Clinical Significance of Somatic Mutations in Hematologic Neoplasia

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SH/EAHP workshop

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BRIGHAM AND WOMEN'S HOSPITAL
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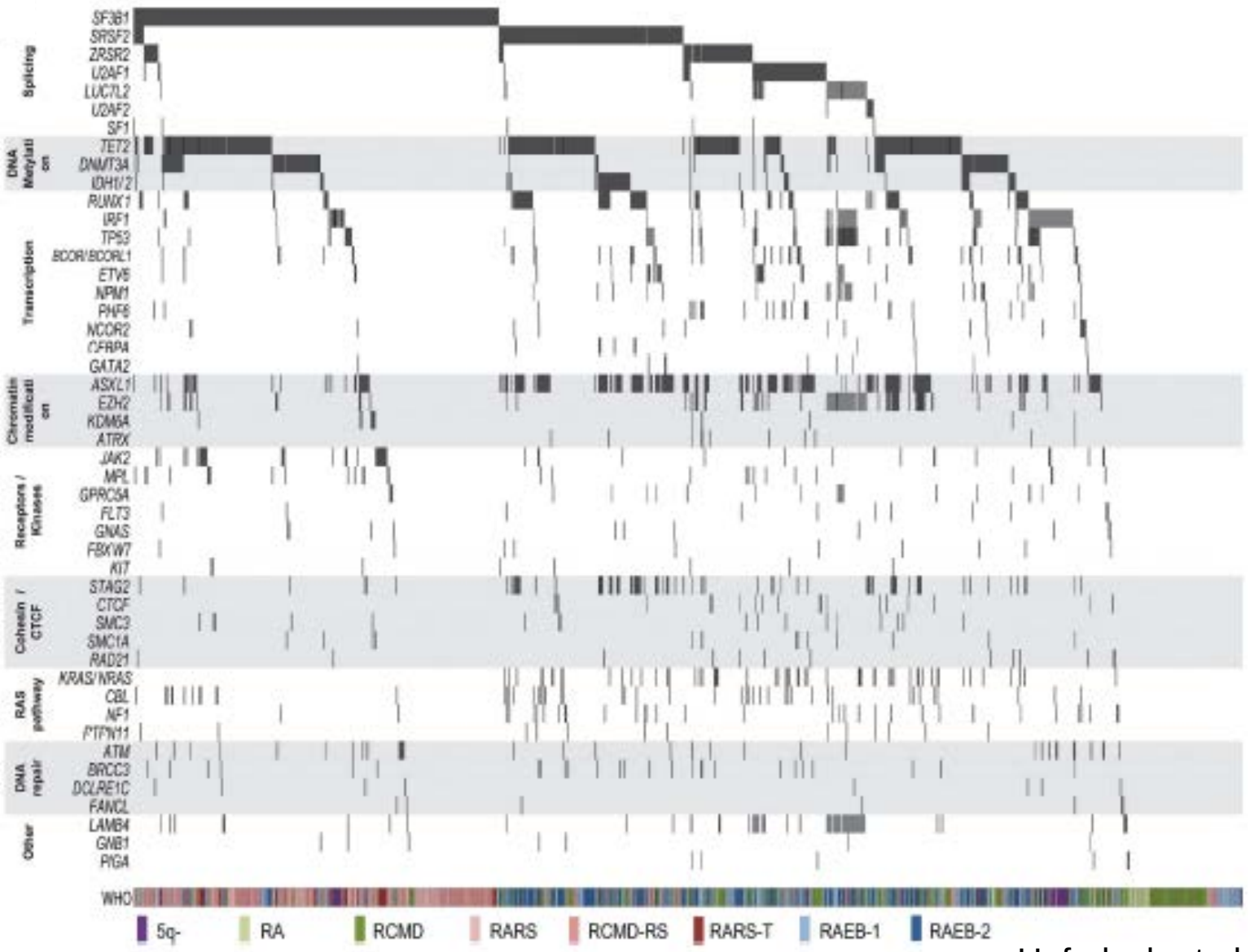
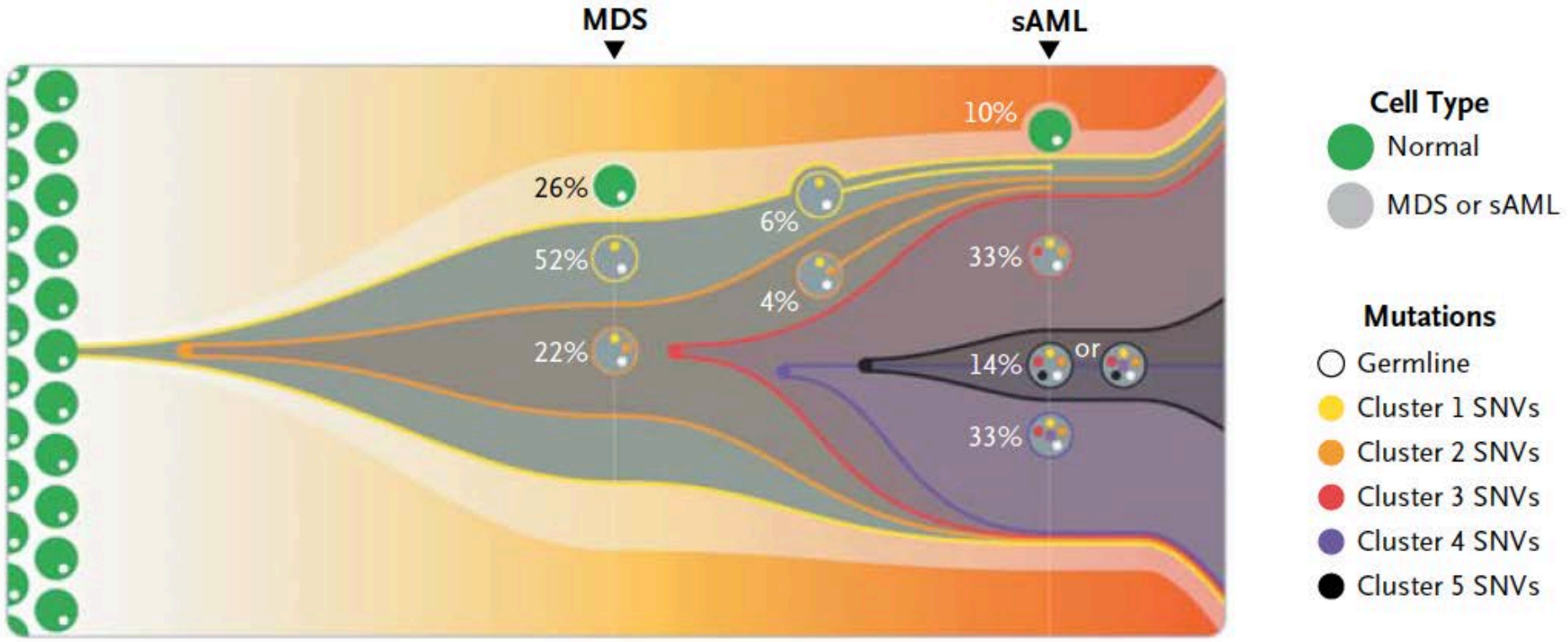
Genetic complexity



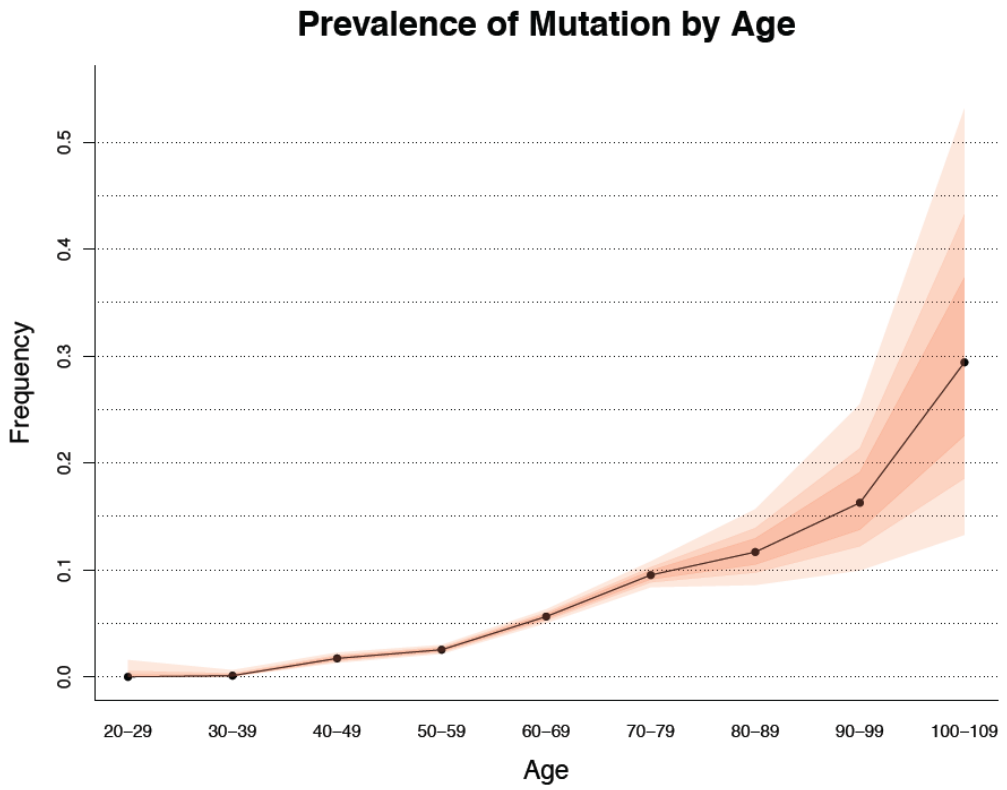
Haferlach et al, *Leukemia* 2014

Serial acquisition of mutations / clonal progression



Walter et al., *NEJM* 2012

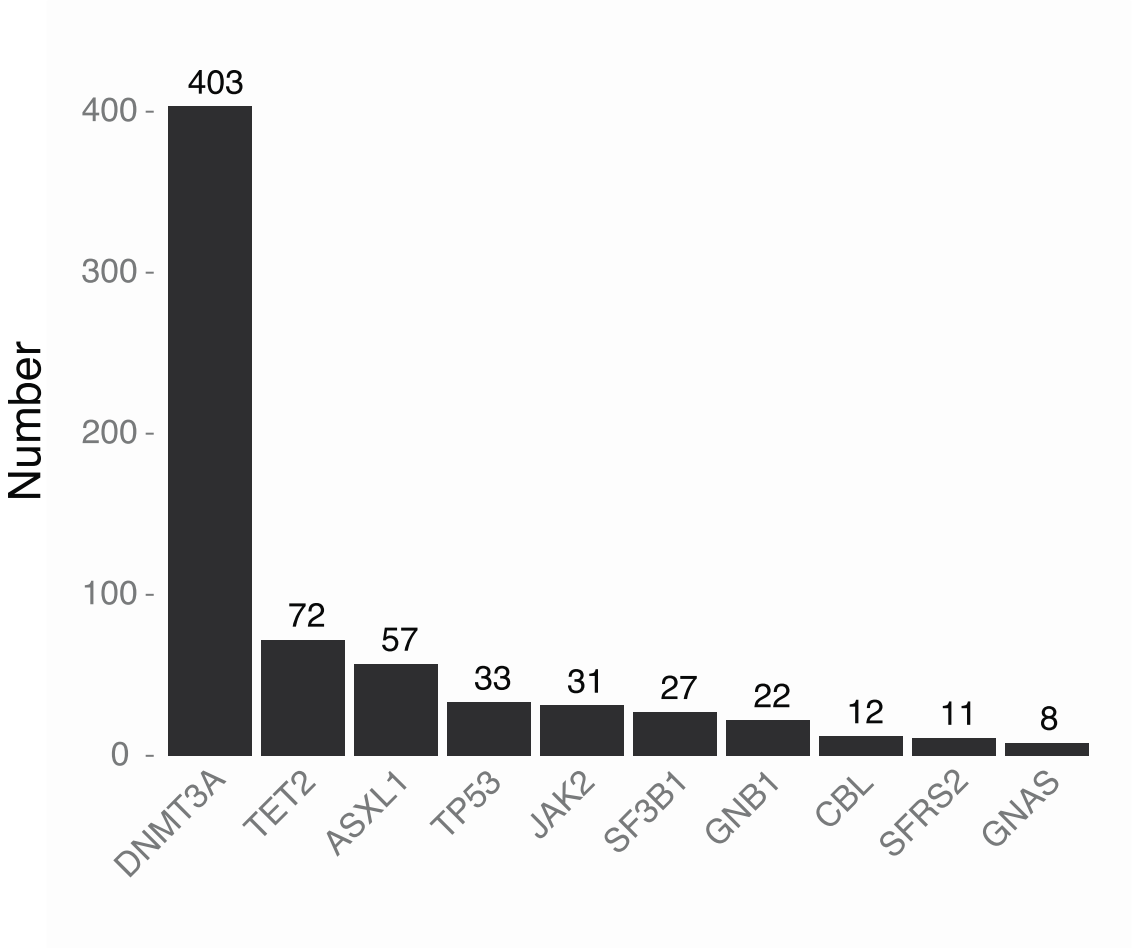
Clonal hematopoiesis



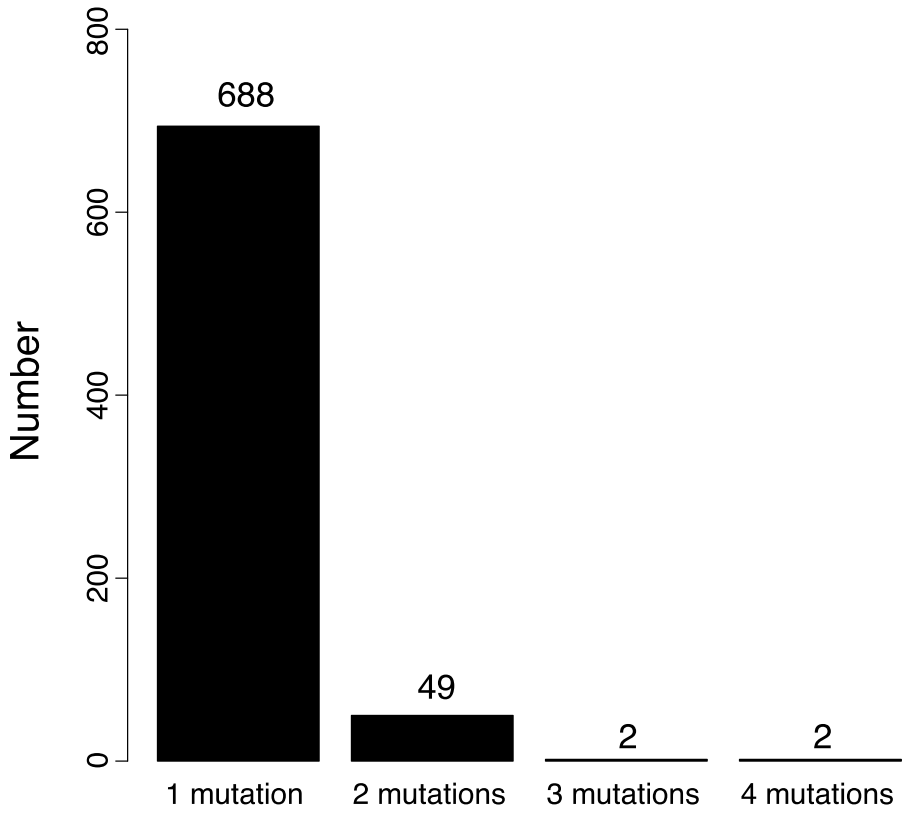
- Exome sequencing data from peripheral blood of >17,000 individuals
- Unselected for hematologic phenotype

Jaiswal et al., *NEJM* 2014

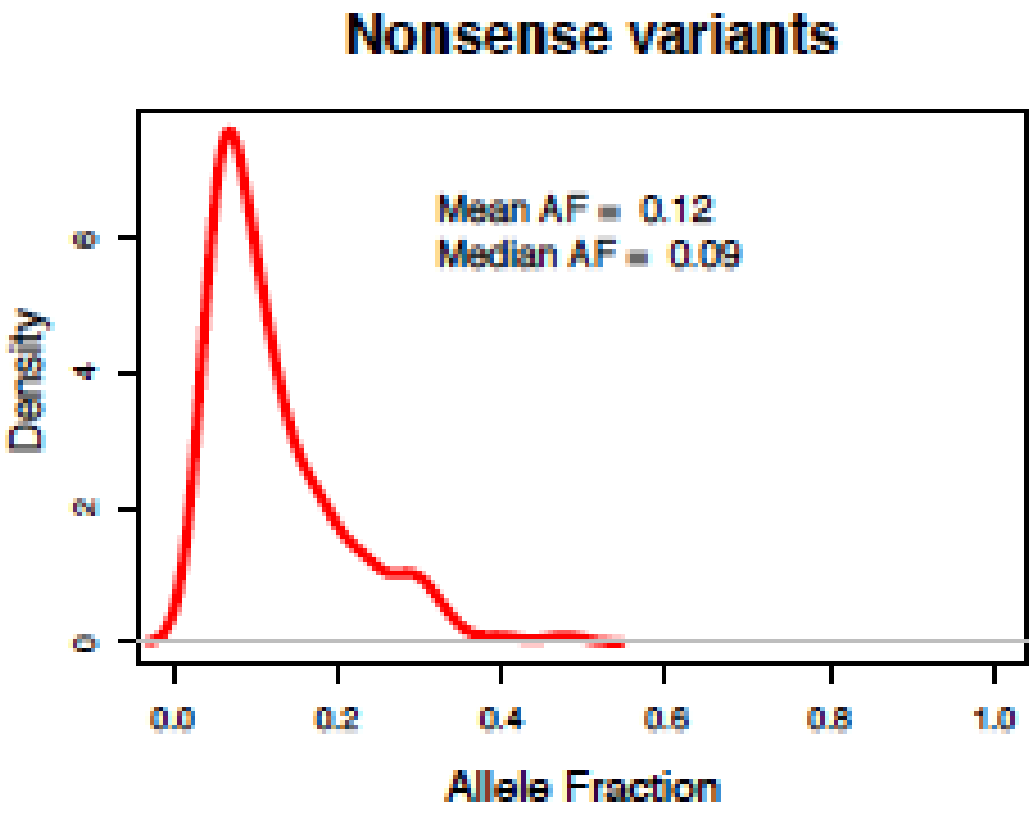
DNMT3A is frequently mutated



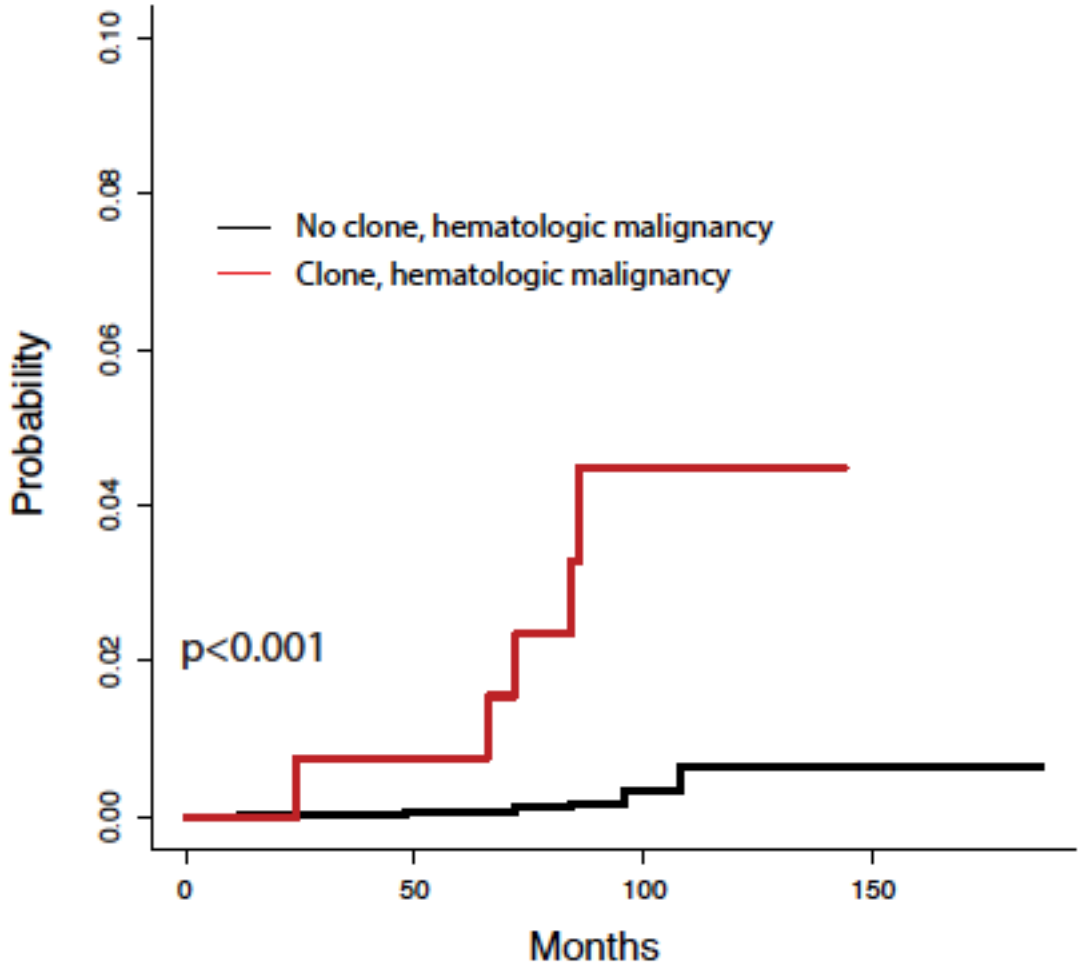
Most subjects had only one mutation



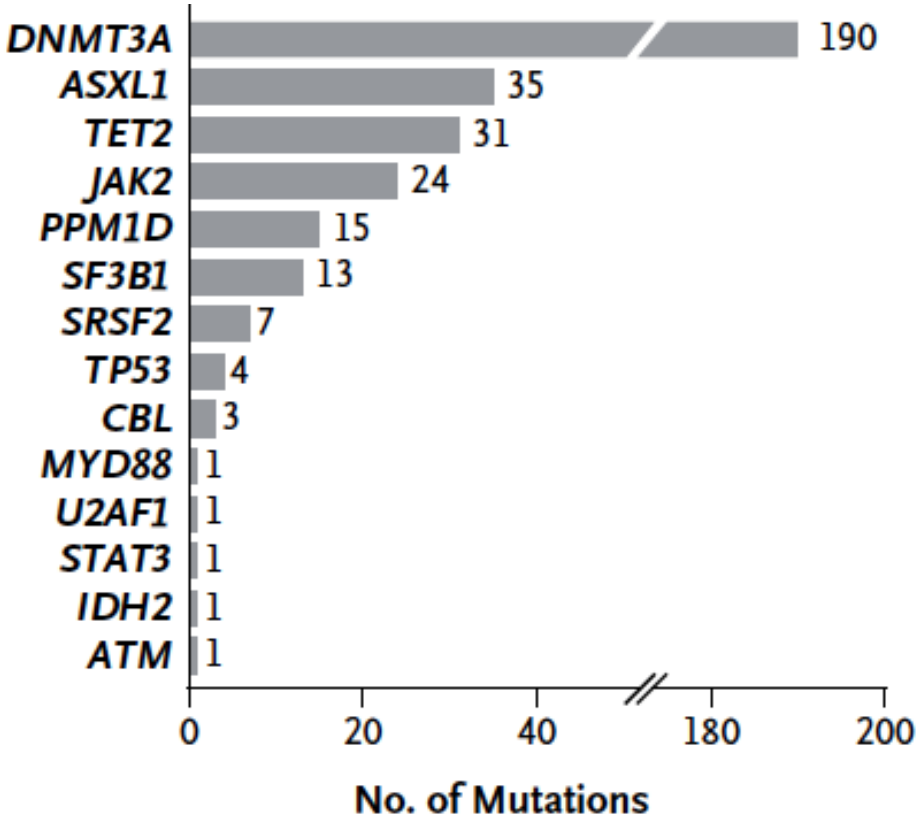
Clonal hematopoiesis of indeterminate potential (CHIP)

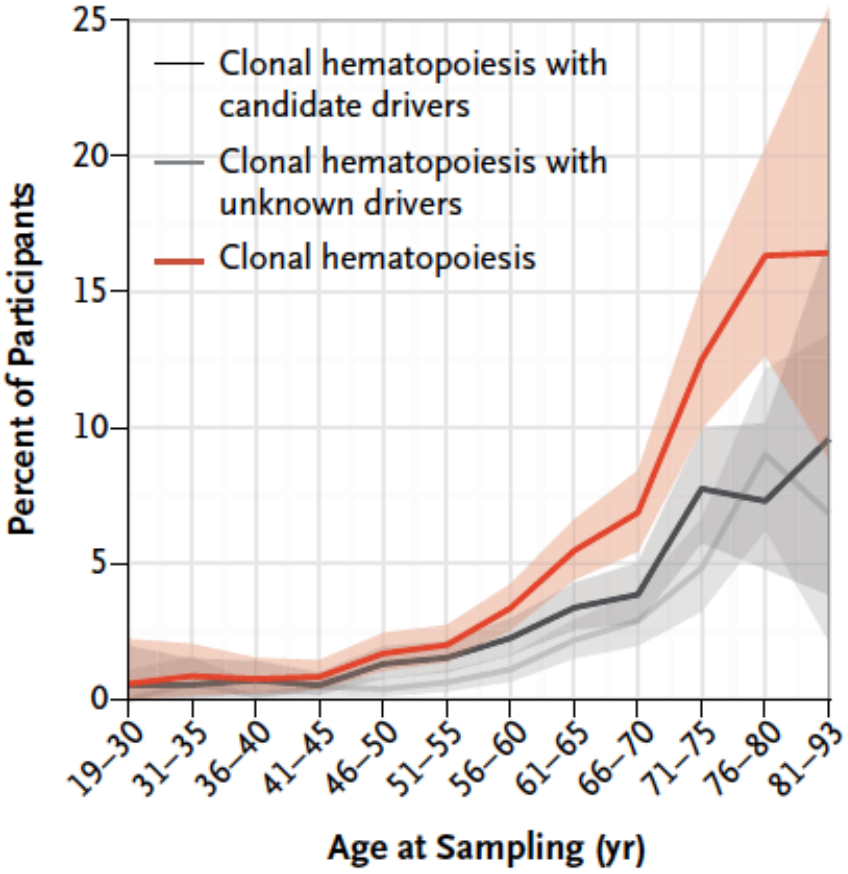


Clonal hematopoiesis increases the risk of hematologic malignancy



Clonal hematopoiesis: concordant findings from multiple studies





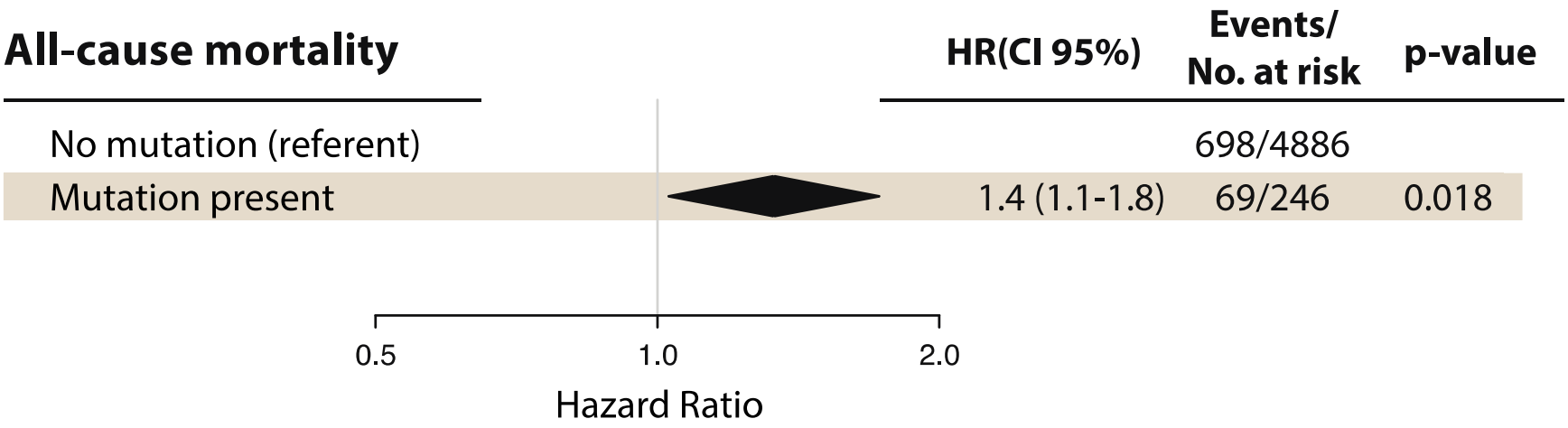
Genovese et al., NEJM 2014
Xie et al., Nat Med, 2014
McKerrell et al., Cell Rep 2015

Clonal **H**ematopoiesis of **I**ndeterminate **P**otential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele fraction of at least 2%
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

Steensma et al., *Blood* 2015

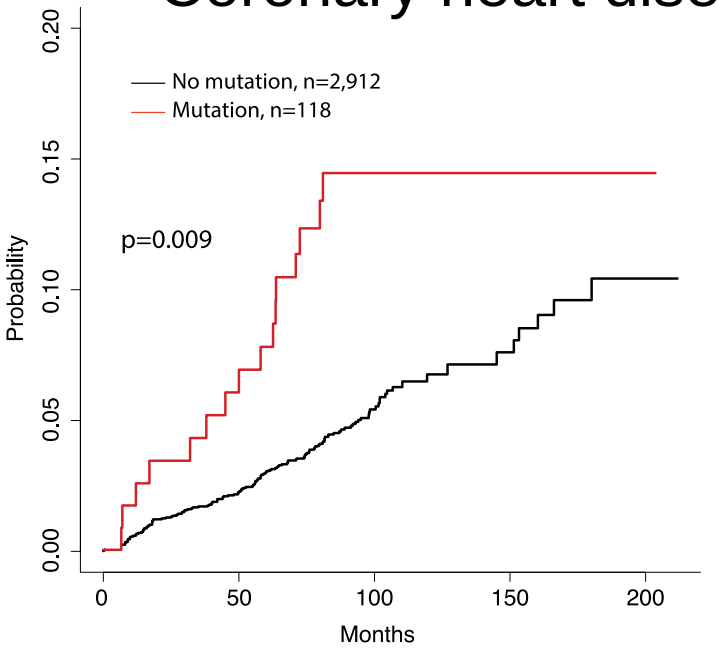
Clonal hematopoiesis is associated with reduced overall survival



Cox proportional hazards models which included age, gender, and diabetes status as covariates, with results for cohorts analyzed as a fixed-effects meta-analysis

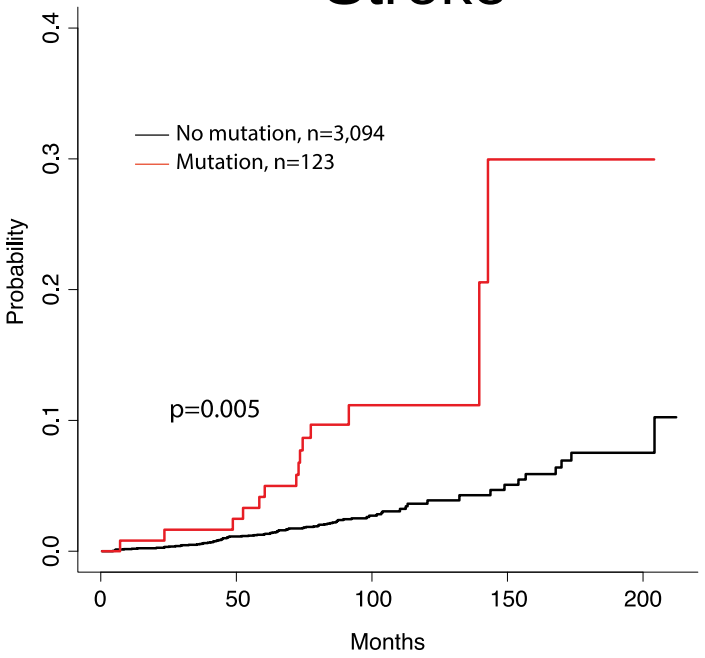
Clonal hematopoiesis is associated with higher risk of heart attack and stroke

Coronary heart disease



HR 2.0, 95% CI 1.2-3.4, p=0.018

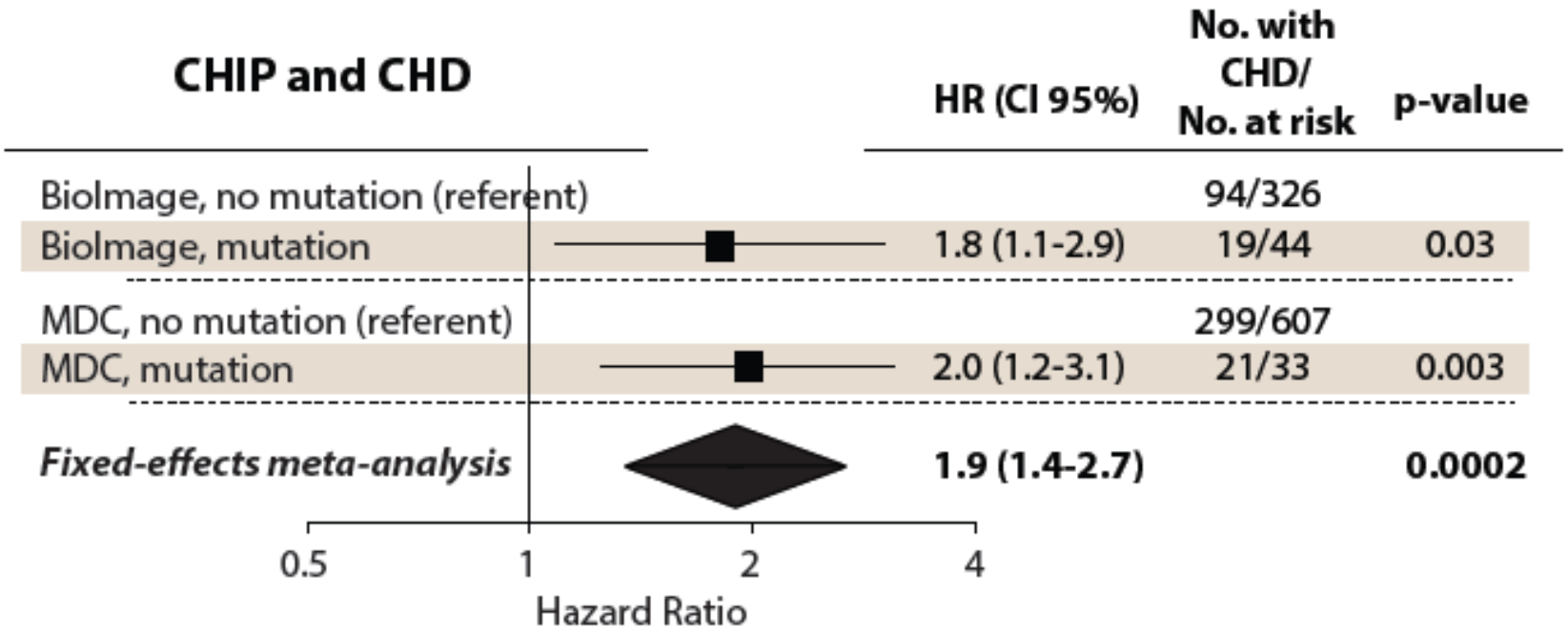
Stroke



HR 2.6, 95% CI 1.4 to 4.8, p=0.003

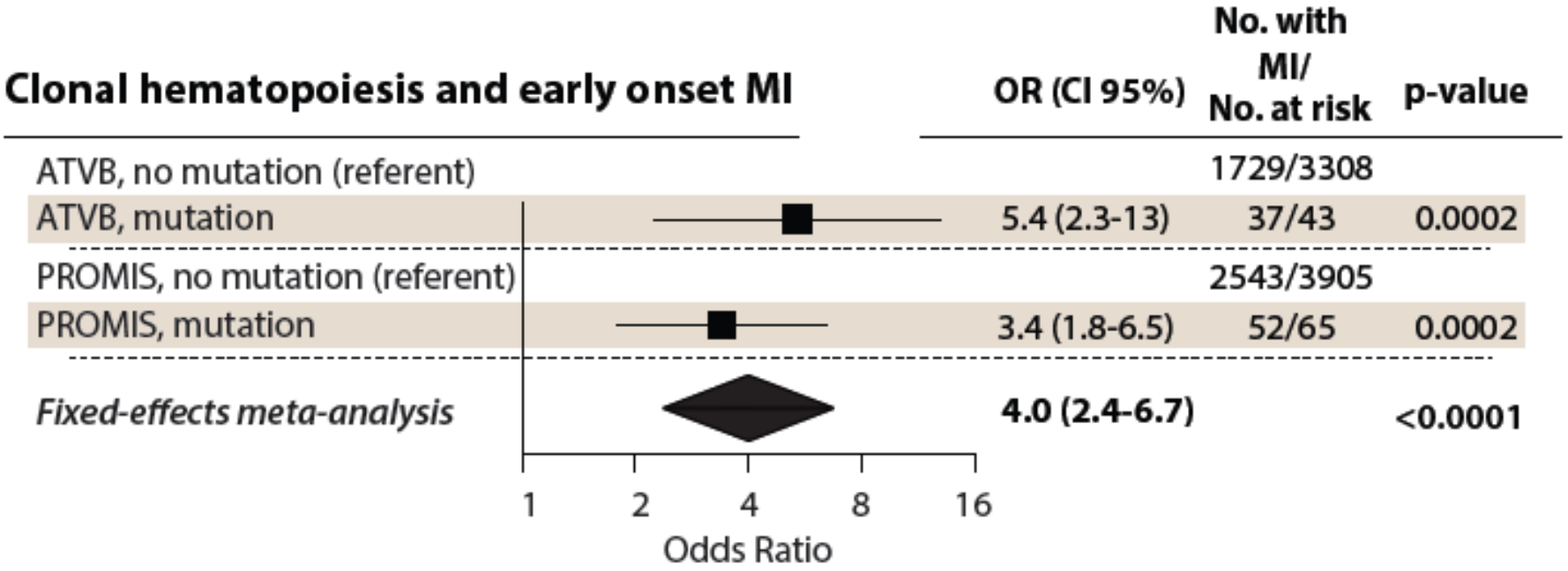
Regression models were adjusted for age, sex, BMI, lipids, blood pressure, and smoking

Replication in additional cohorts



Jaiswal et al., *NEJM* 2017

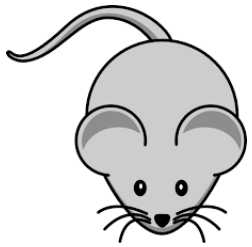
CHIP and early-onset MI



Jaiswal et al., *NEJM* 2017

Experimental examination of CHIP and cardiovascular disease

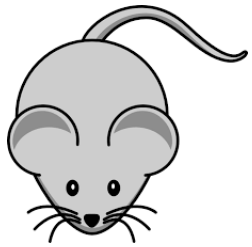
8-12 week old



Vav1-Cre, *TET2* fl/fl
Vav1-Cre (control)

BMT

8 week old

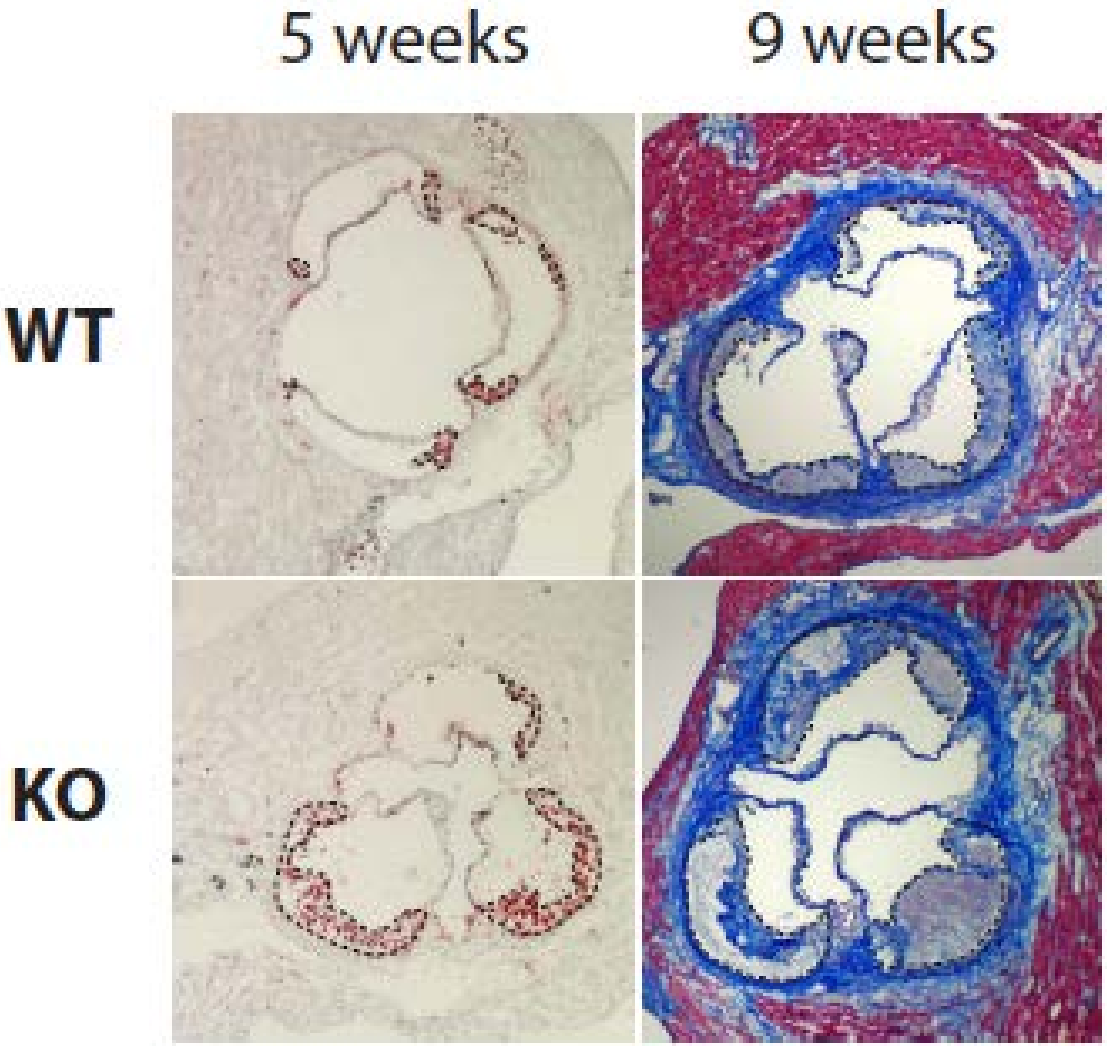


WT
ldlr-/-
female

Diet:
1.25% cholesterol

harvest

Aortic root 9

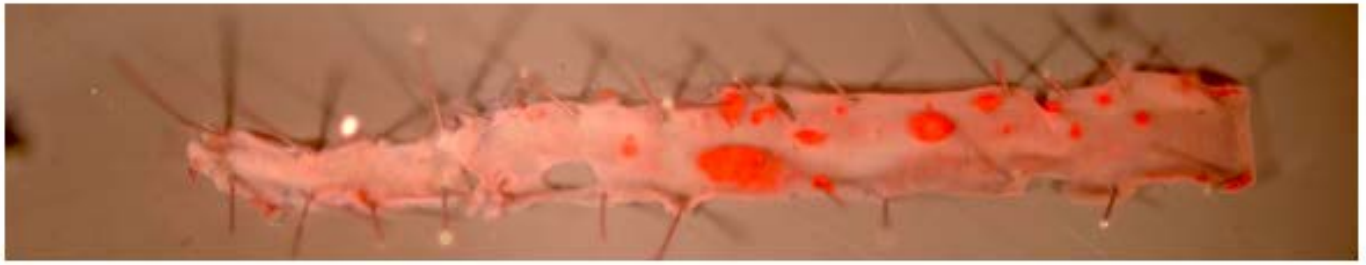


Jaiswal et al., *NEJM* 2017

Descending aorta lesion area is larger in Tet2$^{-/-}$ recipients

Tet2 fl/fl, Vav1-Cre

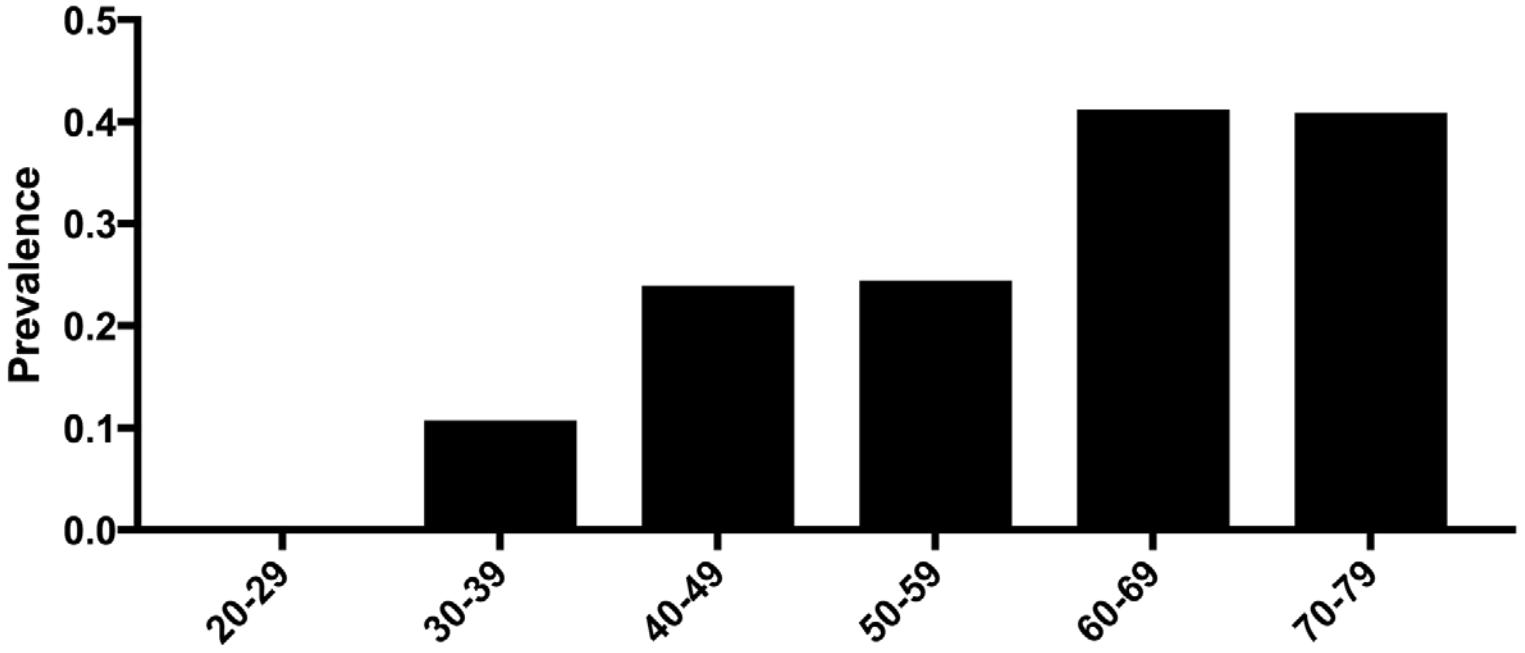
Tet2 +/fl, Vav1-Cre



Vav1-Cre

CHIP and therapy-related malignancies

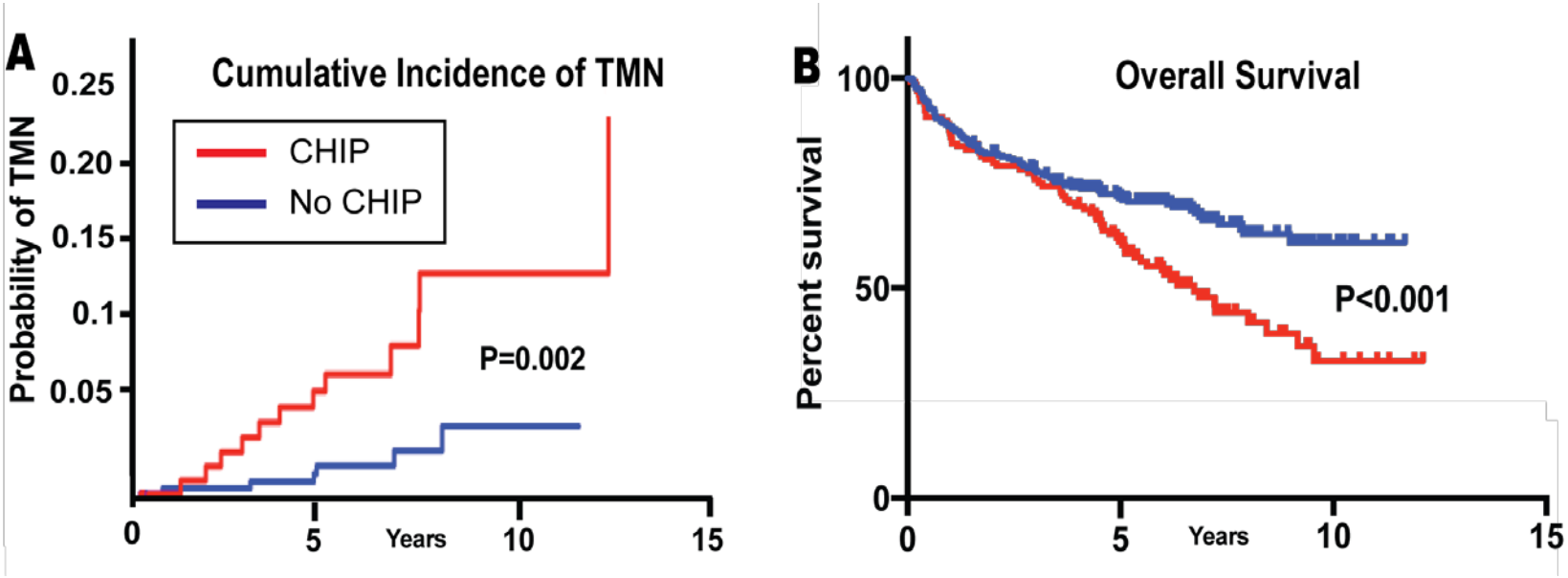
401 samples from non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation



Number affected	0	3	12	35	61	9
Number at risk	10	28	50	143	148	22

Gibson et al., *JCO* 2017

CHIP and therapy-related malignancies



Gibson et al., *JCO* 2017

Clonal **H**ematopoiesis of **I**ndeterminate **P**otential (CHIP) summary

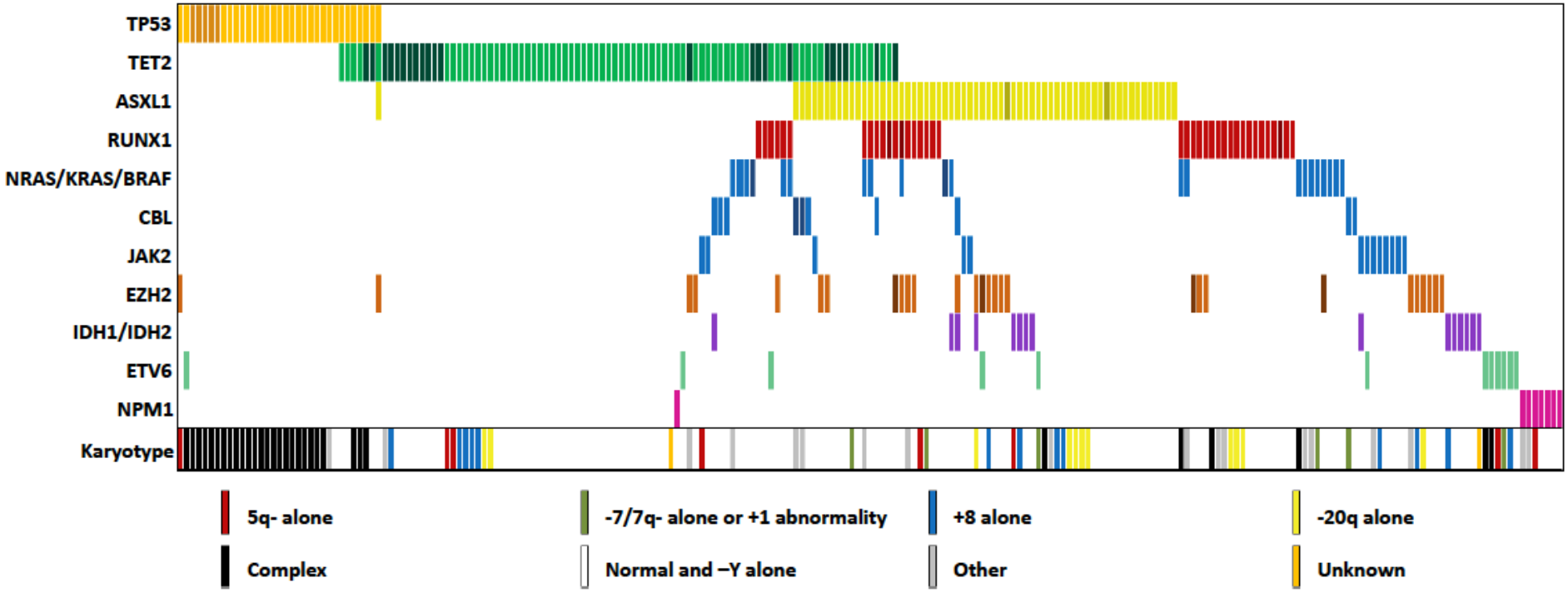
- Common, age-associated, pre-malignant condition
- Most commonly mutated genes include *DNMT3A*, *TET2*, *ASXL1*, *TP53*
- Associated with increased overall mortality
  - Increased risk of hematologic malignacy
  - Increased risk of therapy-related malignancy
  - Increased risk of cardiovascular disease

Clinical genetics for myeloid neoplasms

Prognosis

Prediction of therapeutic response

Distribution of Mutations in MDS



Bejar et al., *NEJM* 2011
Bejar et al., JCO 2012

Risk Modeling – Multivariable Analysis IPSS

	HR (95% CI)	p-value
Age		
≥55 yrs vs. <55 yrs	**1.81 (1.20-2.73)**	**0.004**
IPSS Risk Group		
Int1 vs. Low	**2.29 (1.69-3.11)**	**<0.001**
Int2 vs. Low	**3.45 (2.42-4.91)**	**<0.001**
High vs. Low	**5.85 (3.63-9.40)**	**<0.001**
Mutational Status - Present vs. Absent		
***TP53* Mutation**	**2.48 (1.60-3.84)**	**<0.001**
***EZH2* Mutation**	**2.13 (1.36-3.33)**	**<0.001**
***ETV6* Mutation**	**2.04 (1.08-3.86)**	**0.029**
***RUNX1* Mutation**	**1.47 (1.01-2.15)**	**0.047**
***ASXL1* Mutation**	**1.38 (1.00-1.89)**	**0.049**

137/439 (31.2%) Samples carry a mutation in one or more of these genes

Clinical genetics for myeloid neoplasms

Prognosis

Prediction of therapeutic response

CIBMTR®
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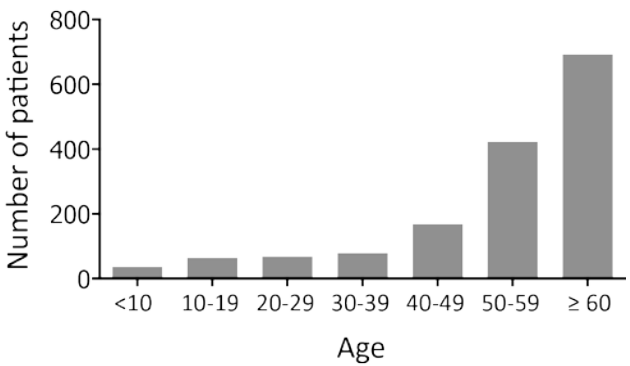
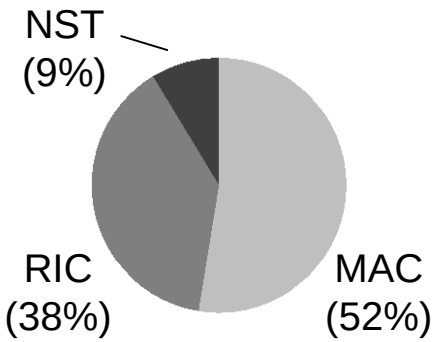
Cohort: 1514 MDS patients

- Broadly representative: 130 transplant centers
- Uniform diagnosis: MDS (<20% blasts)
- No exclusions based on patient or transplant variables

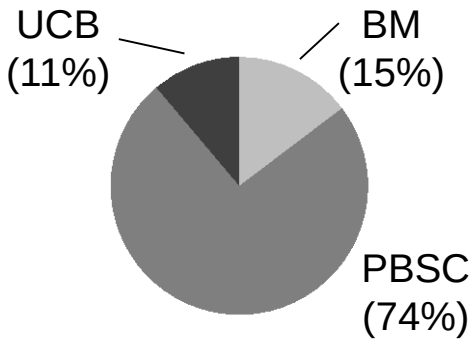
Age



Conditioning intensity

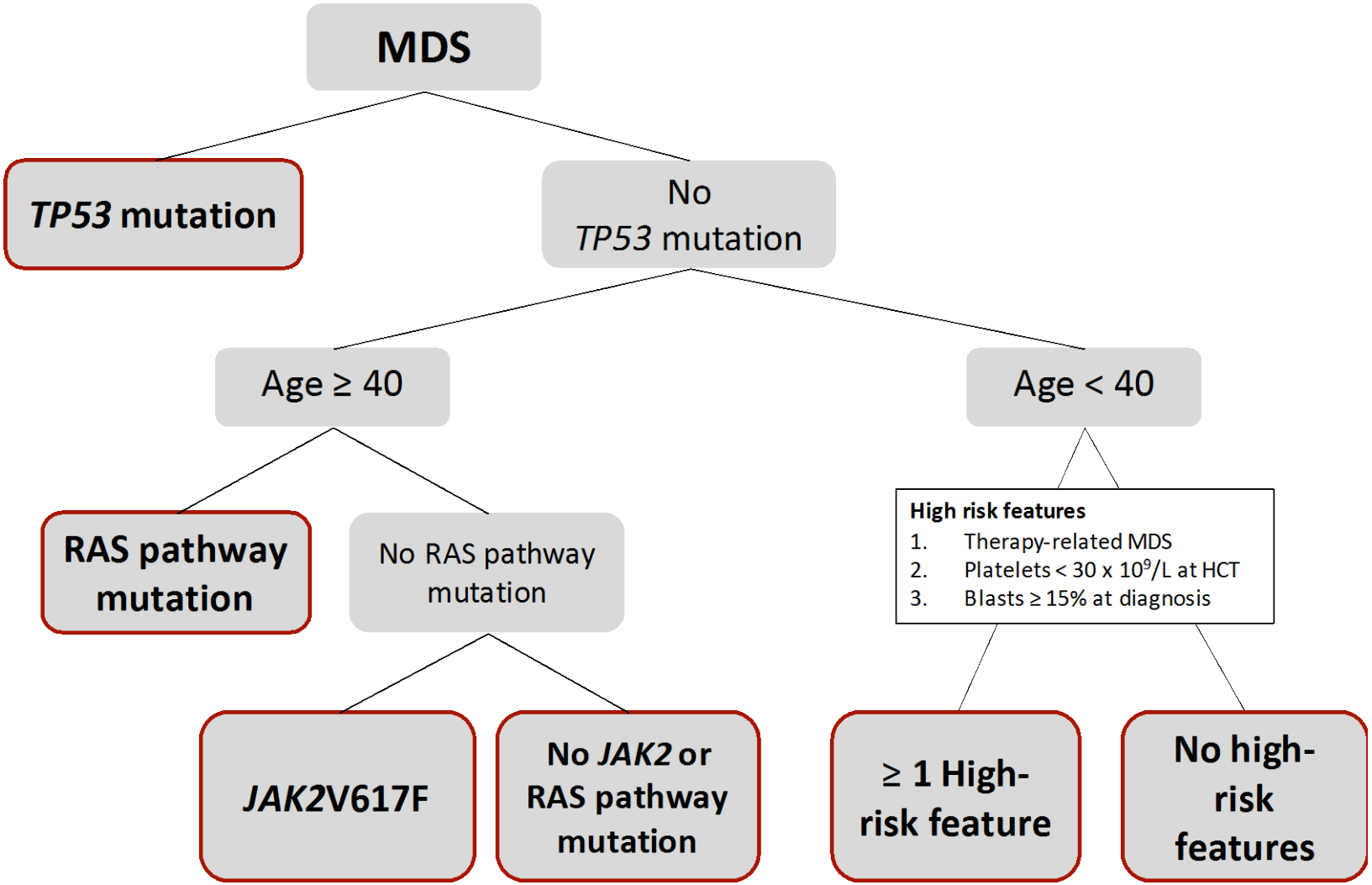


Graft type



Lindsley et al., *NEJM* 2017

Multivariable Model for Overall Survival

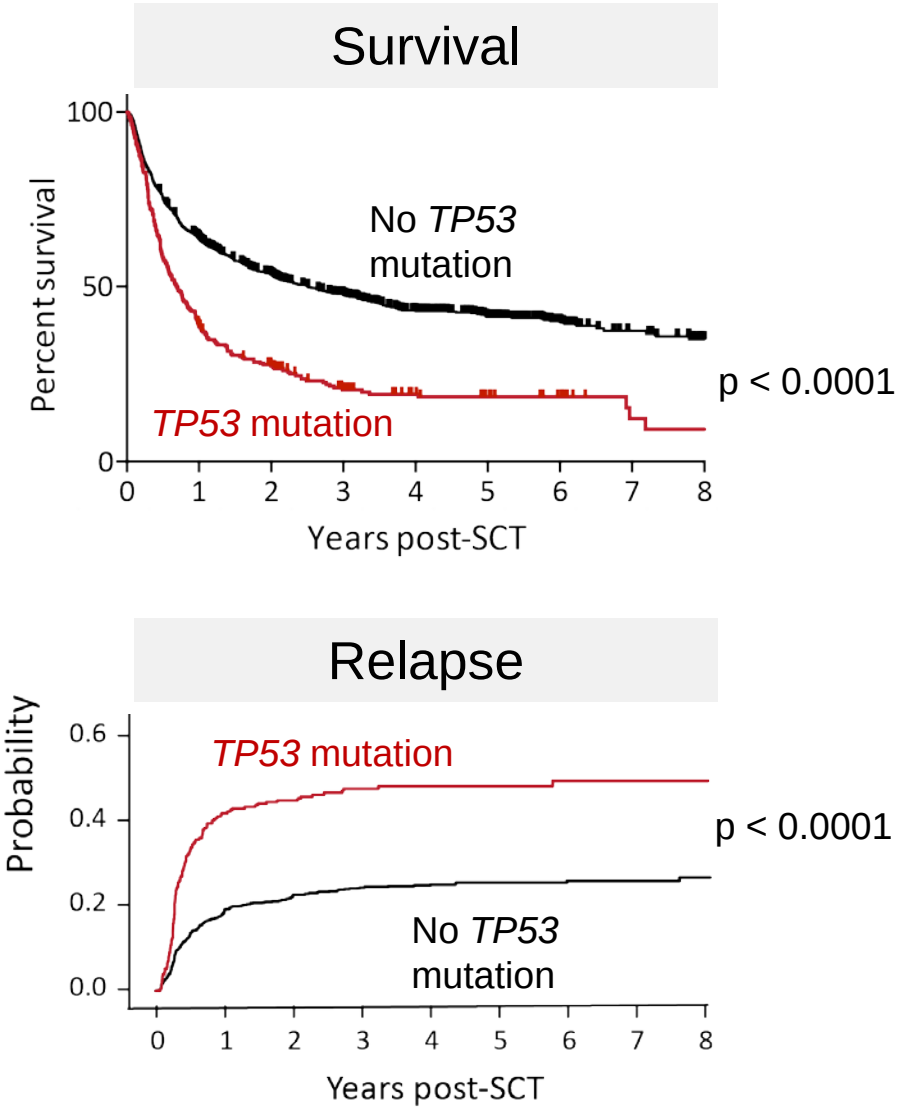


TP53 mutations lead to relapse and poor survival

MDS

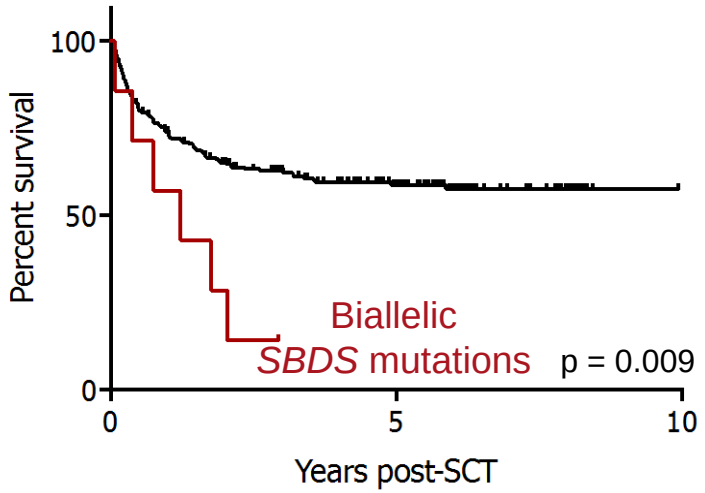
***TP53* mutation**
Median OS = 8 months

No *TP53* mutation

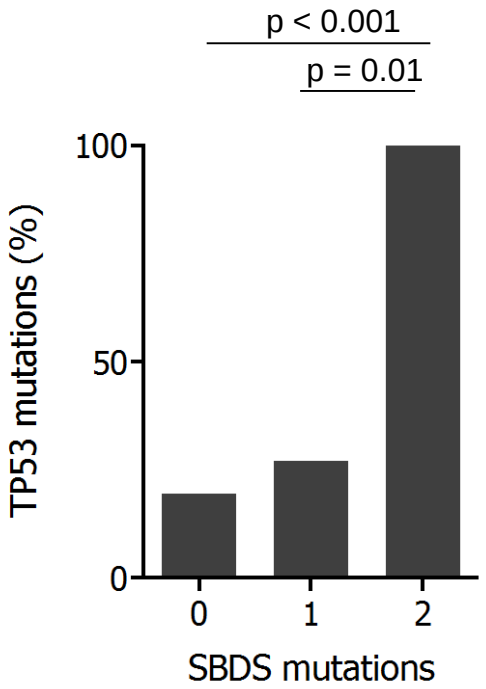


Under-diagnosed Shwachman Diamond Syndrome

Survival
All patients < 40 years old



Somatic *TP53* mutations



Lindsley et al., *NEJM* 2017

Summary

TP53 mutations

- Poor prognosis
- No benefit to myeloablative conditioning

RAS pathway and *JAK2* mutations

- Poor prognosis in patients ≥ 40 without *TP53* mutations
- RAS: high early relapse, improved OS and relapse with MAC
- *JAK2*: high NRM, no decrease in NRM with RIC

SBDS mutations: unrecognized Shwachman-Diamond Syndrome

- Common in young adults (4%)
- Poor prognosis, somatic *TP53* mutations

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