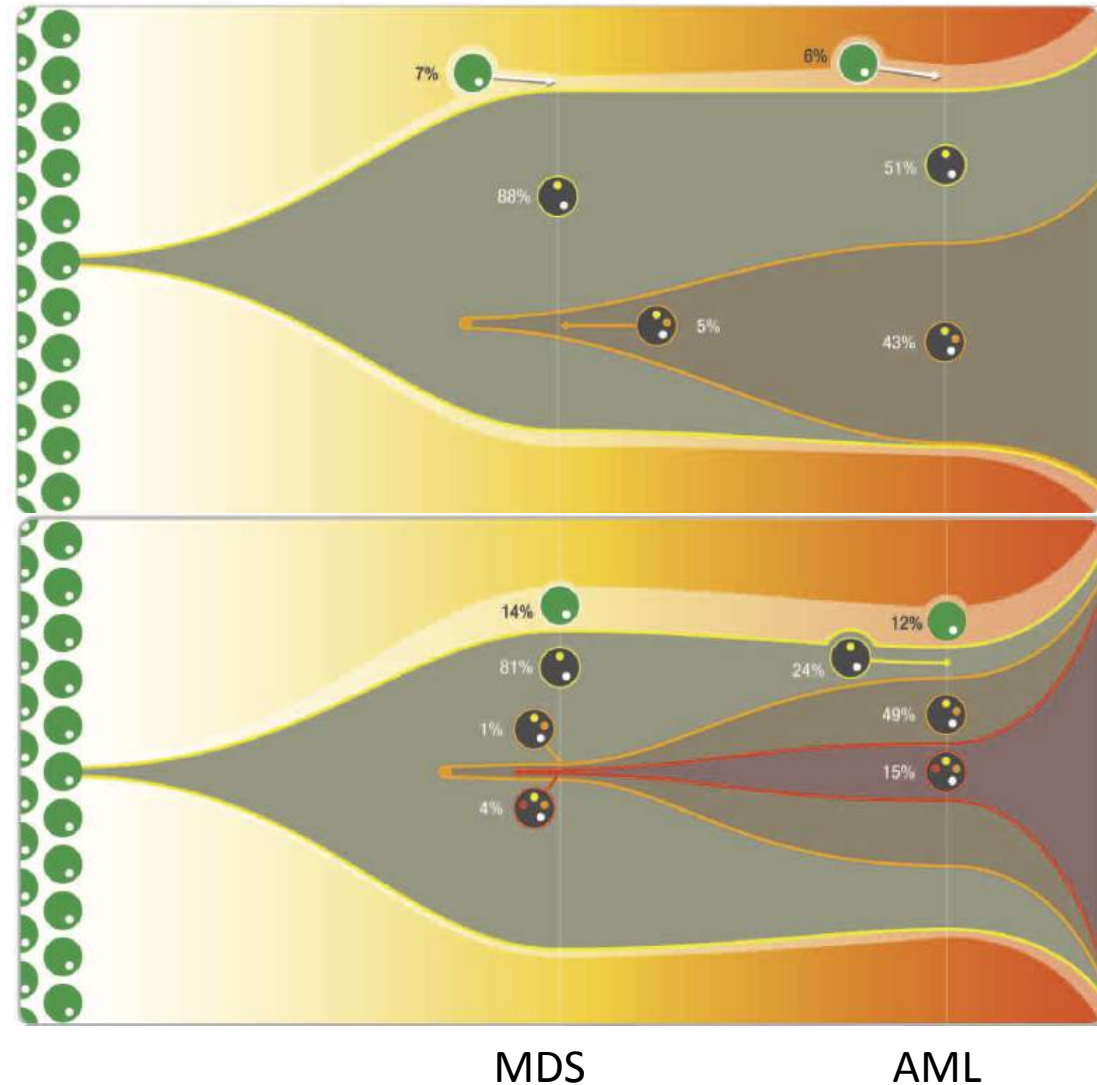
Additional Genes Predict Risk



Clonality and Prognosis

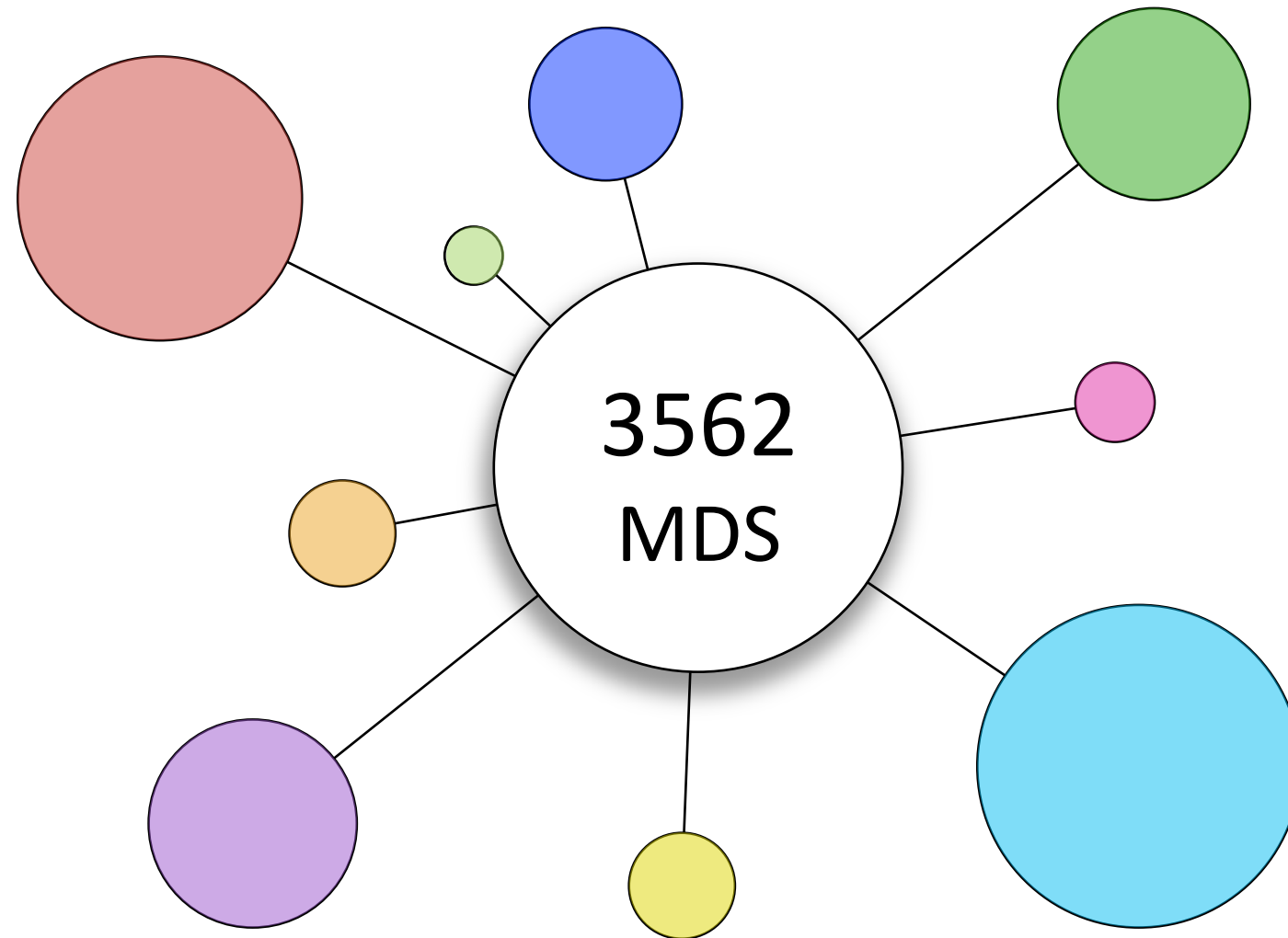


Improved Sensitivity – Early Warning?



Methods: IWG-PM MDS Sample Compilation

MDS sample data collected from 18 centers in Europe, the United States, and Asia



Data Summary

Clinical Features

- age and sex
- blast %
- karyotype
- hemoglobin
- platelet count
- neutrophil count

Overall Survival Data:

- available for 3359
- 3.6 years follow-up
- 1780 deaths
- median OS 2.65 years

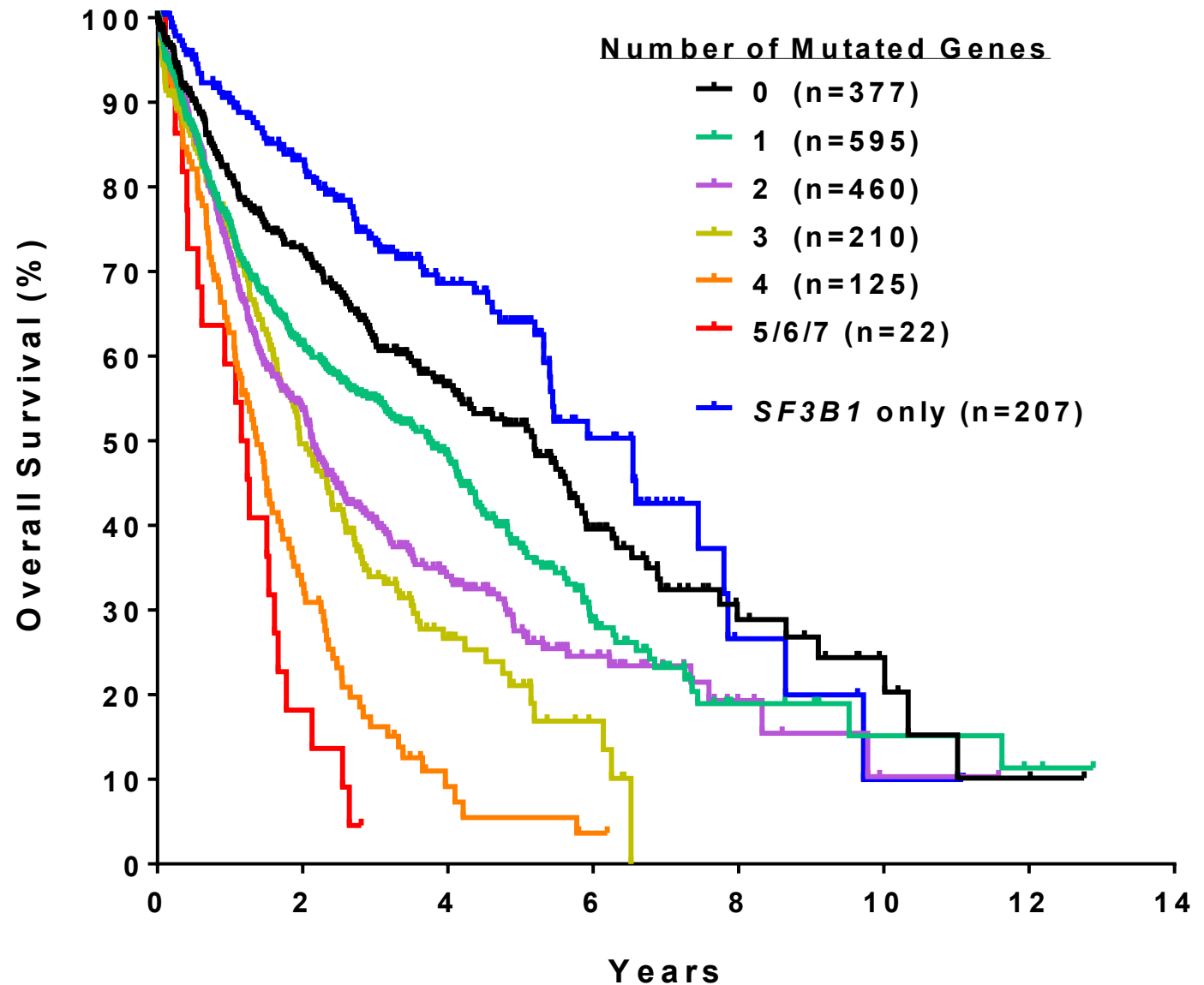
Treatment Status

Gene Mutations

Overall Survival by Mutation Number

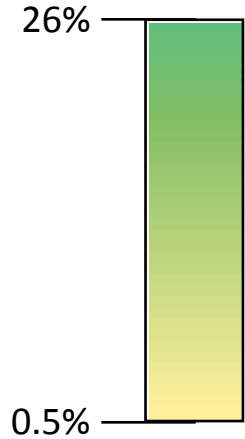
17 genes sequenced in 1996 patients with OS data

ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1
SF3B1

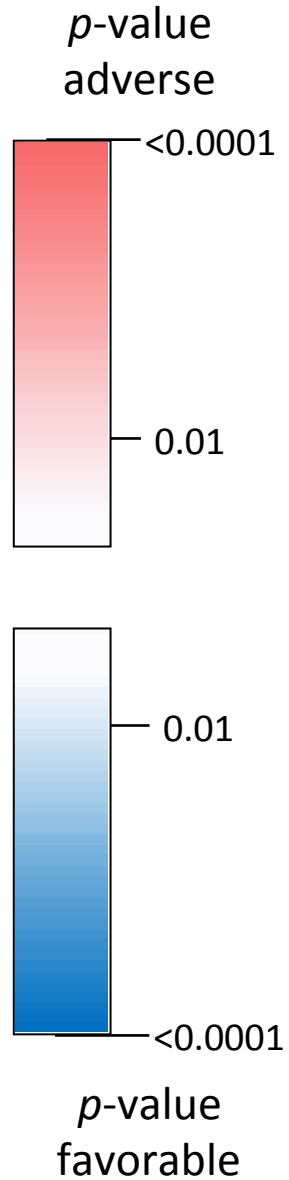


Mutated Genes and Clinical Phenotypes

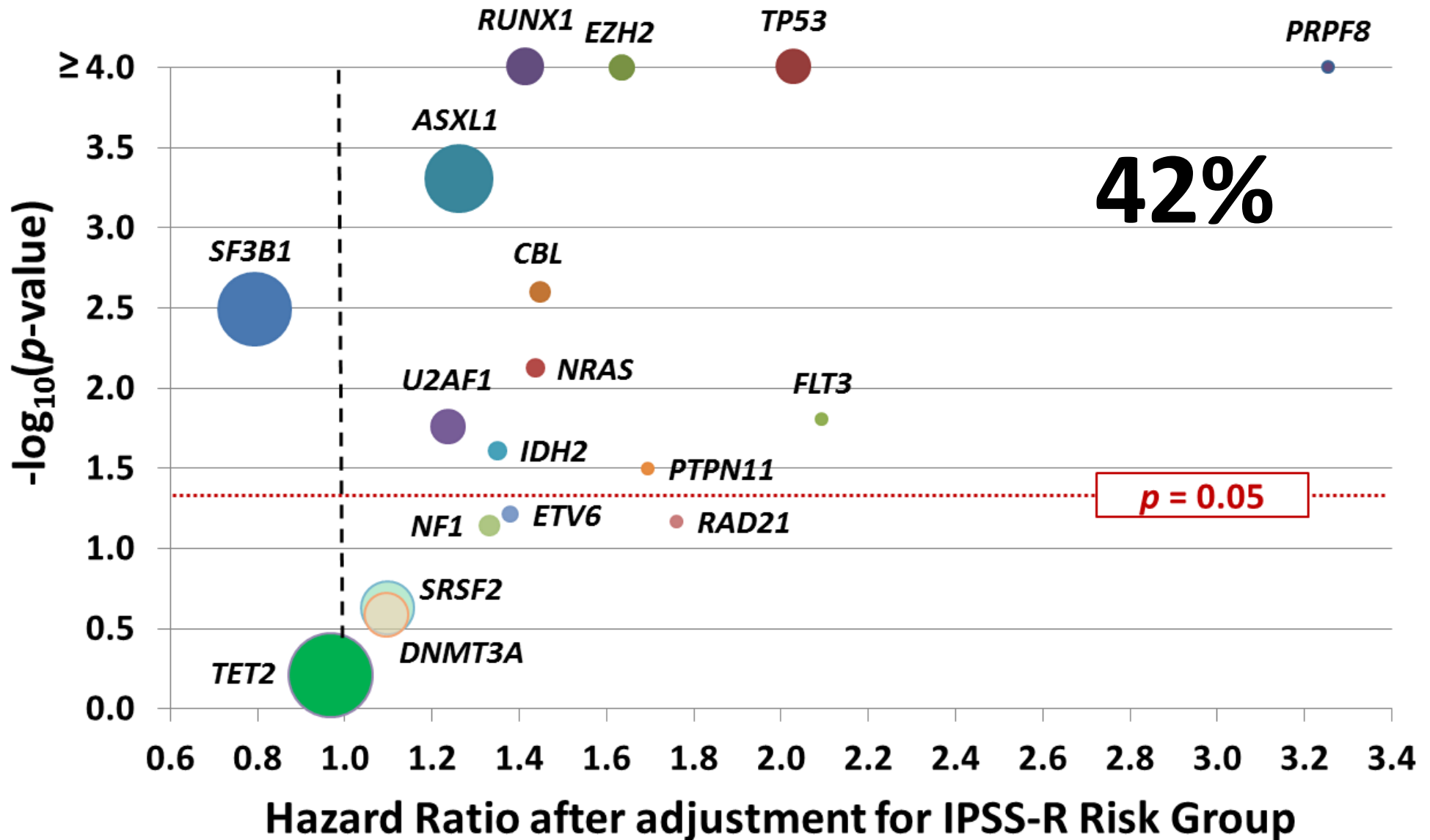
Mutation Frequency



Gene	% Mut	FAB	WHO	IPSS-R	Blast%	Plts	Sex	Age	ANC	Hgb	OS
<i>TP53</i>	8.9										
<i>ASXL1</i>	21										
<i>SRSF2</i>	15										
<i>U2AF1</i>	8.9										
<i>NRAS</i>	3.6										
<i>RUNX1</i>	10										
<i>STAG2</i>	5.6										
<i>IDH2</i>	3.4										
<i>KRAS</i>	2.3										
<i>NPM1</i>	1.5										
<i>BCOR</i>	4.7										
<i>TET2</i>	26										
<i>ZRSR2</i>	6.4										
<i>EZH2</i>	5.9										
<i>CBL</i>	4.4										
<i>RAD21</i>	1.3										
<i>PTPN11</i>	1.5										
<i>GATA2</i>	1.3										
<i>NF1</i>	4.5										
<i>ETV6</i>	2.6										
<i>PRPF8</i>	2.4										
<i>FLT3</i>	0.9										
<i>IDH1</i>	2.3										
<i>PHF6</i>	2.9										
<i>GNAS</i>	0.9										
<i>WT1</i>	1.2										
<i>ATRX</i>	2.1										
<i>U2AF2</i>	1										
<i>SMC3</i>	1.3										
<i>KIT</i>	1.1										
<i>MPL</i>	1.8										
<i>DNMT3A</i>	12										
<i>JAK2</i>	3.6										
<i>SF3B1</i>	22										



IPSS-R Adjusted Odds Ratios for Mutated Genes



Response to Therapy - Respuesta al tratamiento

TET2 Mutations and HM Response

	Including SD with HI		Excluding SD with HI	
	OR (95% CI)	P	OR (95% CI)	P

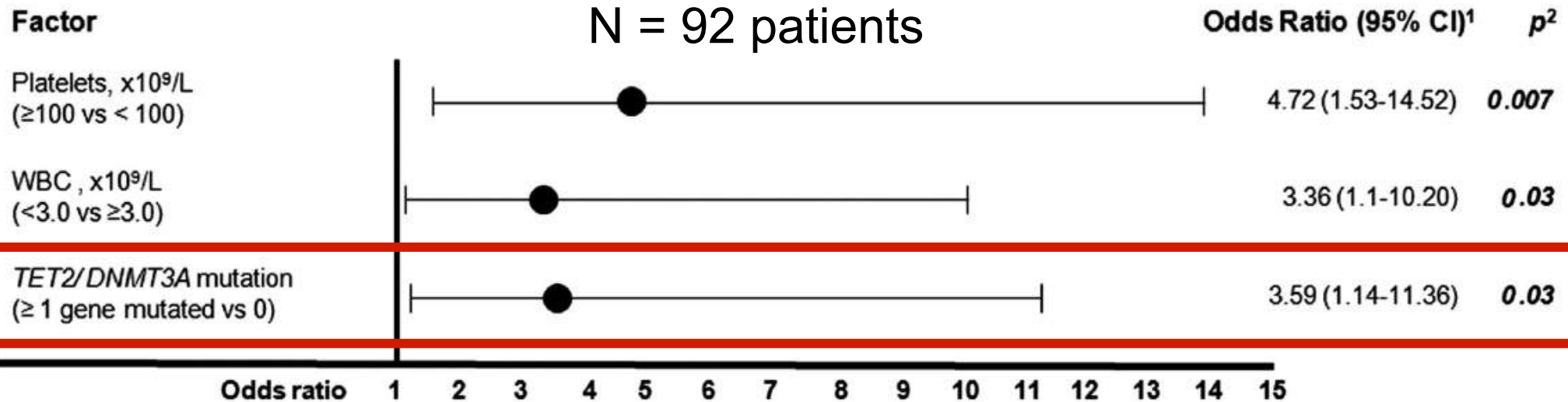
N = 86 patients

Mutated TET2	5.92 (1.05–33.33)	0.044	5.92 (1.43–24.39)	0.014
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Cytogenetic risk^a

Intermediate	0.24 (0.06–0.98)	0.048	2.41 (0.60–9.71)	0.22
Poor	0.33 (0.11–0.95)	0.040	2.11 (0.68–6.45)	0.19
Previous therapy	1.56 (0.47–5.15)	0.47	0.47 (0.13–1.65)	0.24

Itzykson *et al. Leukemia*. 2011

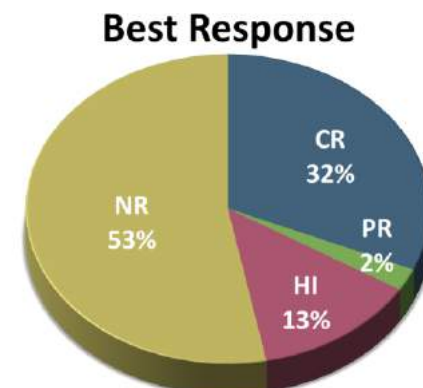
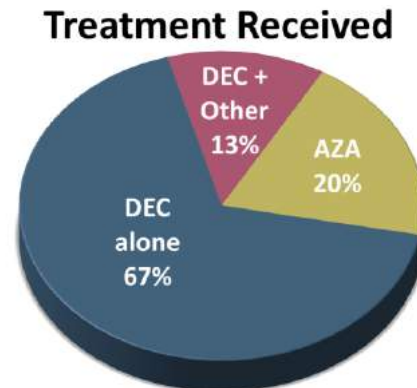
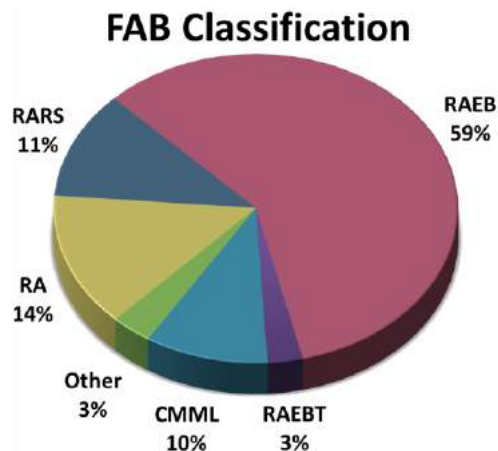
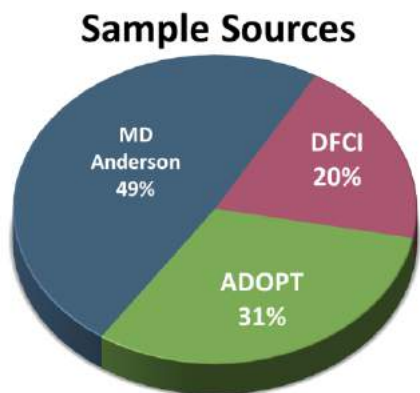
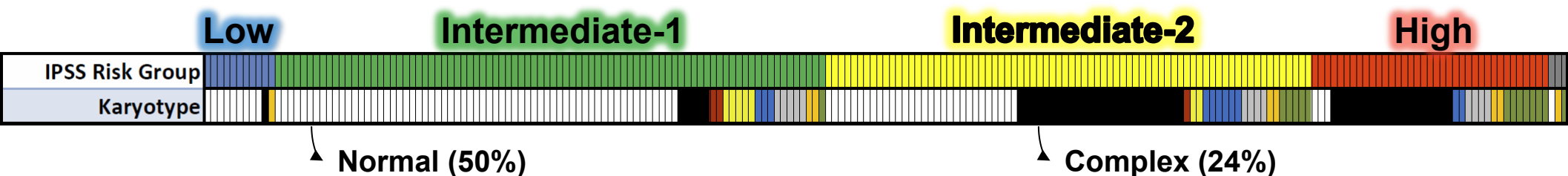


Traina *et al. Leukemia*. 2014

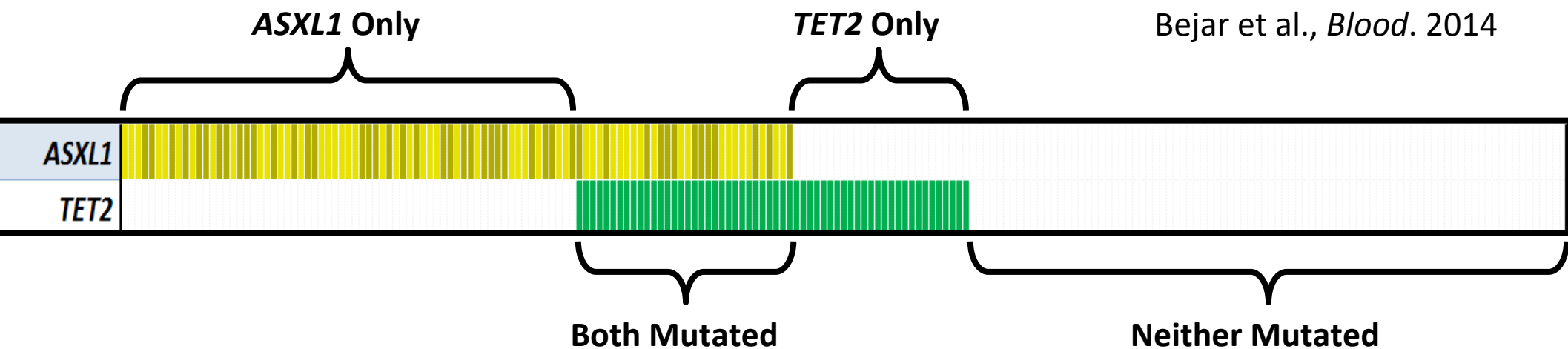
Hypomethylating Agent Response

Bejar et al., *Blood*. 2014

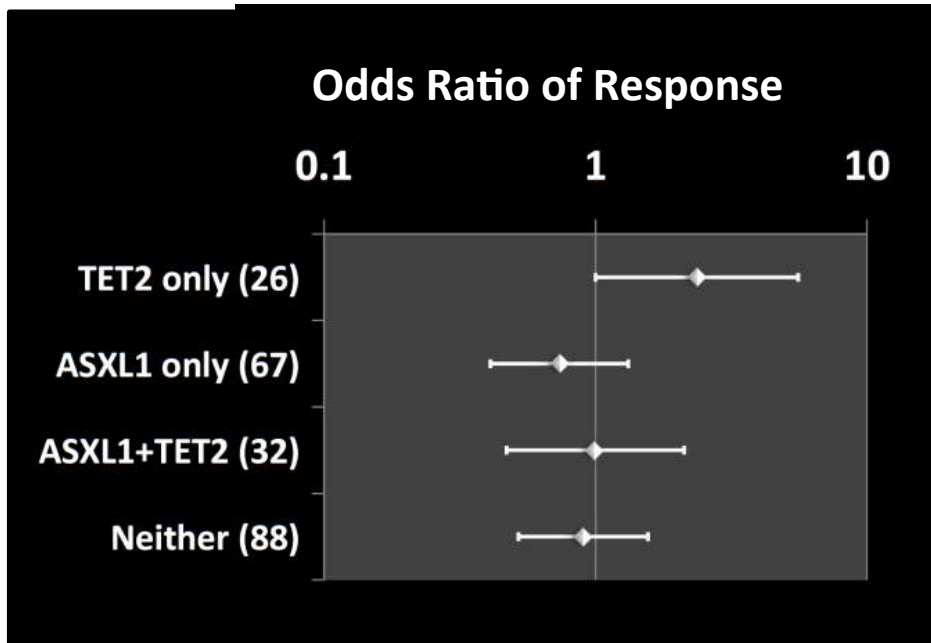
213 MDS patients Treated with Hypomethylating Agents



ASXL1 and TET2 Mutations

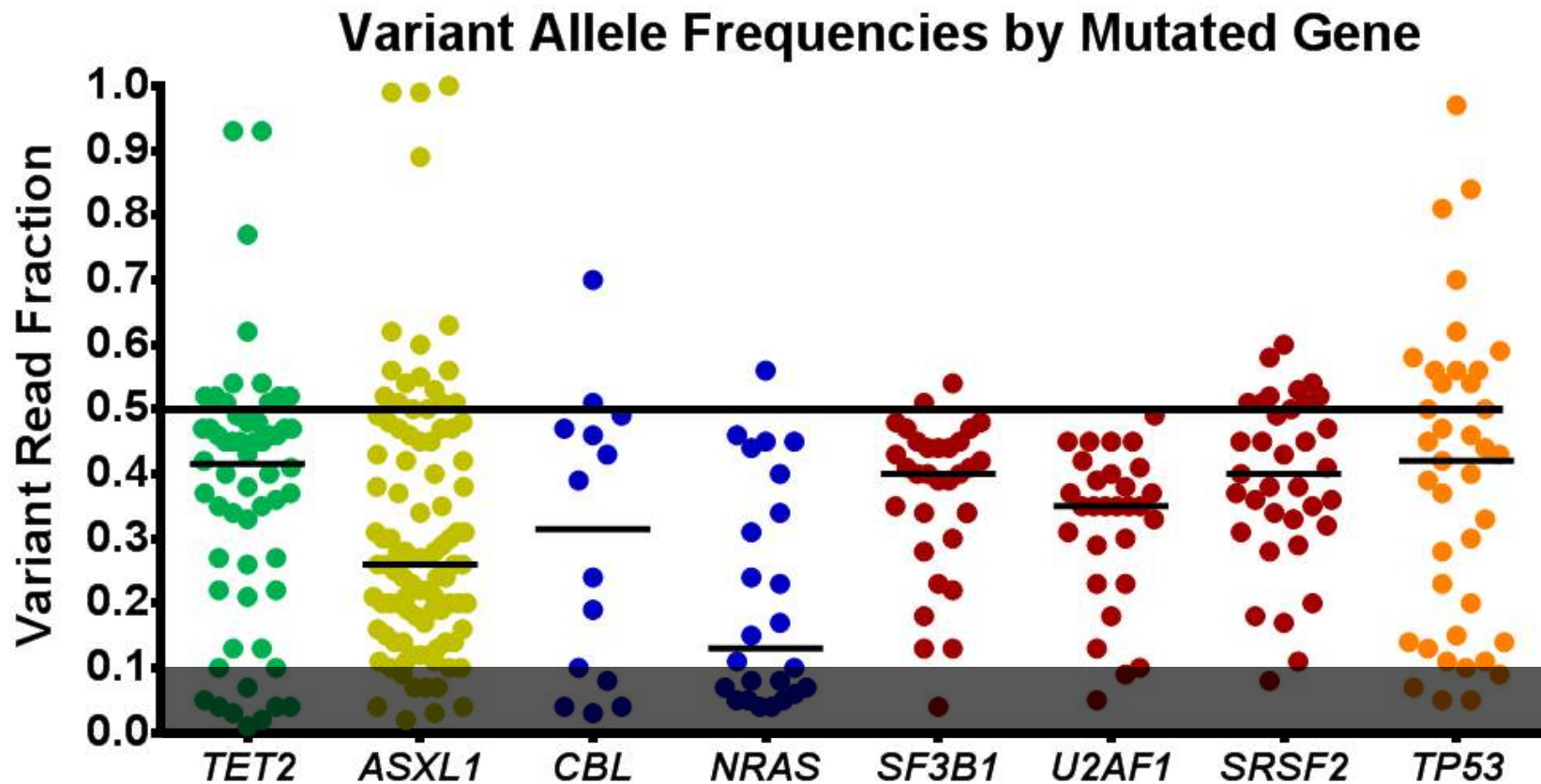


Two Gene Analysis: *ASXL1* and *TET2*



Gene	Unadjusted OR (95% CI)	p-value
<i>TET2</i> mutant + <i>ASXL1</i> wt	2.37 (1.00, 5.58)	0.049

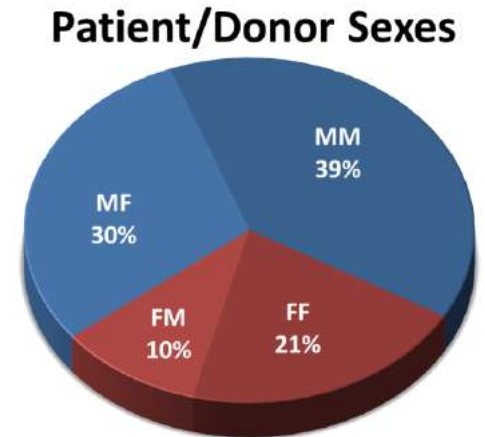
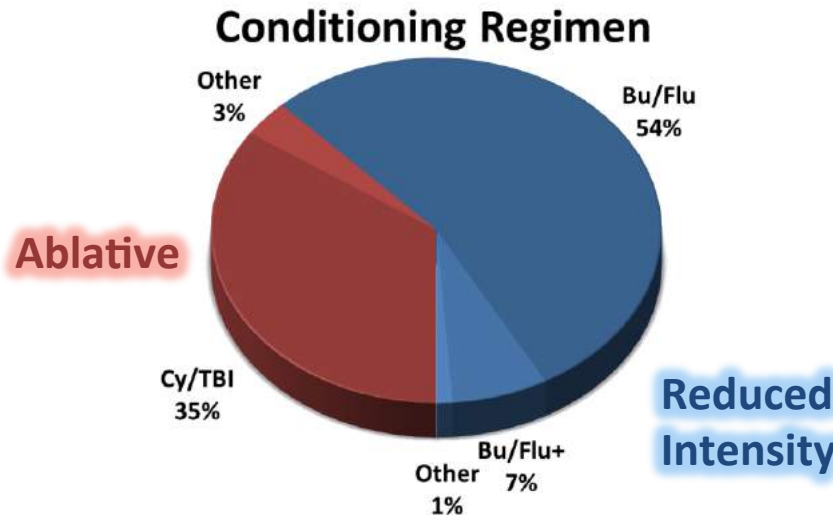
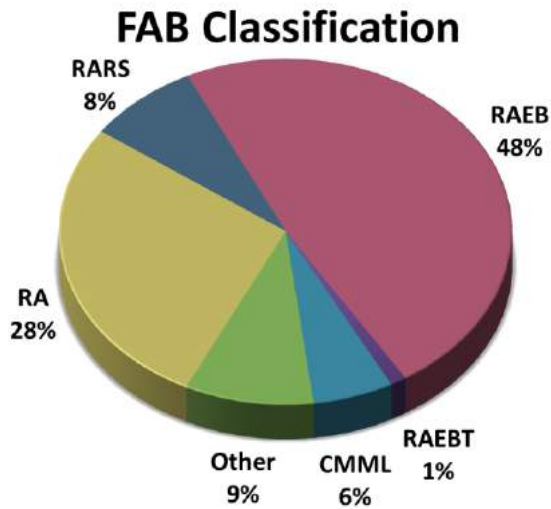
Response by Variant Abundance



Gene (n) VAF \geq 0.1	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
TET2 (50)	1.99 (1.05, 3.80)	0.036	1.98 (1.02, 3.85)	0.044

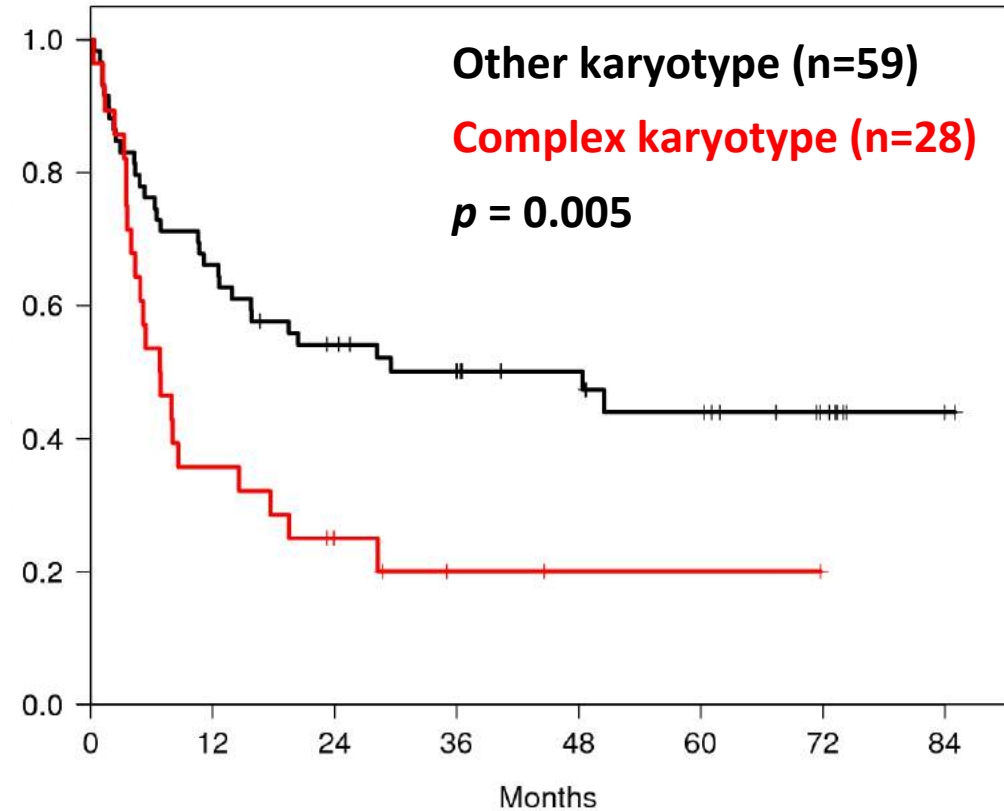
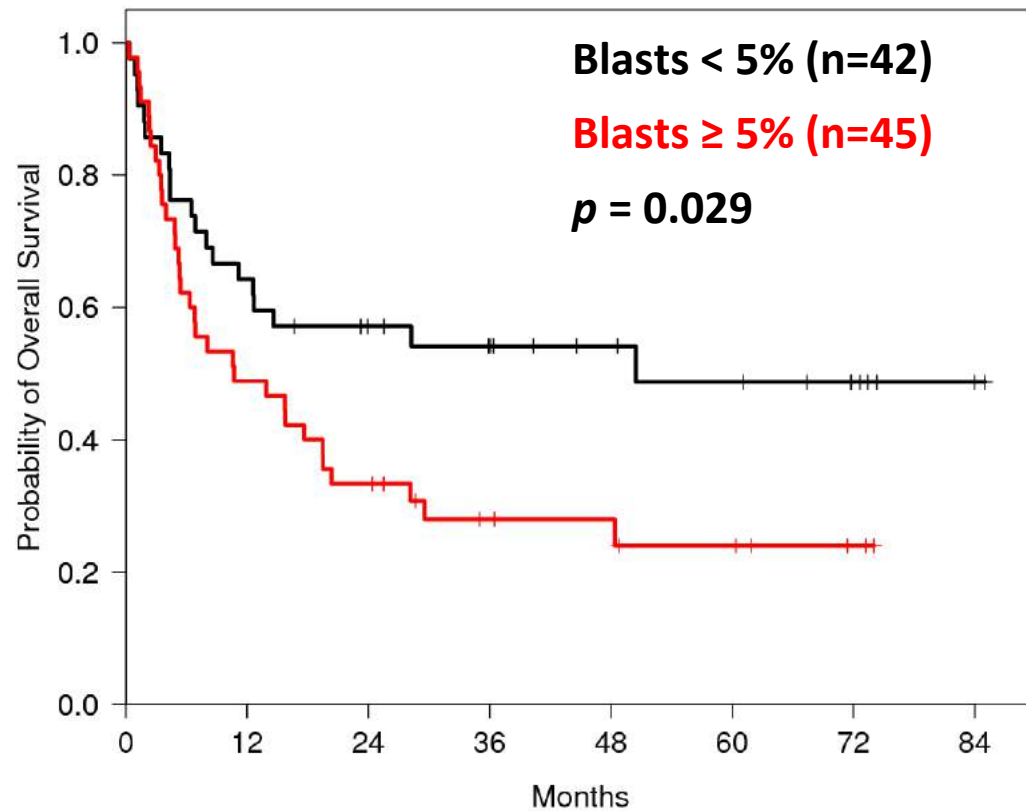
MDS Patients – Stem Cell Transplant

87 MDS patients transplanted at DFCI from 2004-2009



Clinical Associations

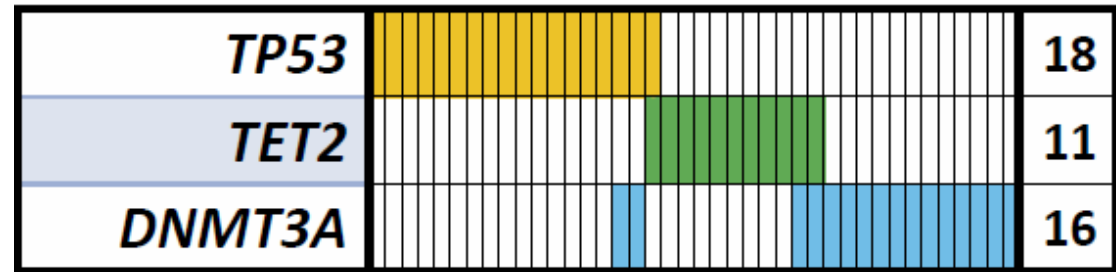
Overall Survival After Transplant



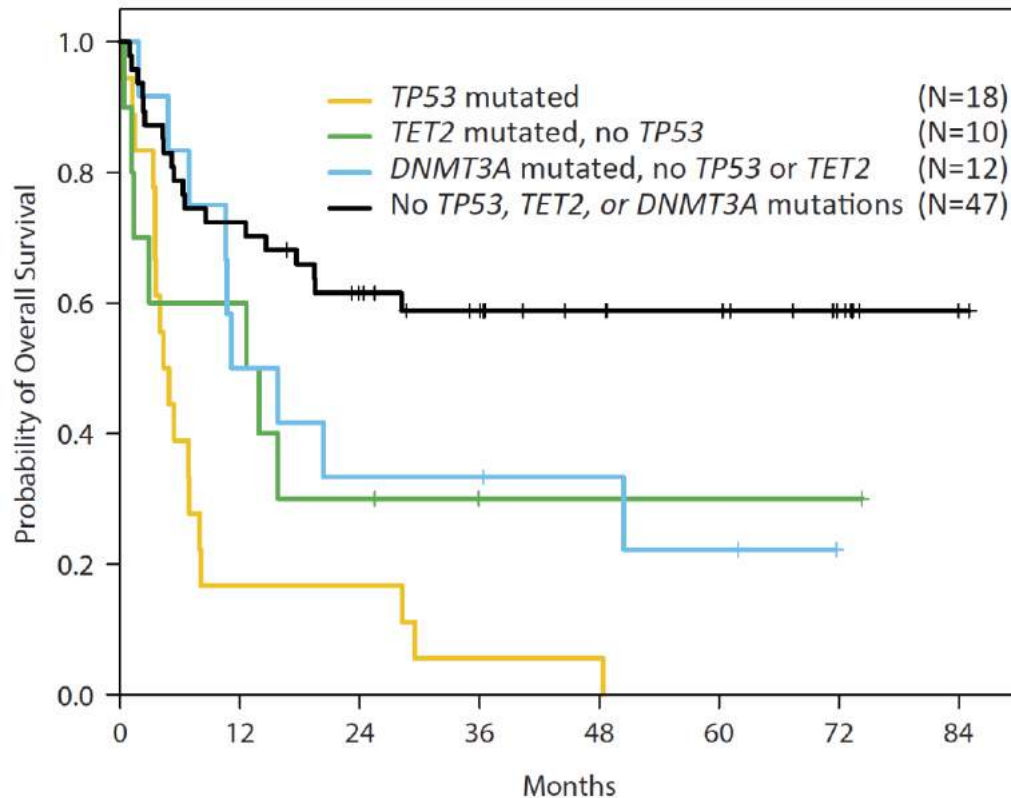
Mutations and Transplantation

Bejar et al., *JCO*. 2014

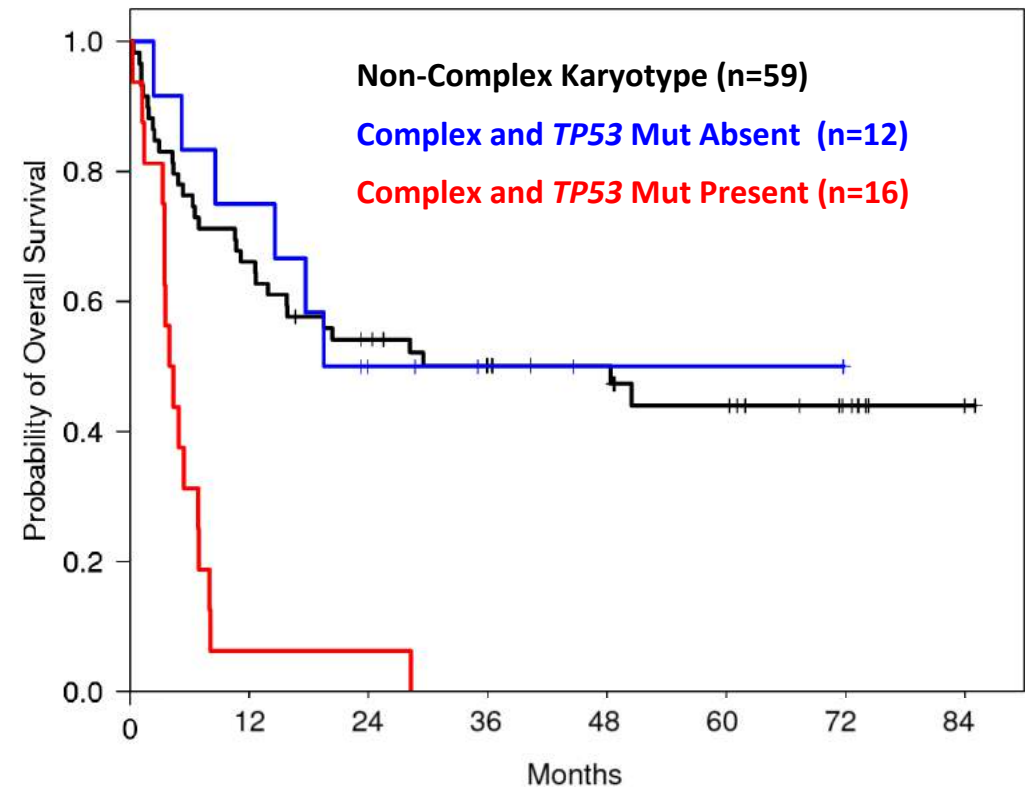
Gene	Adjusted HR (95% CI)	p-value
<i>TP53</i> (n=18)	2.30 (1.10, 4.81)	0.027
<i>TET2</i> (n=11)	2.40 (1.07, 5.38)	0.033
<i>DNMT3A</i> (n=16)	2.08 (1.00, 3.26)	0.049



Survival by Adverse Mutation Status

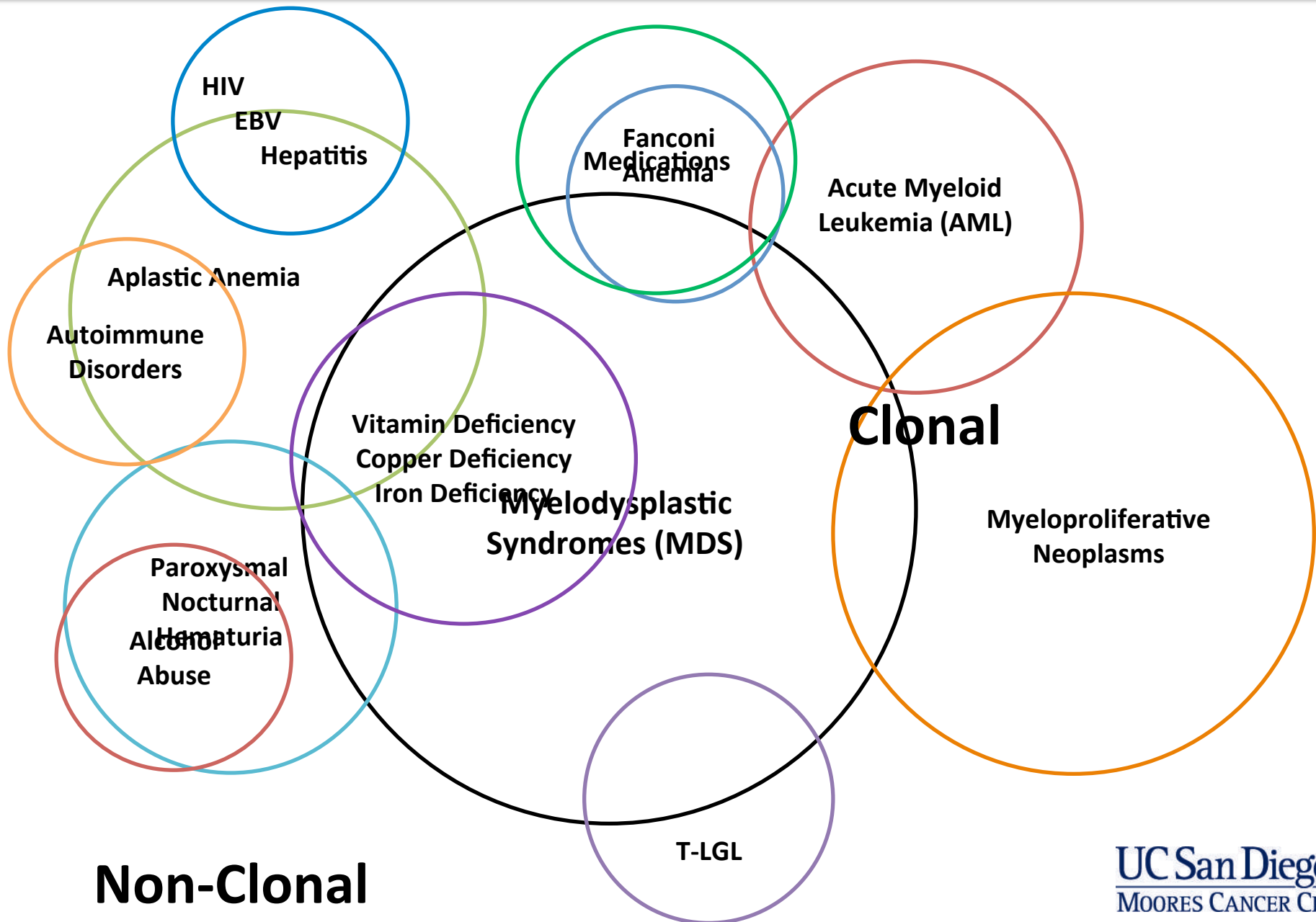


Survival in Complex +/- *TP53* Mutation



Diagnosis – Diagnóstico

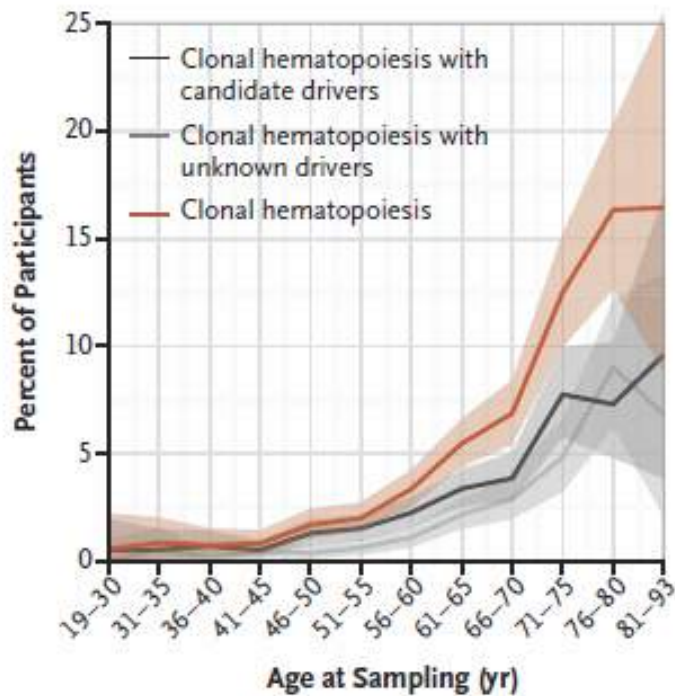
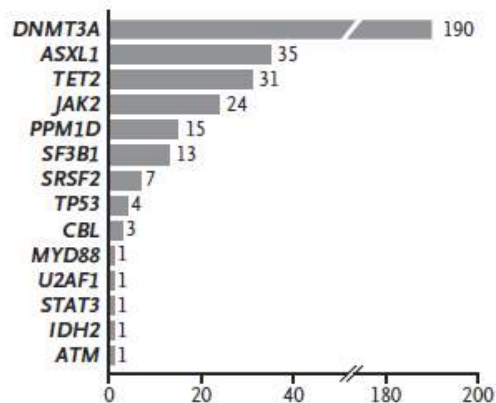
Diagnostic Overlap



ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

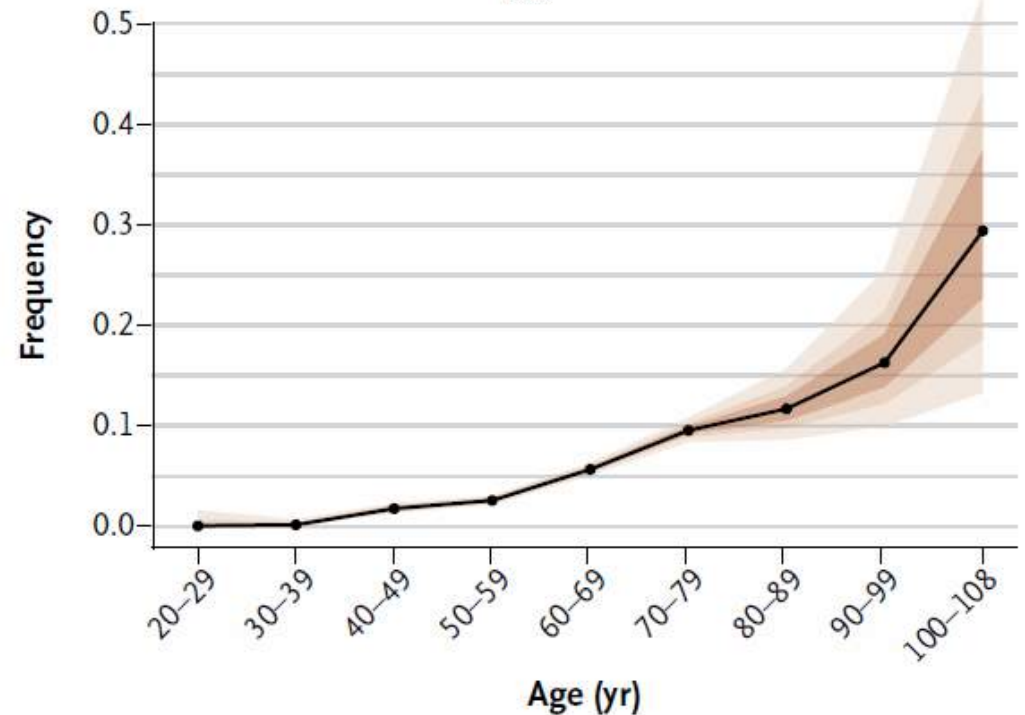
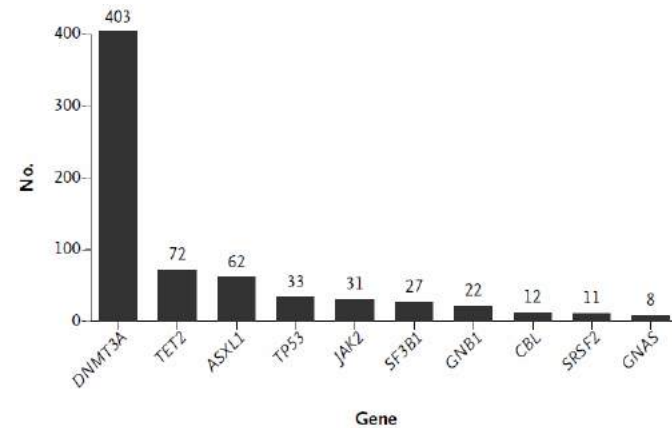
Giulio Genovese, Ph.D., Anna K. Köhler, Ph.D., Robert E. Handsaker, B.S.,



ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,

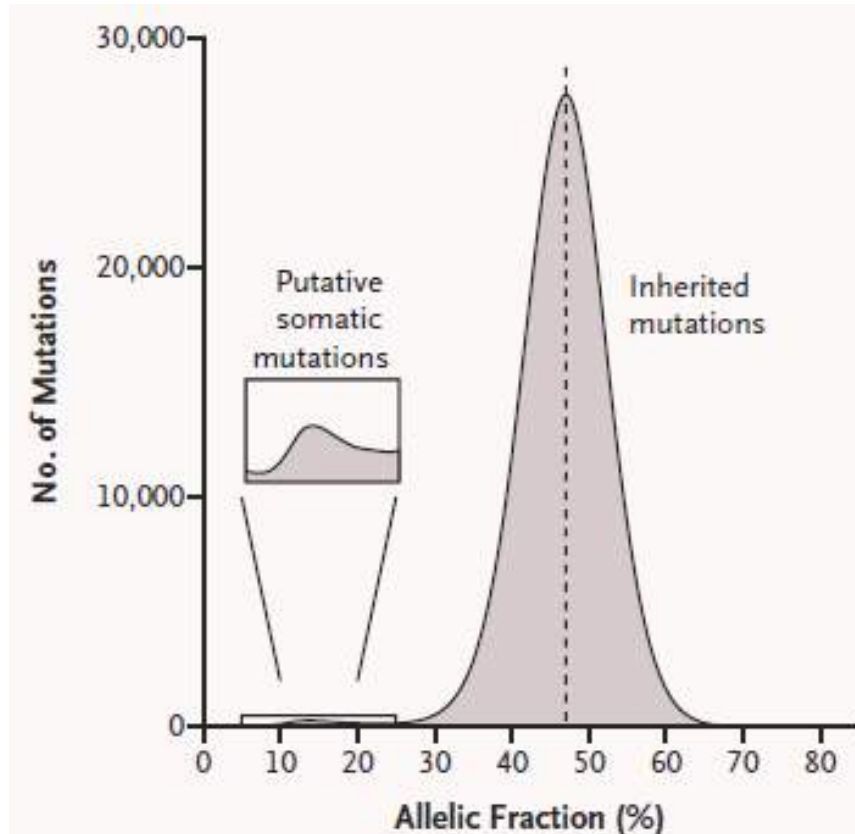


Hematopoiesis Clonal de Potencial Indeterminado

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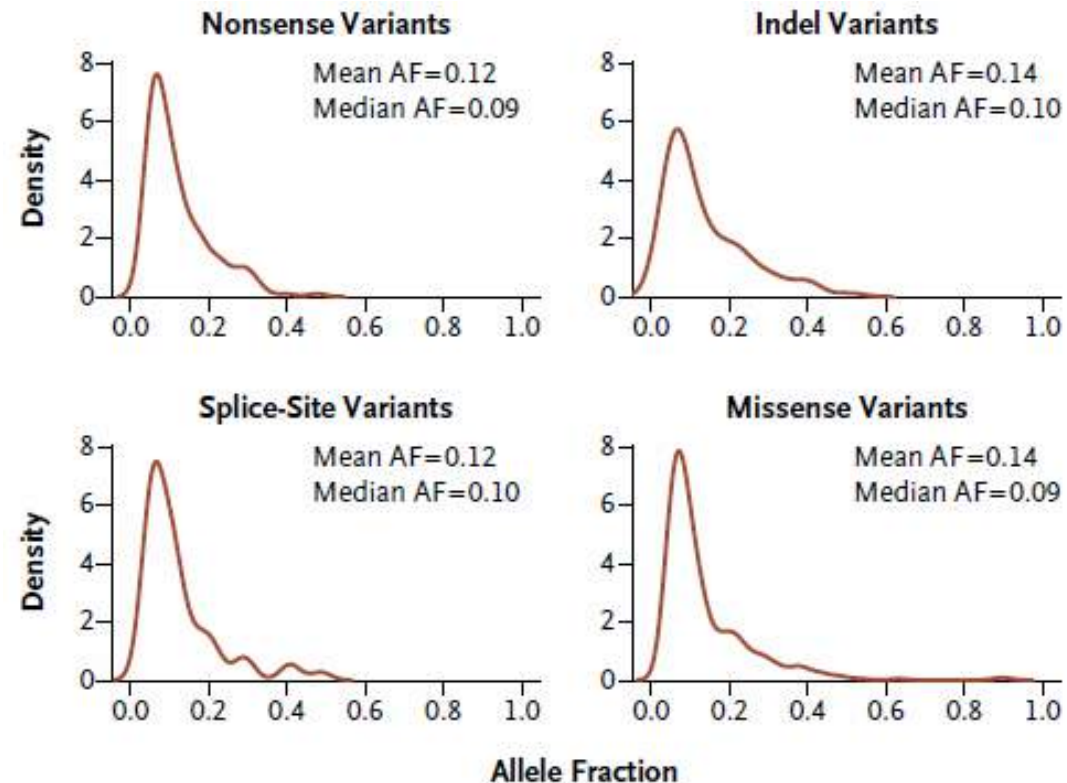
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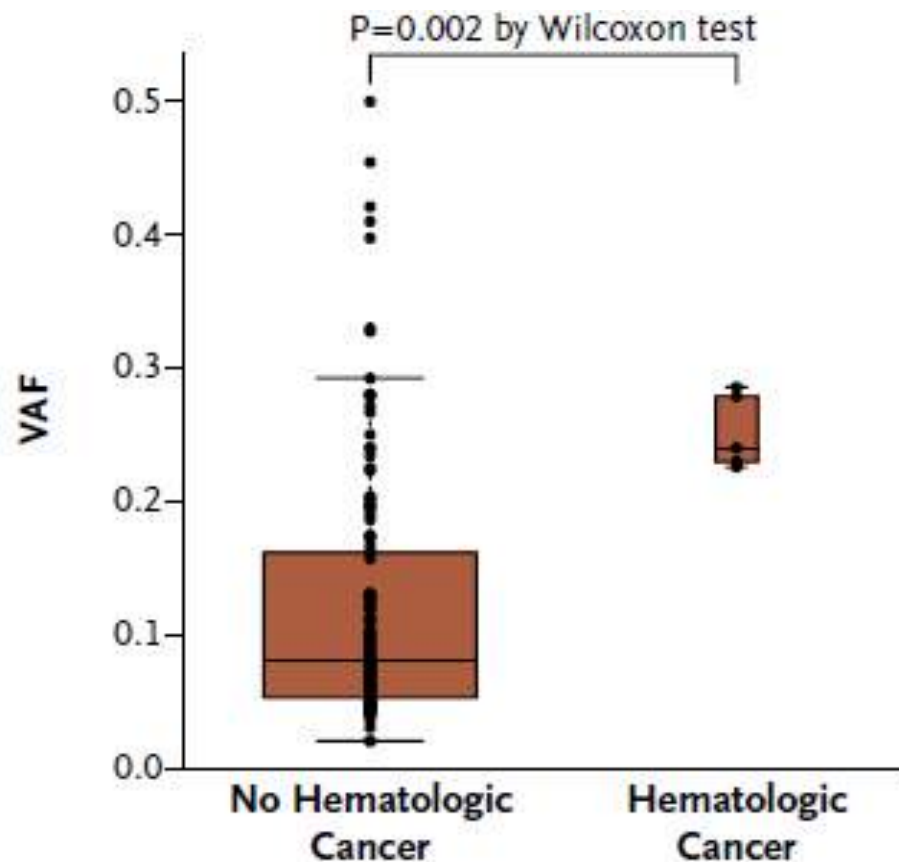
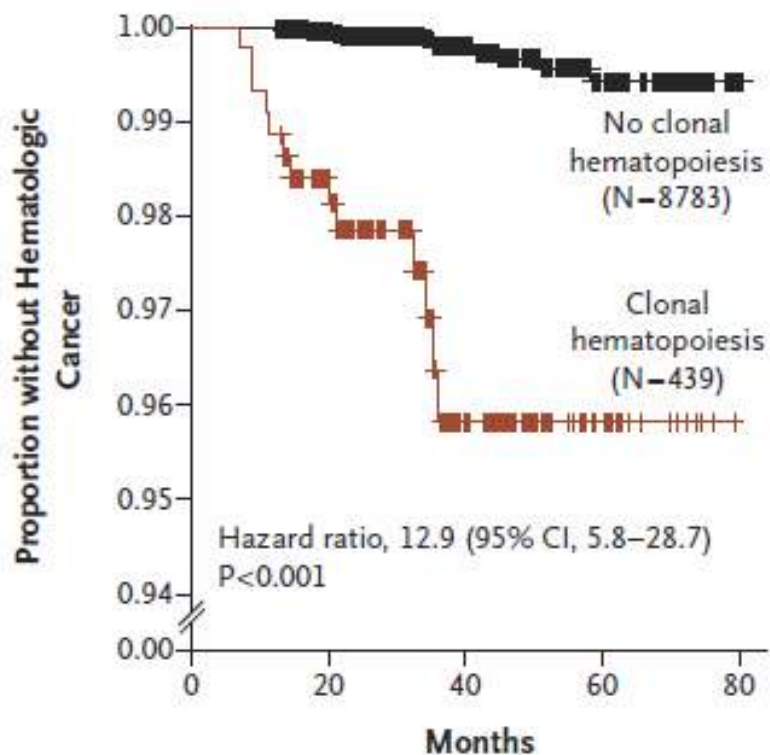
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Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

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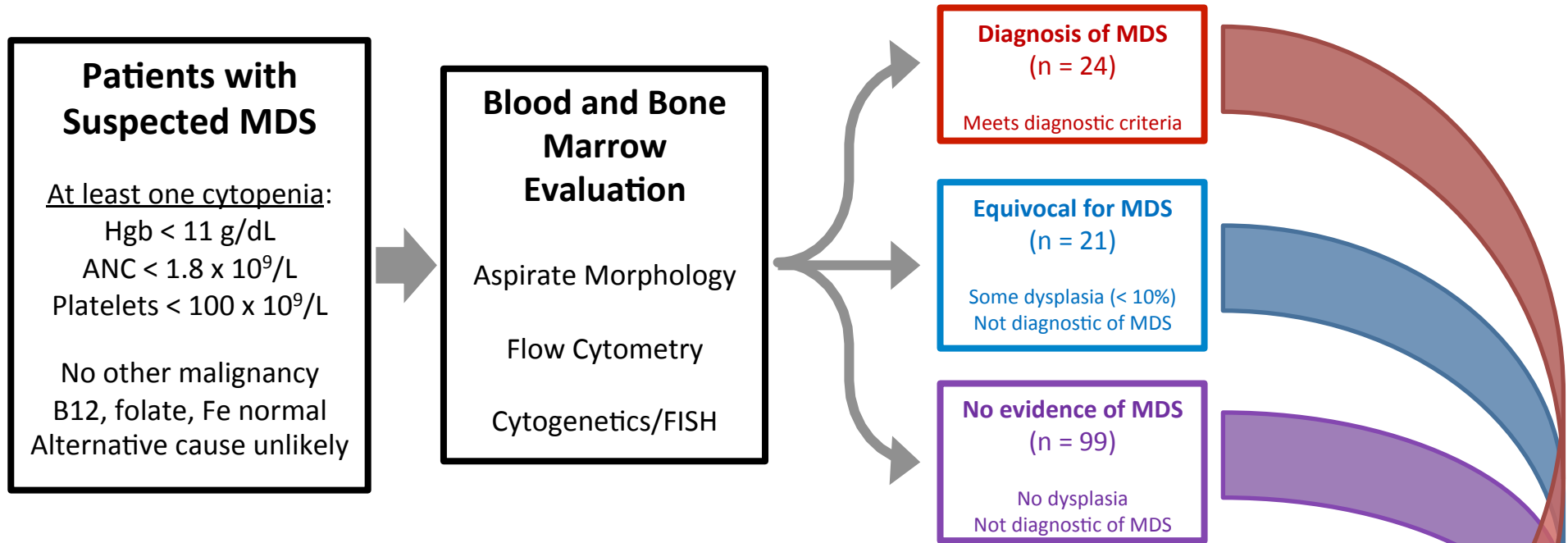
C.H.I.P.



Category	No. of Patients	Hazard Ratio for Hematologic Cancer (95% CI)
No mutations	8783	1.00 (1.00–1.00)
One mutation	1122	0.47 (0.06–3.56)
Two mutations	237	1.99 (0.26–15.27)
CH-UD	170	11.34 (3.44–37.41)
CH-CD	269	13.73 (5.74–32.83)
CH	439	12.89 (5.78–28.72)

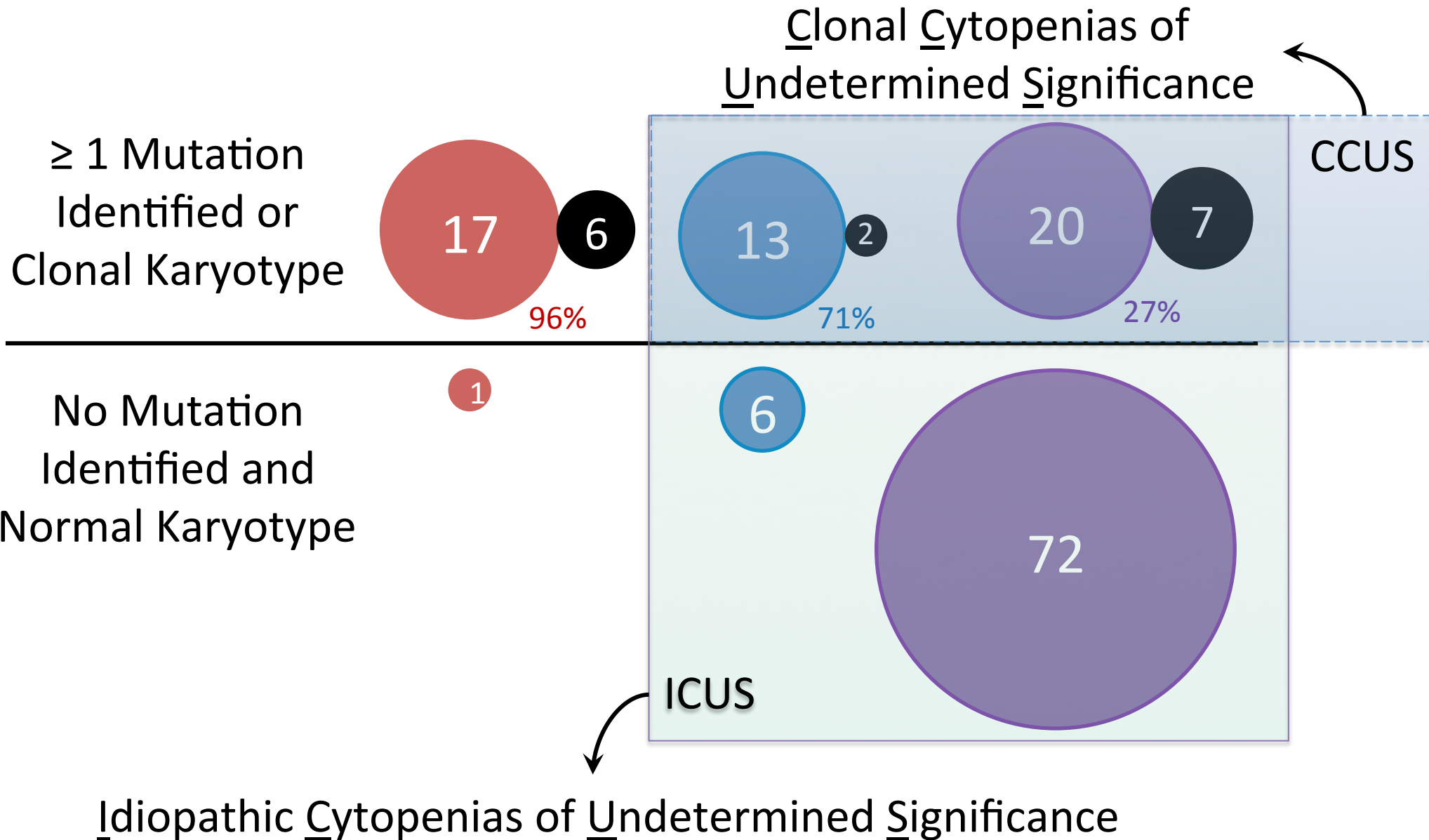
Mutation	No. of Patients	Hazard Ratio (95% CI)	P-value
No mutation (referent)	11/3208	1.00	
JHS	10/2326	0.47 (0.06–3.56)	
MEC	1/882	1.99 (0.26–15.27)	
Mutation	5/134	11.34 (3.44–37.41)	<0.001
JHS	3/83	13.73 (5.74–32.83)	0.002
MEC	2/51	12.89 (5.78–28.72)	<0.001
Mutation, VAF ≥0.10	5/57	11.34 (3.44–37.41)	<0.001
JHS	3/34	13.73 (5.74–32.83)	<0.001
MEC	2/23	12.89 (5.78–28.72)	<0.001

Prospective Trial

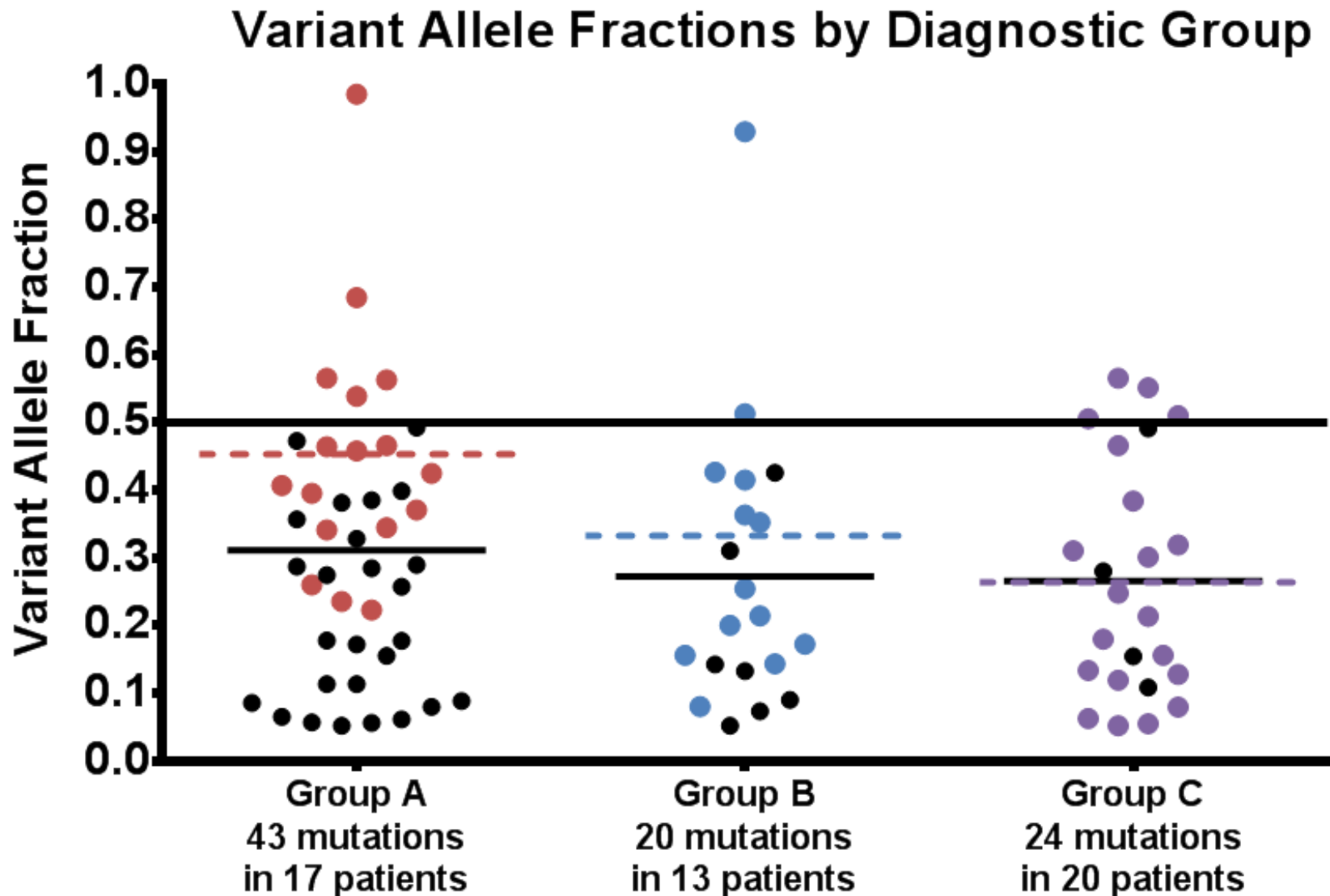


Pathways	Genes
RNA Splicing	SF3B1, SRSF2, U2AF1, ZRSR2
Epigenetic Regulation	TET2, IDH1, IDH2, DNMT3A, EZH2, ASXL1, SETBP1
Tumor Suppression	TP53, PHF6
Transcription	RUNX1, ETV6
Activated Signaling	CBL, NRAS, KIT, JAK2, MPL, FLT3 (TKD)
Other	NPM1

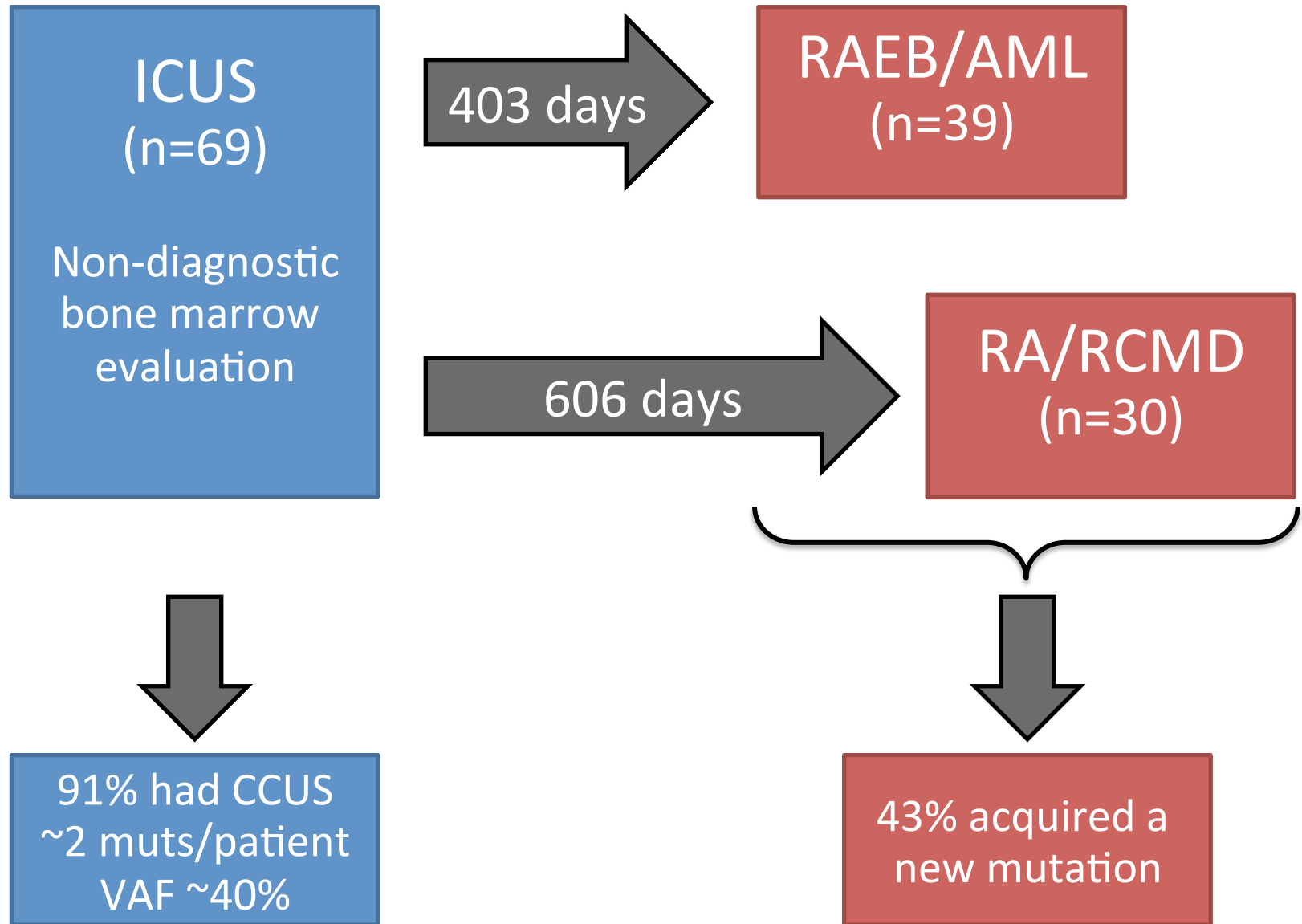
Prospective Trial



Prospective Trial



CCUS to Malignancy



Comparisons

	CHIP Unselected Population	CCUS At Diagnosis	CCUS Prior to MDS/AML Progression	MDS All Risk Groups
Mutated Genes	<i>DNMT3A, TET2, ASXL1, JAK2, TP53 ...</i>	<i>TET2, DNMT3A, ASXL1, SRSF2, TP53, ...</i>	<i>TET2, SRSF2, ASXL1, U2AF1, DNMT3A, ...</i>	<i>SF3B1, TET2, ASXL1, SRSF2, DNMT3A, ...</i>
# of Mutations	~1	~1.6	~2	~2.6
Typical VAF	9-12% (>10% with ↑ risk)	30-40%	~40%	30-50%
Notes	~10% of 70 year-olds	About 35% of ICUS	About 90% of ICUS	Maybe <20% of cytopenic patients!

This suggests increasing risk from CHIP through CCUS to MDS

But we lack prospective follow-up data to quantify risk!

Summary

- Mutations have clear prognostic value independent of existing clinical models
- Mutations may predict treatment response but are not yet sufficient to direct therapy
- Sequencing cytopenic patients may find clonal hematopoiesis at risk for MDS, but mutations alone are not diagnostic.

Analysis of Combined Datasets from the International Working Group for MDS- Molecular Prognosis Committee

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On behalf of the IWG for MDS
investigators



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Erin Reid Tom Kipps

Annette Von Drygalski

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And most of all – our incredible patients and families!

Bejar Lab

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Tiffany Tanaka Brian Reilly

Emily Wheeler Armon Azizi

Fiona Gowen-Huang



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