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HOTEL INTERCONTINENTAL | SÃO PAULO

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society of hematologic oncology

APOIO
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Educação
e Pesquisa



How do I navigate between ICUS, CCUS, CMUS, and MDS?

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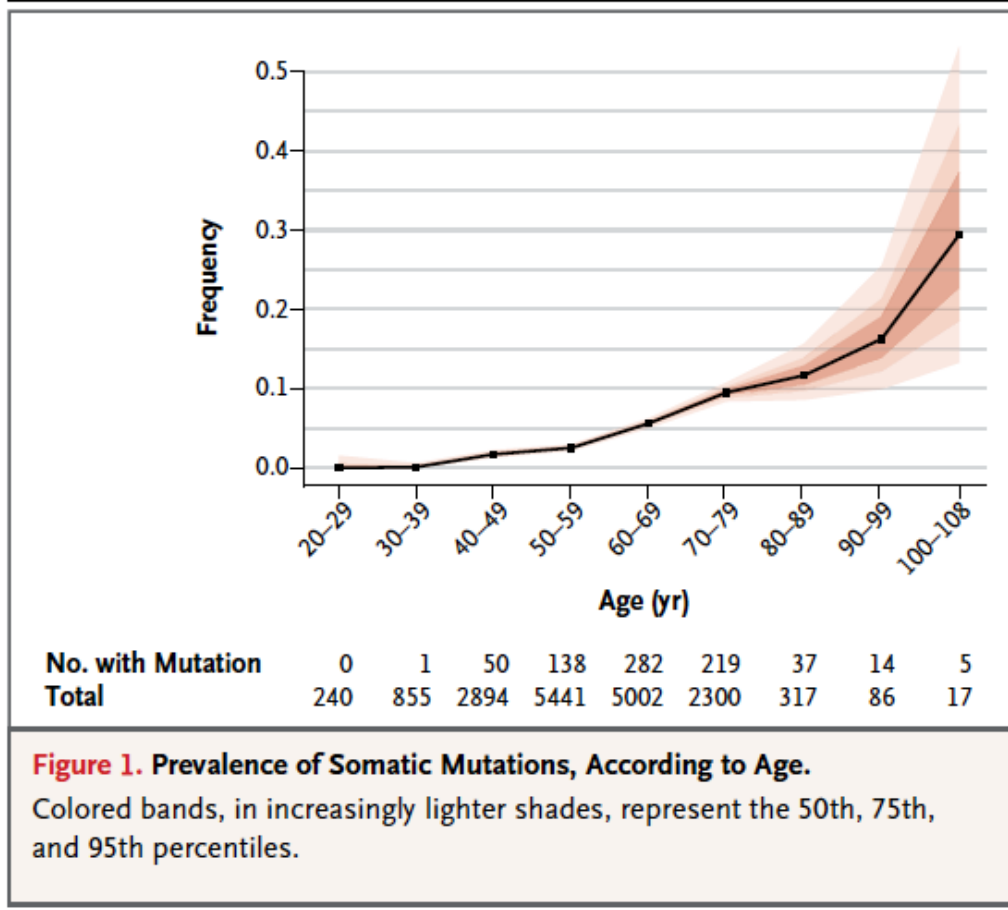
Sylvester Comprehensive Cancer Center

Presentation Roadmap:

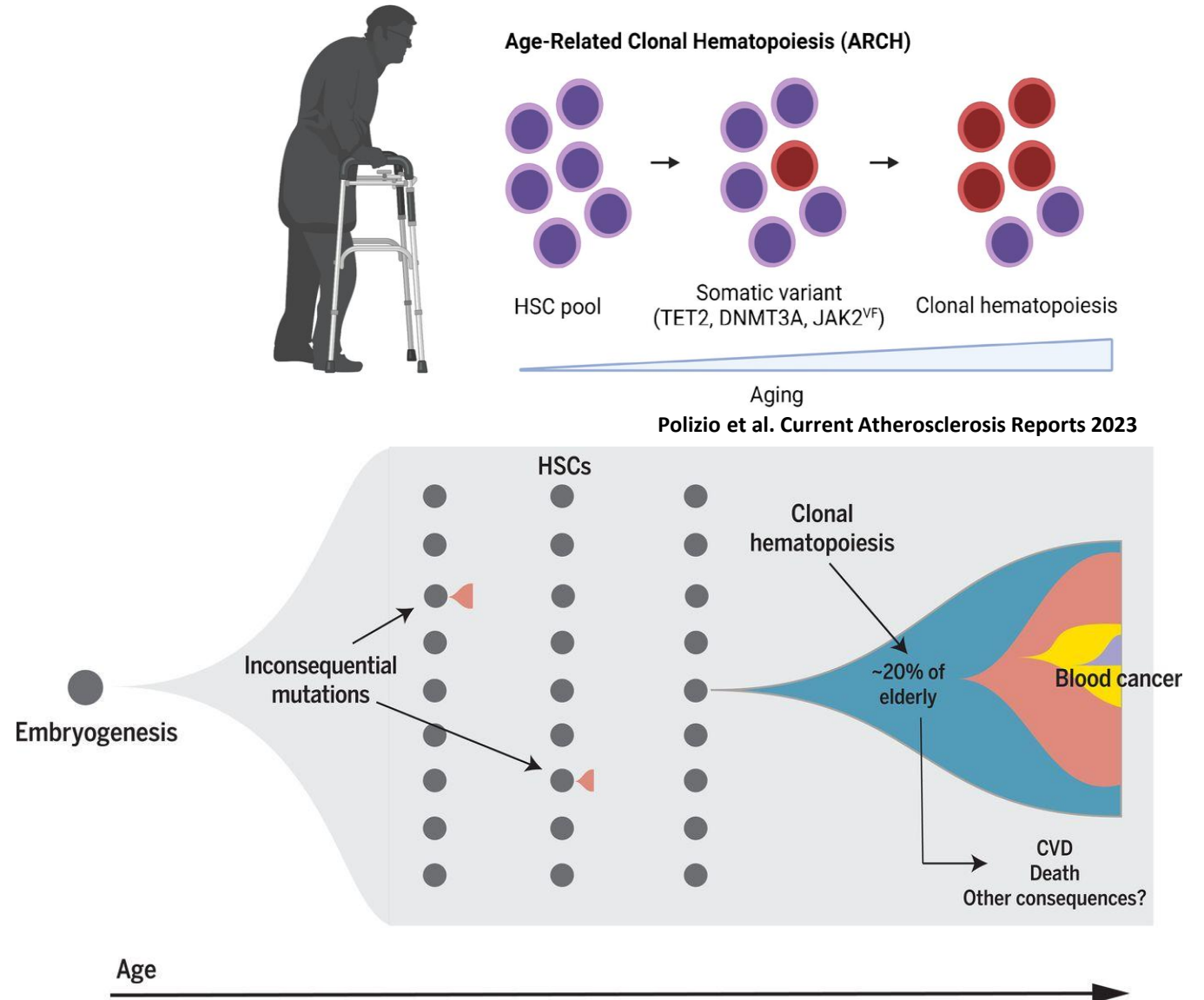
1. What is Clonal Hematopoiesis? CHIP? CCUS? All the Acronyms!
2. Implications of CH- Blood and Beyond
3. Risk Stratification

There is currently no data to support screening for CHIP/CCUS outside of a research setting

Somatic genetic events are inevitable and ubiquitous

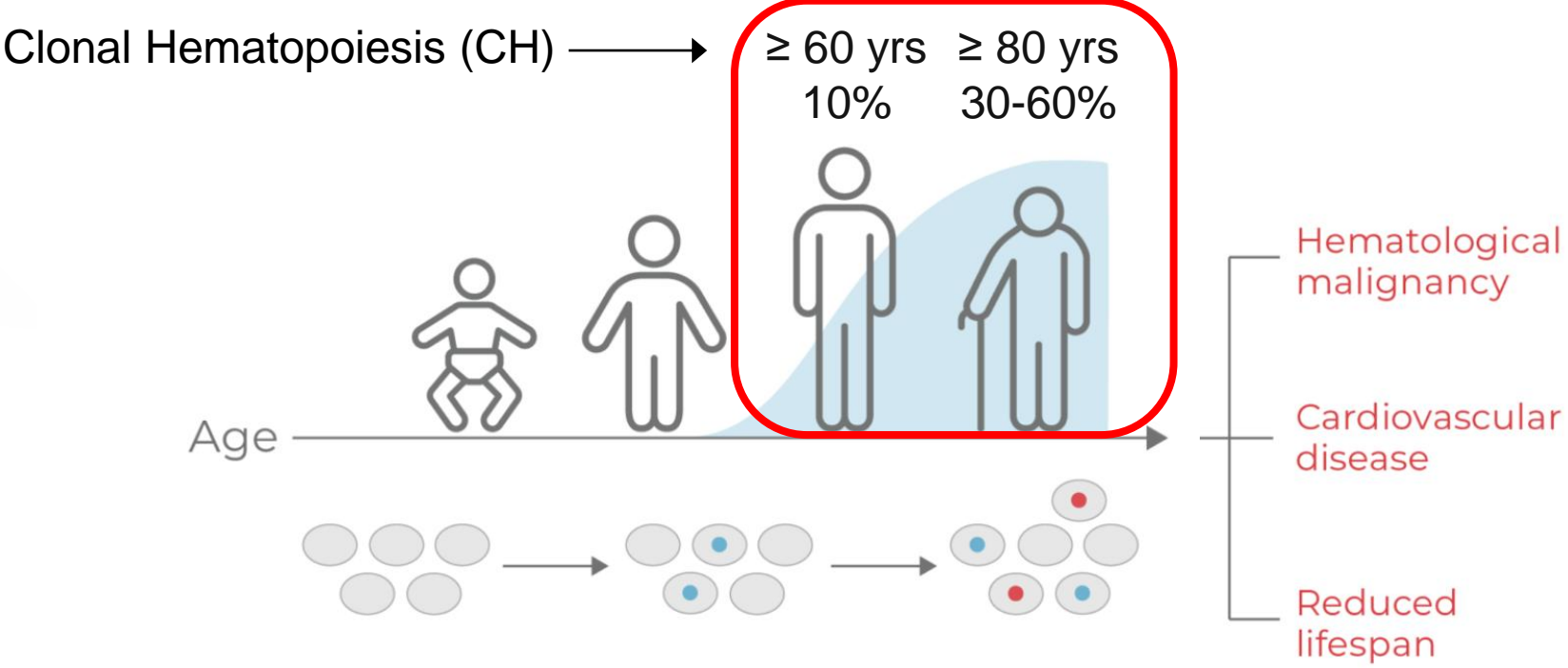


Jaiswal et al. NEJM 2014



Jaiswal and Ebert Science. 2019

Aged individuals living with CH will double by 2050

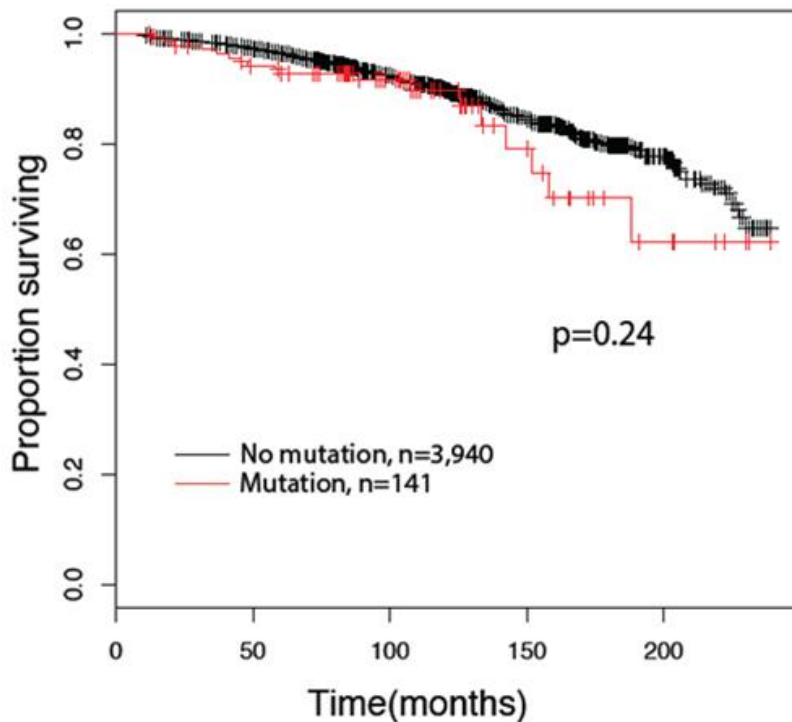


Year	Age	US Census Bureau	CH individuals
2020	≥60 years	74.6 million	7.5 million
2050	≥60 years	120-150 million	12-15 million

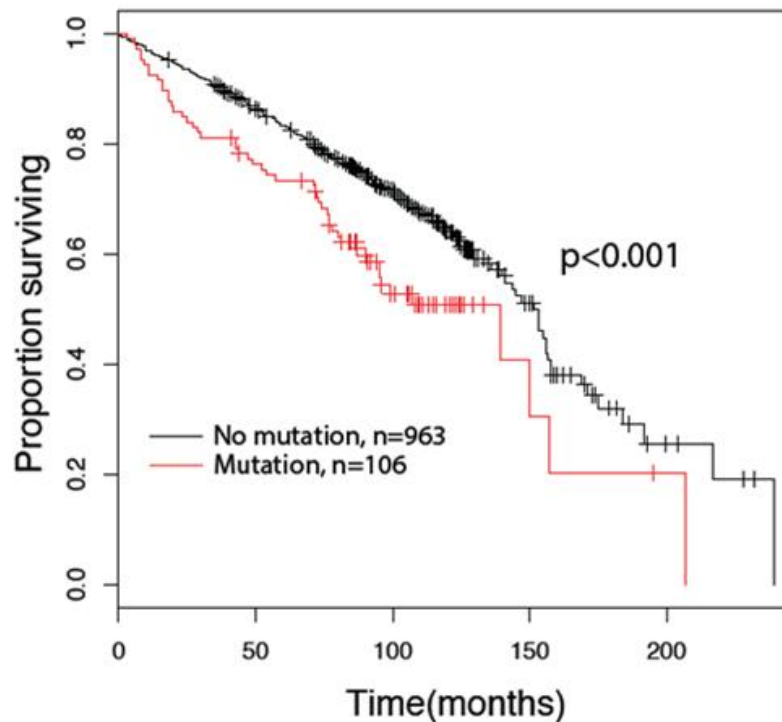
WHO: By 2050, the world's population of people aged 60 years and older will double (2.1 billion)

If it is inevitable, why study it?

Age < 70

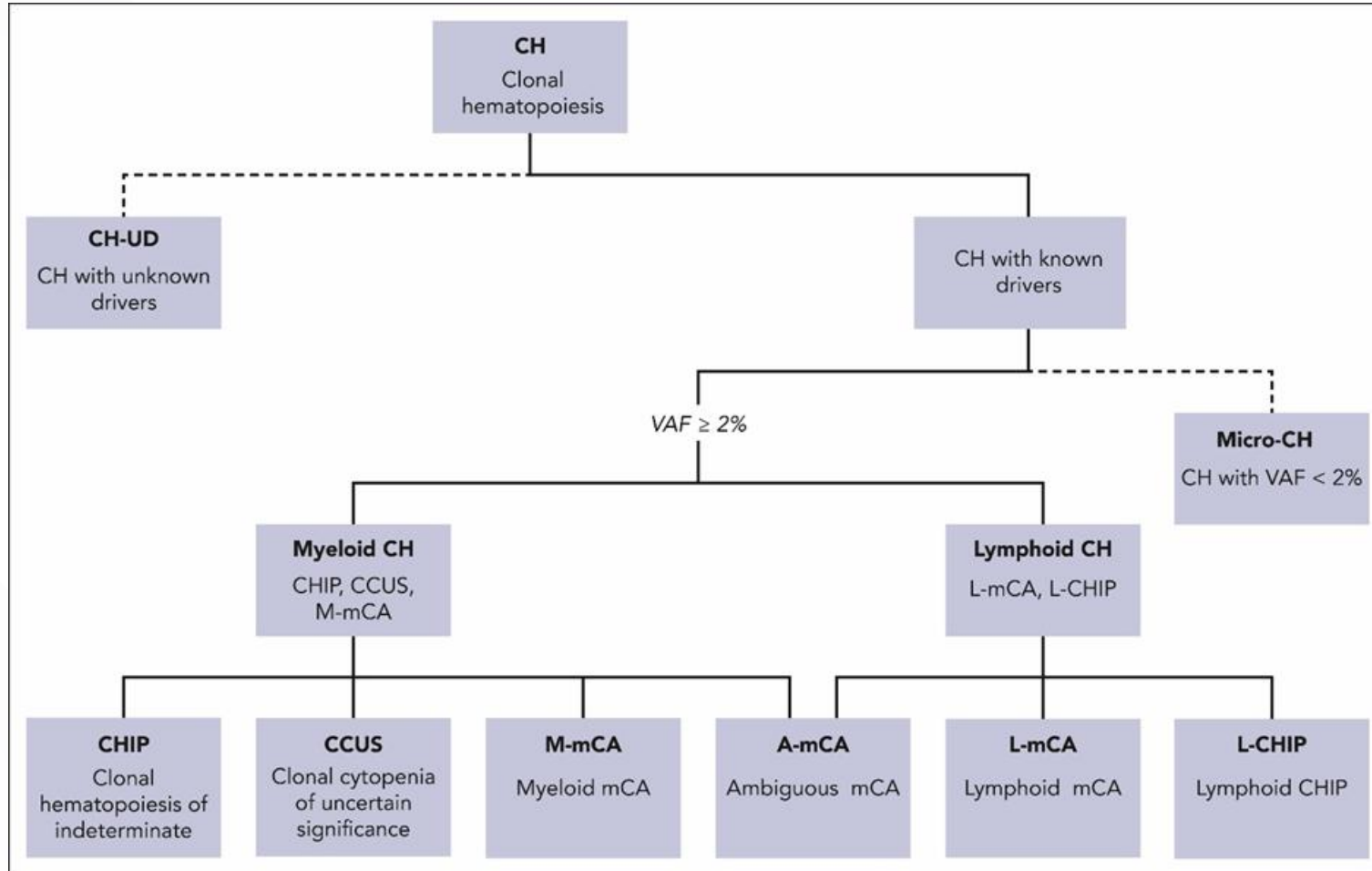


Age ≥ 70



Risk	Hazard Ratio (HR)
Hematologic Malignancy	11
All-Cause Mortality	1.4
Stroke	2.4

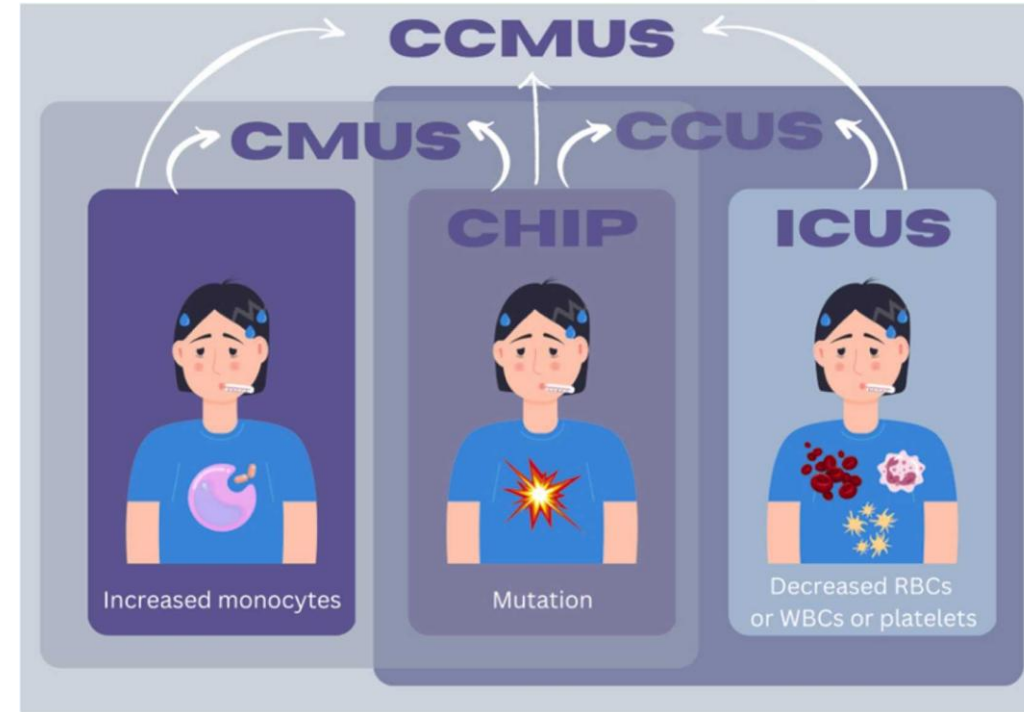
Clonal Hematopoiesis



Term	Key Point
CH	Expansion of clonal HSPCs
CHUD	CH with unknown drivers
Myeloid CH	Known myeloid driver mutations (VAF $\geq 2\%$)
CHIP	Myeloid CH without cytopenias
CCUS	Myeloid CH with cytopenias
m-MCA	Myeloid CH from chromosomal alterations
Lymphoid CH	Known lymphoid driver mutations or mCAs
L-CHIP	Lymphoid CH (mutations, VAF $\geq 2\%$)
L-mCA	Lymphoid CH (chromosomal alterations)
Micro-CH	Low-abundance clones (VAF $< 2\%$)

Definitions of the Acronyms.

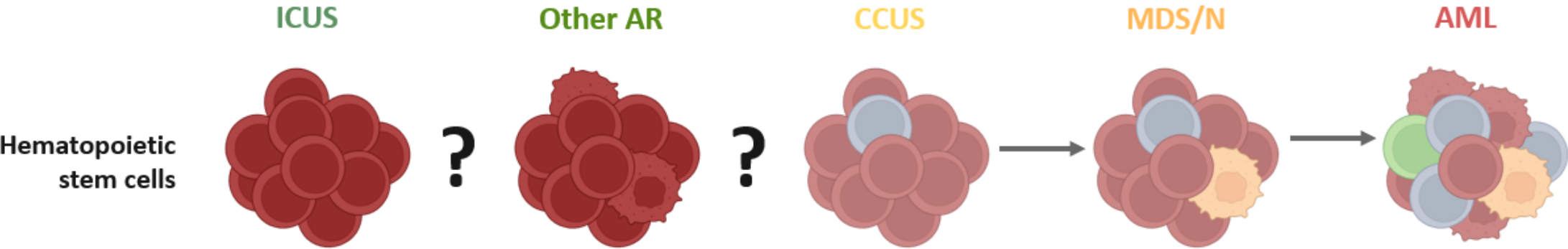
Cytopenias	Dysplasia	Clonal mutation =	ICUS Idiopathic cytopenia of uncertain significance
Cytopenias	Dysplasia	Clonal mutation =	CHIP Clonal Hematopoiesis Of Indeterminate Potential
Cytopenias	Dysplasia	Clonal mutation =	CCUS Clonal cytopenia of uncertain significance
Cytopenias	Dysplasia	Clonal mutation =	IDUS Idiopathic dysplasia of uncertain significance



CHIP+ increased monocytes= CMUS
clonal monocytosis of undetermined significance

CCUS+ increased monocytes= CCMUS
clonal cytopenia and monocytosis of undetermined significance

Progression to an overt myeloid malignancy



	Idiopathic Cytopenias	Other At-Risk	Clonal Cytopenias	Myelodysplastic Syndromes	Acute Myeloid Leukemia
Mutation	No	Maybe	Yes	Yes	Yes
Cytopenia	Yes	Maybe	Yes	Yes	Yes
Dysplasia	No	Yes	No	Yes	Yes
Blasts	< 5%	< 5%	< 5%	< 5 – 19%	> 20%
5-yr survival	?	?	62%	38% (≥65y 35%)	32% (≥65y 11%)



Træden et al. *Blood* 2023; SEER MDS 2014-2020; SEER AML 2014-2020 (Image courtesy of Dr. Nancy Gillis)

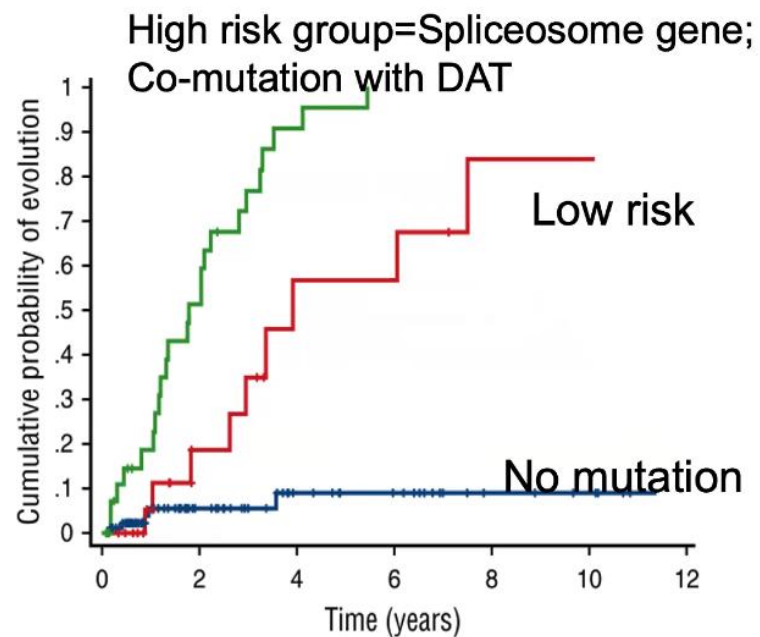
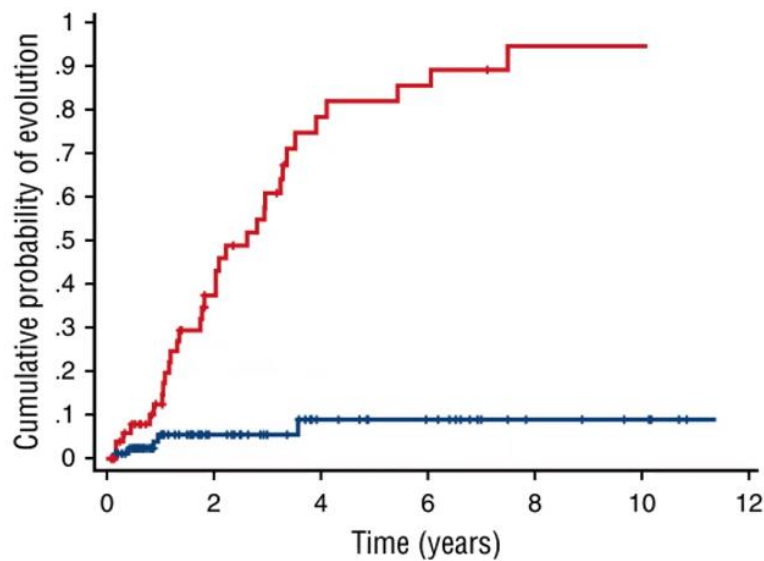
Who is at the highest risk?

Risk Stratification



Who is at risk of progression to myeloid disease?

Early Identifiers of Risk with CH



873 patients

**Risk of Progression
(10-year period)**

ICUS ~9%

CCUS ~82%

Peripheral blood profiling → ≥ 2 mutations or VAF $\geq 10\%$ = high risk

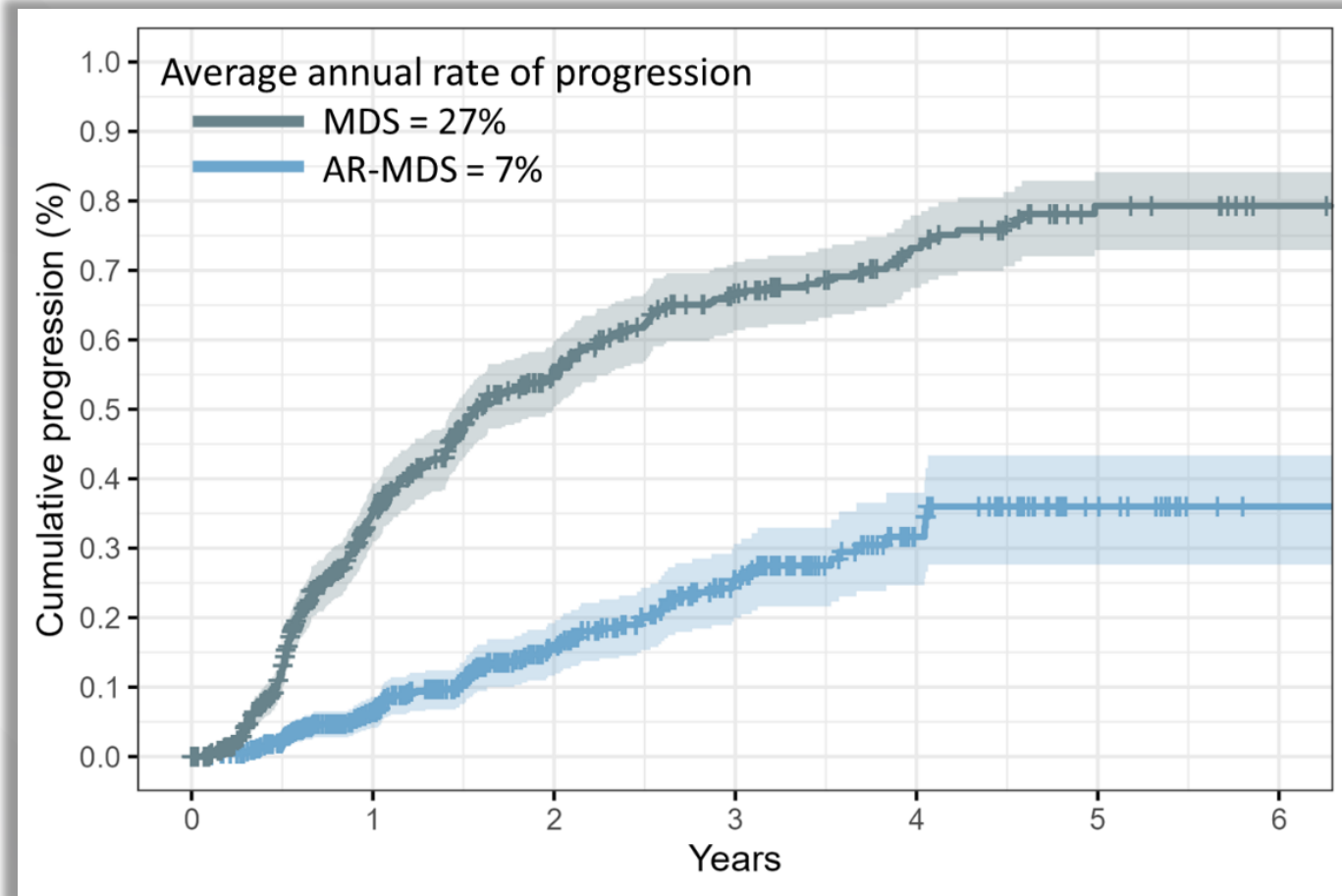
Spliceosome mutations → highly predictive; TET2/DNMT3A/ASXL1 less specific

Clonal cytopenia → 14 \times risk

High-risk patterns → 95% 5-year progression (MDS like)

Mutation analysis → better accuracy, noninvasive diagnosis; larger panels → higher negative predictive value

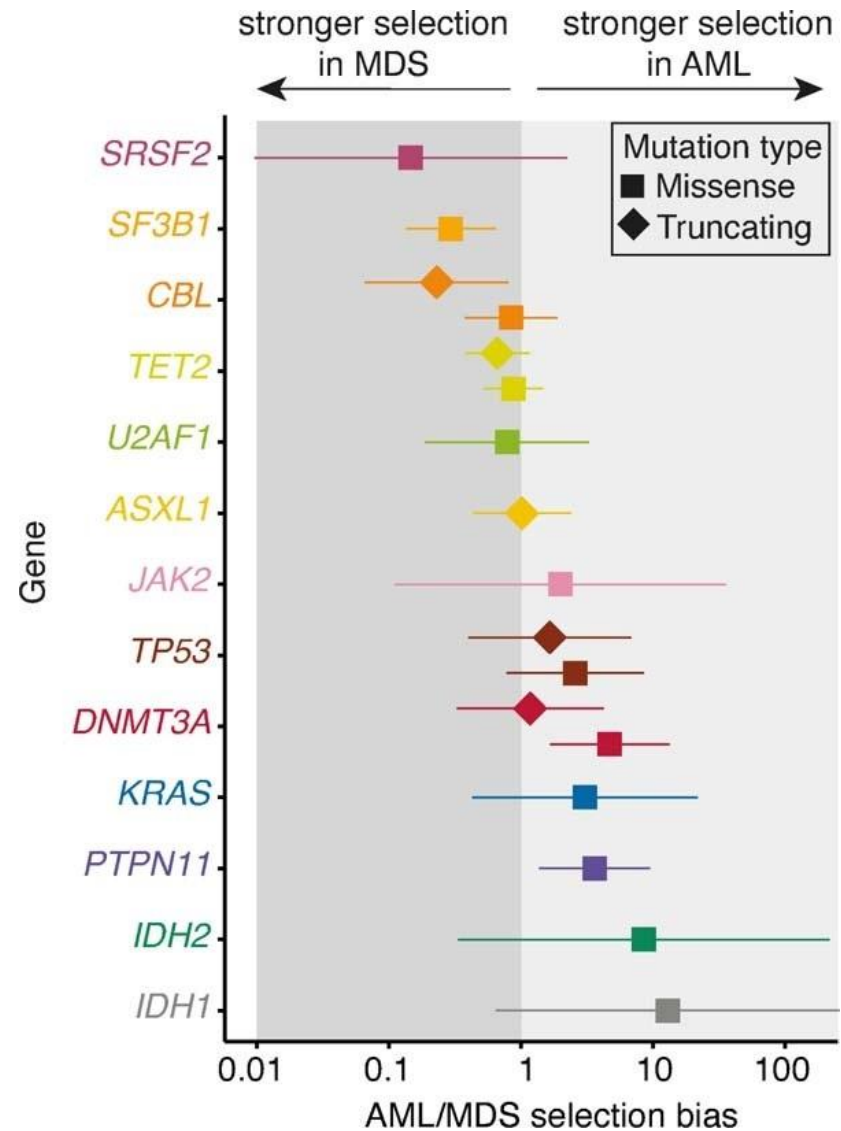
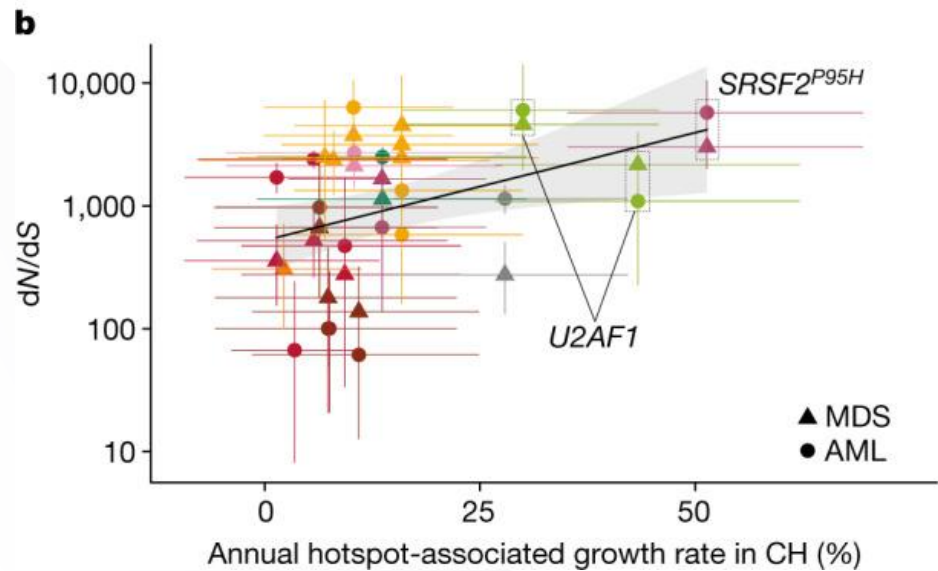
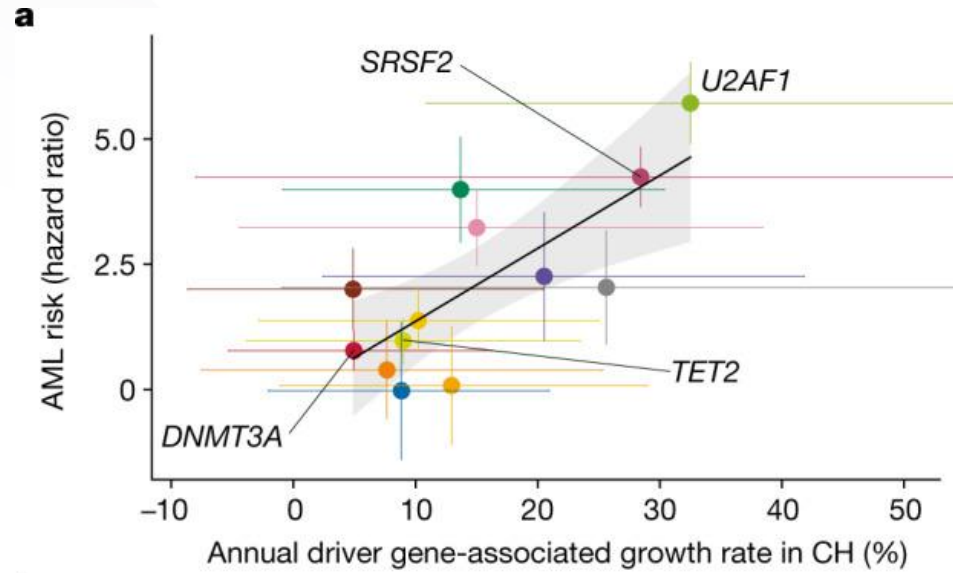
Data From the MDS Natural History Study



At-risk MDS (AR-MDS) = CCUS or cytopenia + (dysplasia or abnormal karyotype)

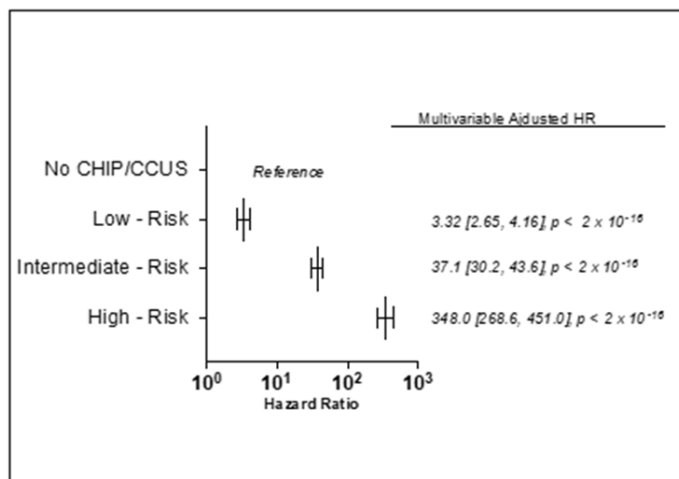
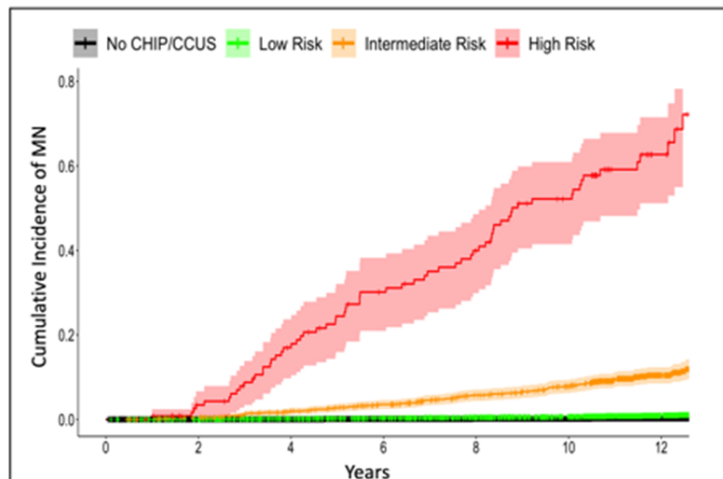
Progression: Worsening disease / advanced diagnosis, change in disease-directed therapy due to worsening disease (including HCT), increase in transfusion dependency, disease-related death

Mutation specific growth and pathogenicity



Clonal Hematopoiesis Risk Score

CHRS defines 3 distinct risk strata for CHIP/CCUS



<http://www.chrsapp.com/>

Clonal Hematopoiesis Risk Score (CHRS) Calculator

Patient Characteristics

CHIP or CCUS:

Number of mutations:

High risk mutations:

Maximum VAF:

Mean corpuscular volume (MCV):

Red cell distribution width (RDW):

Age:

[About this calculator](#)

Score
11.00

Cumulative Incidence of MN: 100%, 75%, 50%, 25%, 0%

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%

Model performance: (C- index)

- UKB derivation cohort: 0.807
- UKB validation cohort: 0.799

Weeks et al. NEJM Evidence 2023

Clonal cytopenia risk score (CCRS)

Real World

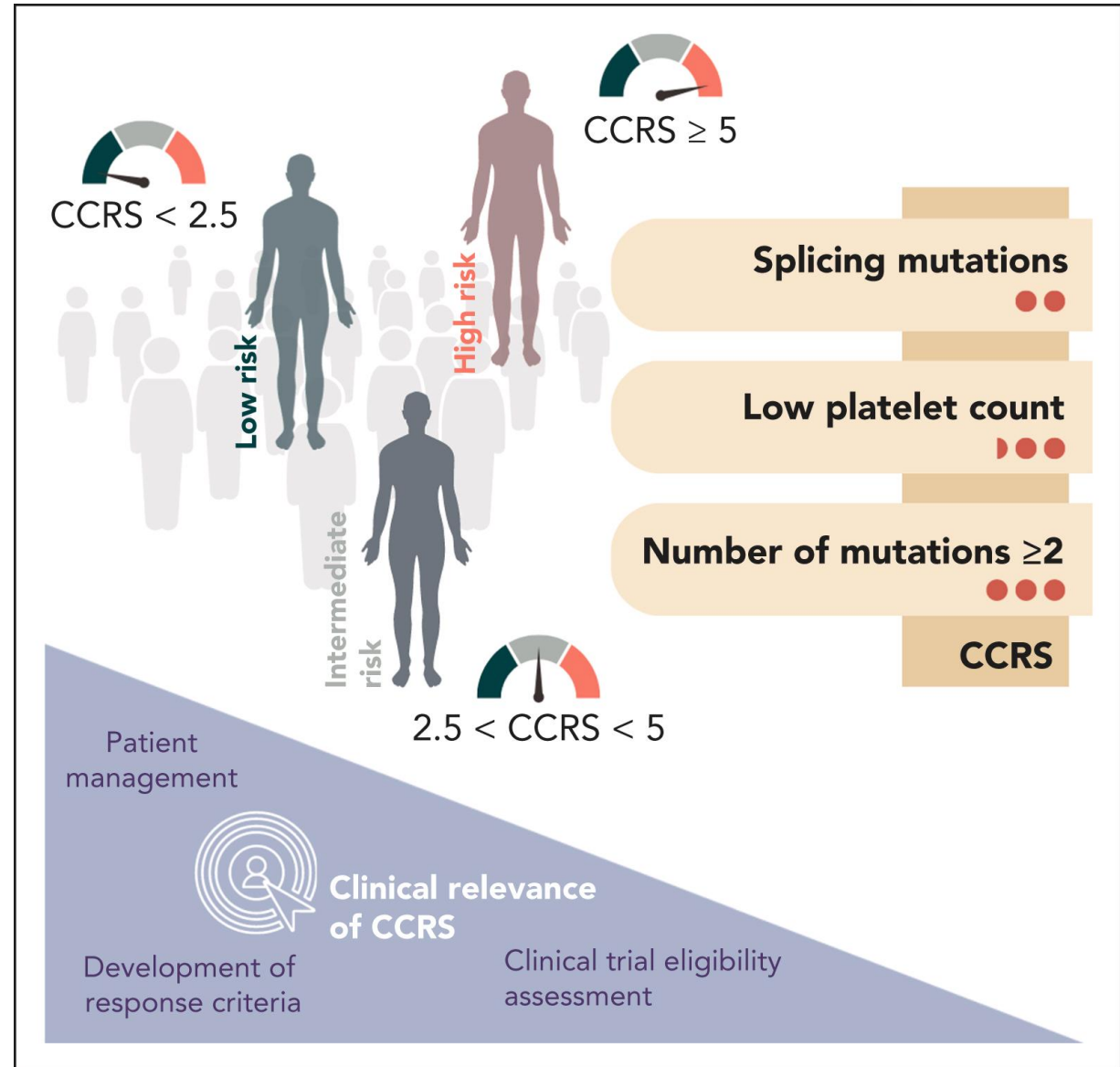
17 academic sites → 3 key prognostic factors

Prognostic Factors:

- splicing mutations (score = 2 points)
- platelet count $<100 \times 10^9/L$ (score = 2.5 points)
- ≥ 2 mutations (score = 3 points)

2-year cumulative risk of myeloid malignancy (P <.0001)

- low risk (6.4%)
- intermediate risk (14.1%)
- high risk (37.2%)



Interventional Opportunities



Thoughtful testing

There is currently no data to support screening for CHIP/CCUS outside of a research setting

Patient perspectives on testing for clonal hematopoiesis of indeterminate potential

How do patients feel about CHIP testing?



- Survey sent to young women ≤ 40 years of age with a history of early breast cancer (n = 642)
- Participants marked their interest in CHIP testing after being presented with a hypothetical patient story and 5 scenarios

Interest in CHIP testing for hypothetical patient?



after being presented with:

- CHIP-associated risks
- Dedicated CHIP clinic
- Hypothetical CHIP treatment



after being presented with:

- Population-based 10 year risks
- Current CHIP management

Interest in CHIP testing for self?



75.8%

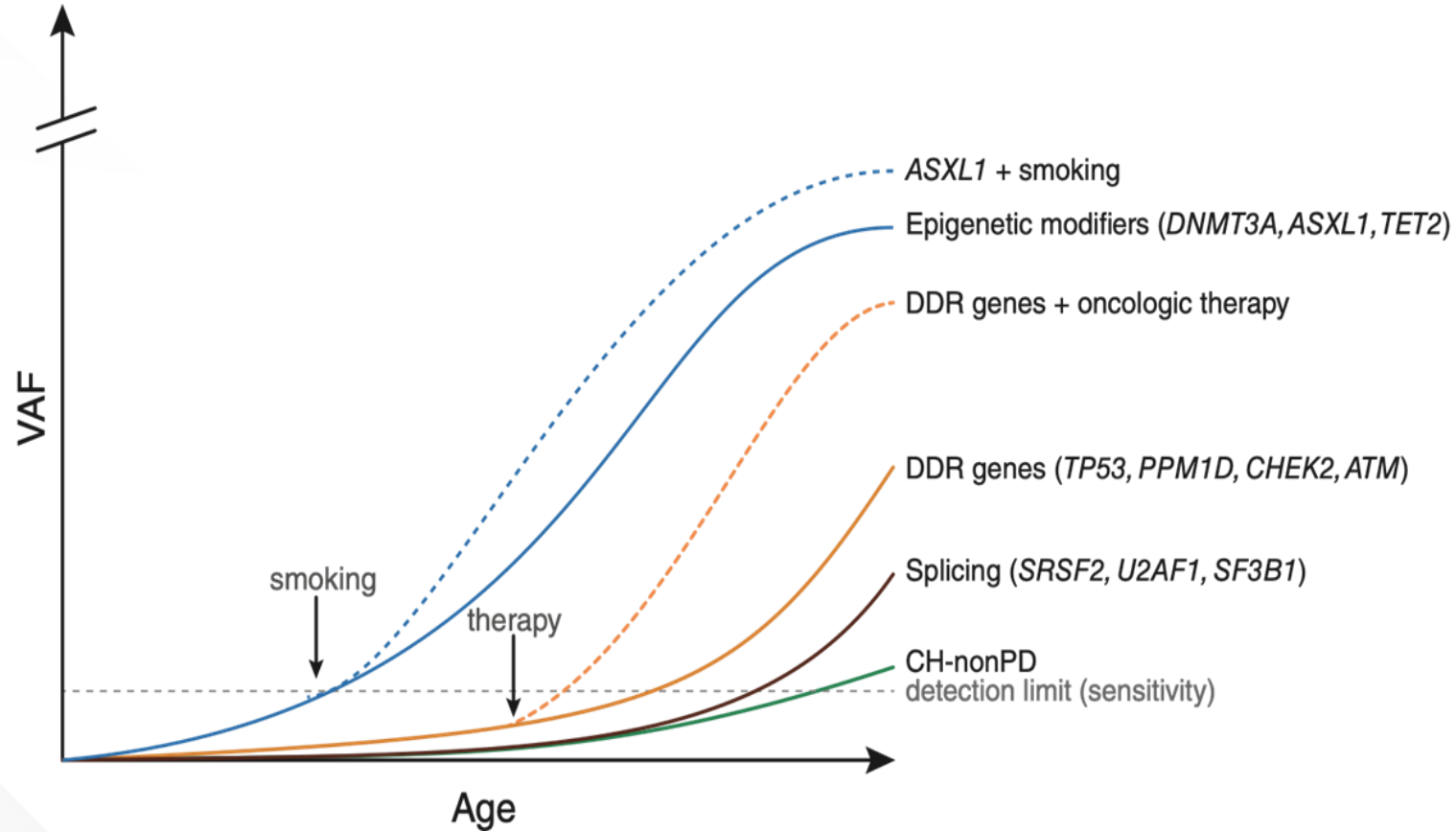


28.2% reported moderate anxiety after learning about CHIP

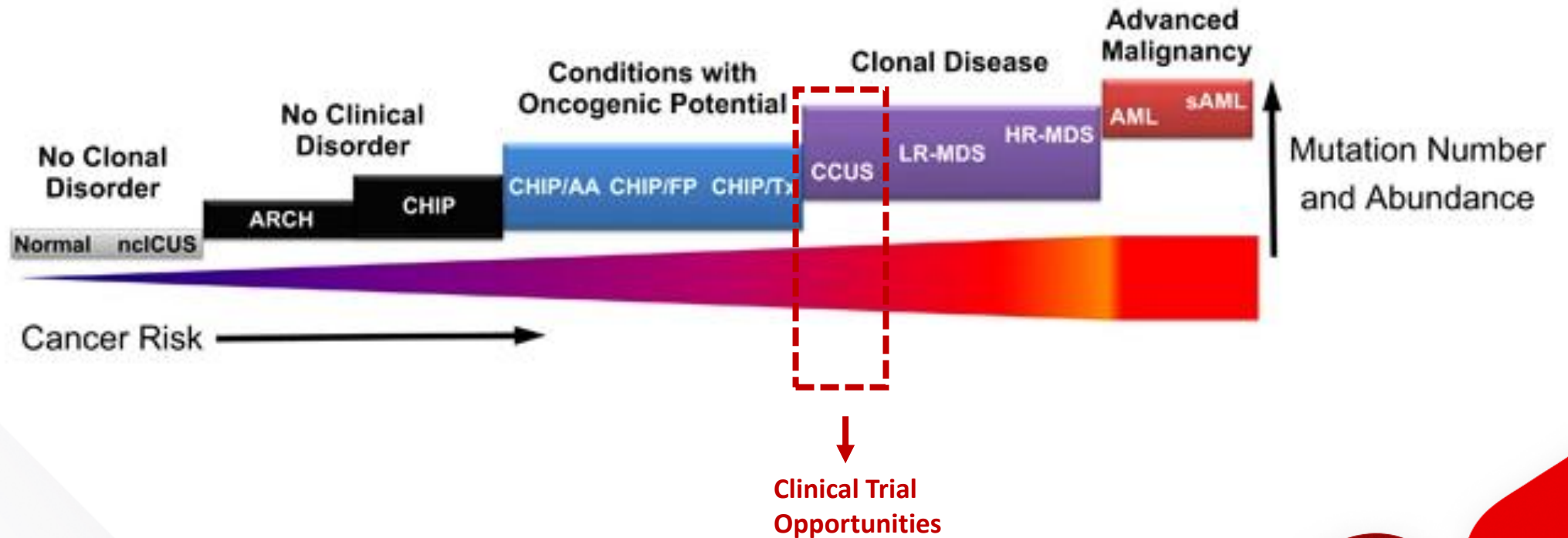
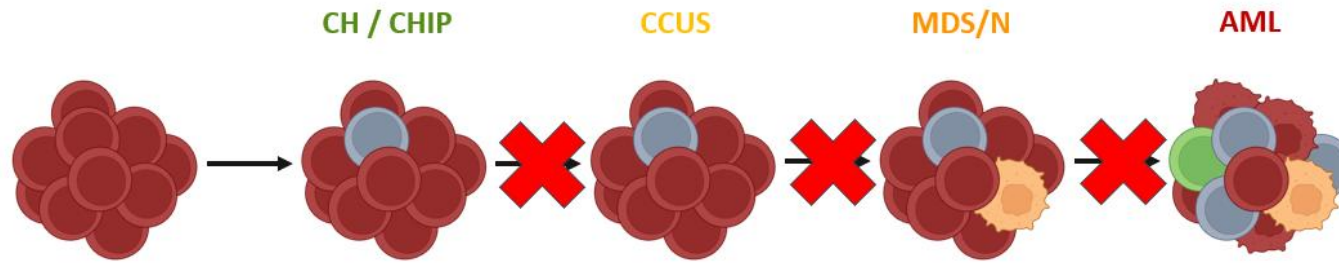
Most young survivors favored CHIP testing mainly influenced by risks and potential management strategies



Consider the underlying risk factors/ clinical context



Where are the Prevention Strategies?

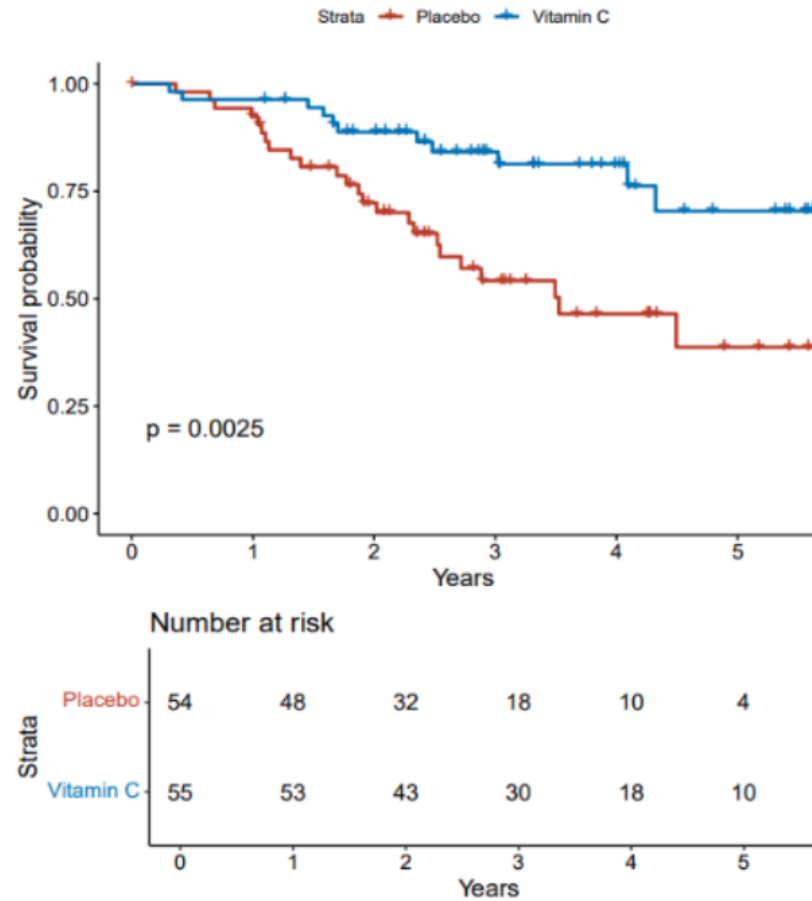


Clinical Trials for CCUS

Study Name	NCT Number	Interventional Drug
Early Intervention in High Risk CCUS	NCT06802146	Decitabine/cedazuridine
Enasidenib for Patients With Clonal Cytopenia of Undetermined Significance and Mutations in IDH2	NCT06240754	Enasidenib
Ivosidenib for Patients With Clonal Cytopenia of Undetermined Significance and Mutations in IDH1	NCT05030441	Ivosidenib
Statins in Patients With CCUS and Myelodysplastic Syndromes (MDS)	NCT05483010	Atorvastatin, Rosuvastatin
Canakinumab for the Prevention of Progression to Cancer in Patients With Clonal Cytopenias of Unknown Significance (IMPACT Study)	NCT05641831	Canakinumab
Luspatercept for Clonal Cytopenias of Uncertain Significance	NCT06788691	Luspatercept
Curcumin to Improve Inflammation and Symptoms in Patients With CCUS, Low Risk MDS, and Myeloproliferative Neoplasms	NCT06063486	Curcumin supplement
Repurposing Metformin as a Leukemia-preventive Drug in CCUS and LR-MDS	NCT04741945	Metformin
Ascorbic Acid and Chemotherapy for the Treatment of Relapsed or Refractory Lymphoma, CCUS, and Chronic Myelomonocytic Leukemia	NCT03418038	Ascorbic acid for CCUS

Vit C in CCUS + low grade myeloid malignancies

Figure 1. Kaplan-Meier curve for overall survival in the group of patients treated with oral vitamin C 1000 mg/day and placebo, respectively, for 12 months.



Keywords: CCUS, MDS, Randomized, Myeloid malignancies

Is “high risk” CCUS just MDS?

Dataset Analysis:

National MDS Natural History Study.

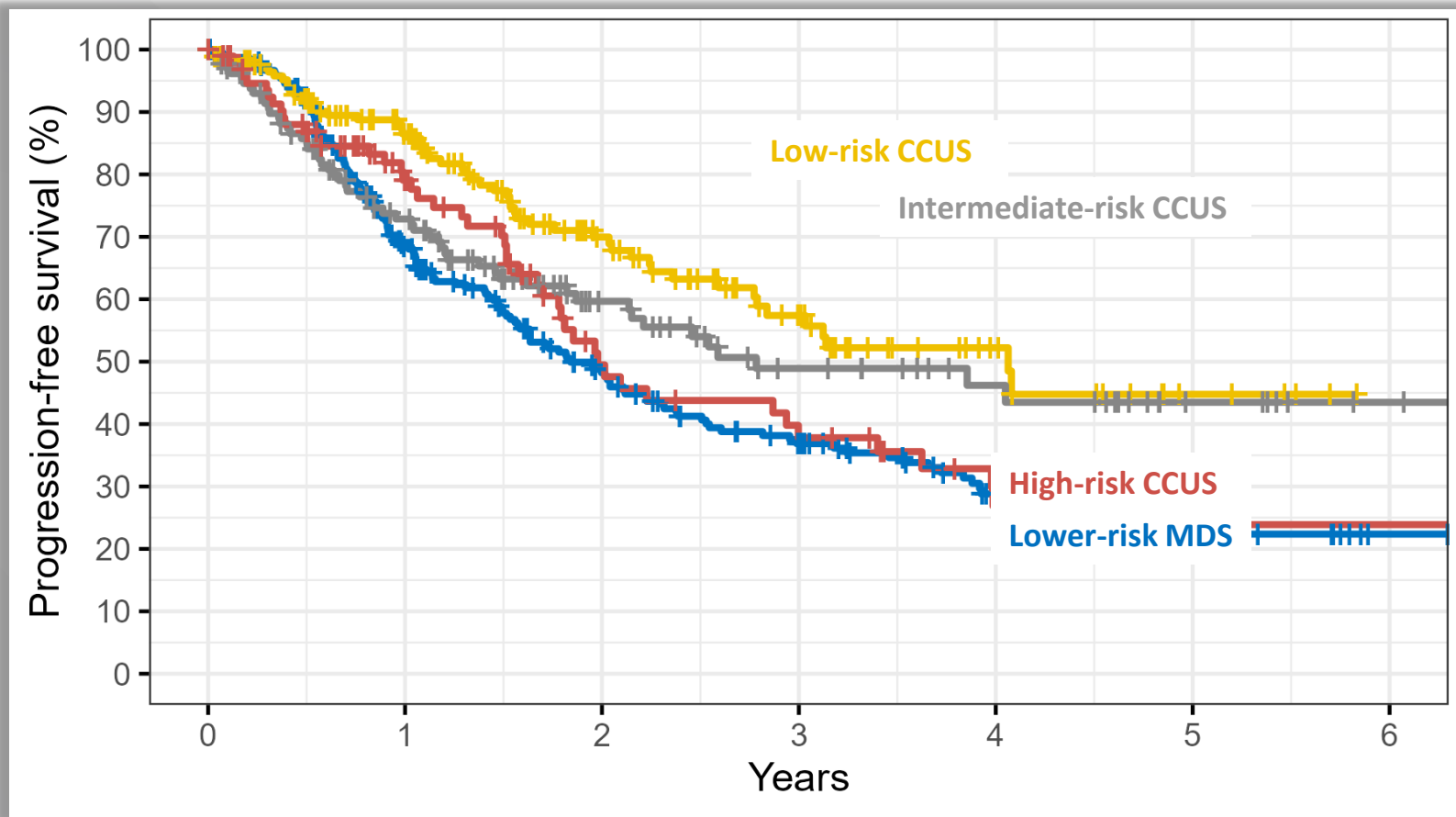
Stratified by CHRS and CCRS

Results:

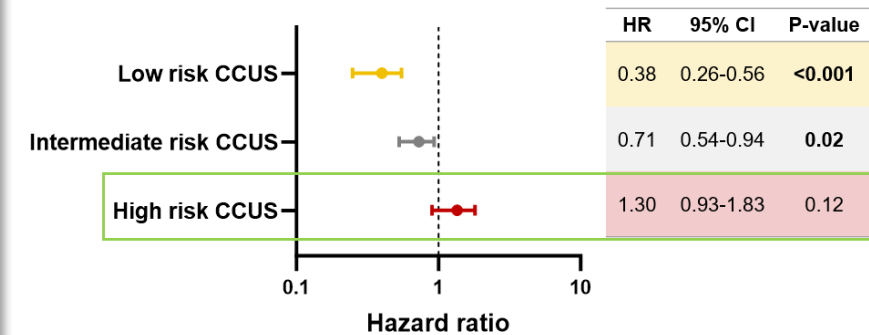
Low and intermediate-risk CCUS had better PFS and OS compared to LR-MDS.

High-risk CCUS had similar outcomes to LR-MDS.

Progression Free Survival

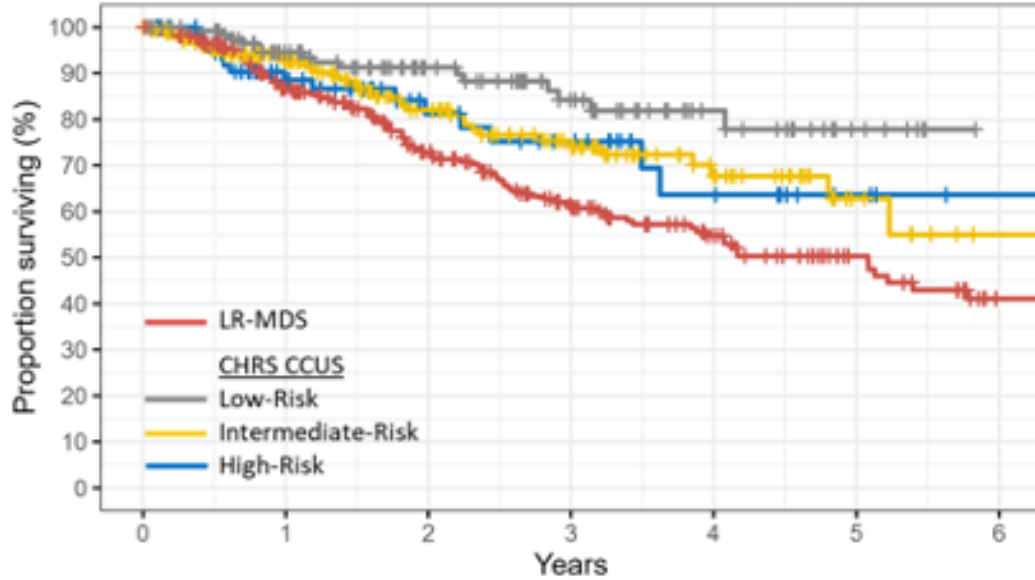


Risk classified based on **CCRS** (for CCUS), and **IPSS-R** (for MDS)

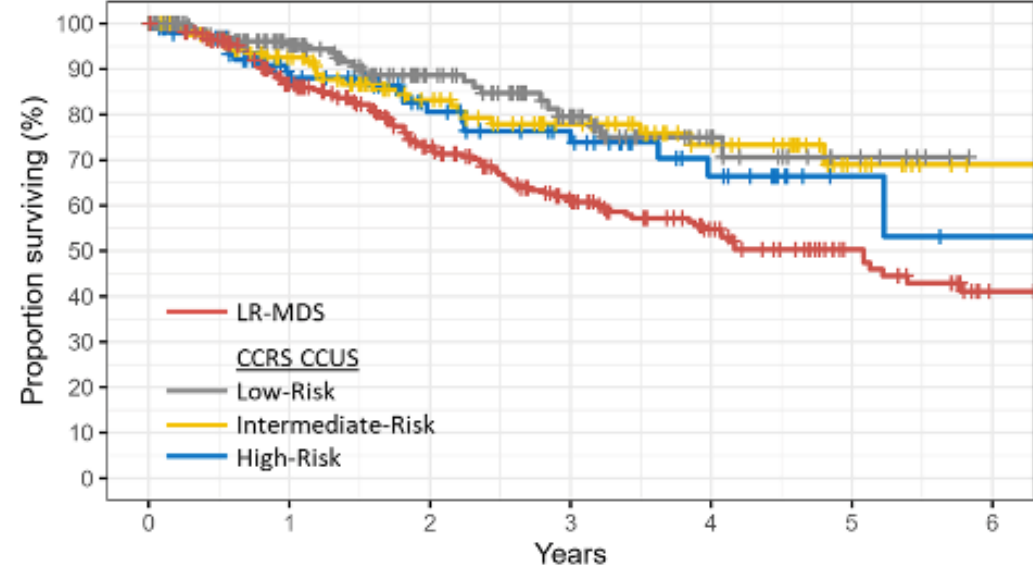


High risk CCUS and Lower-risk MDS
have similar progression risk

Overall Survival

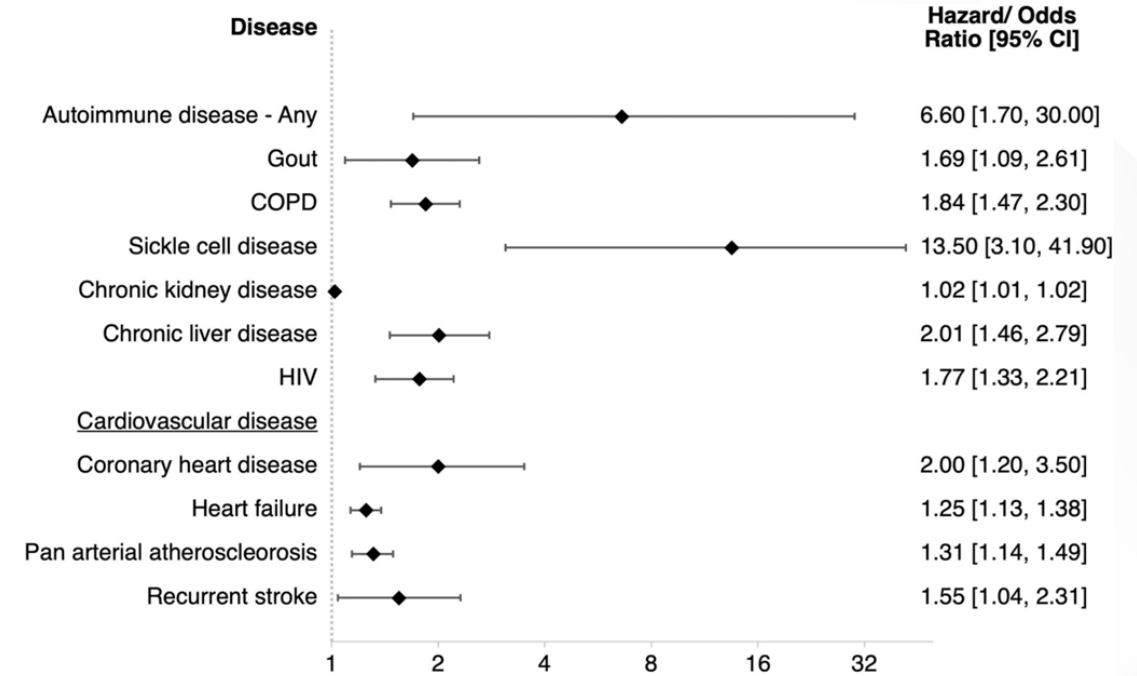
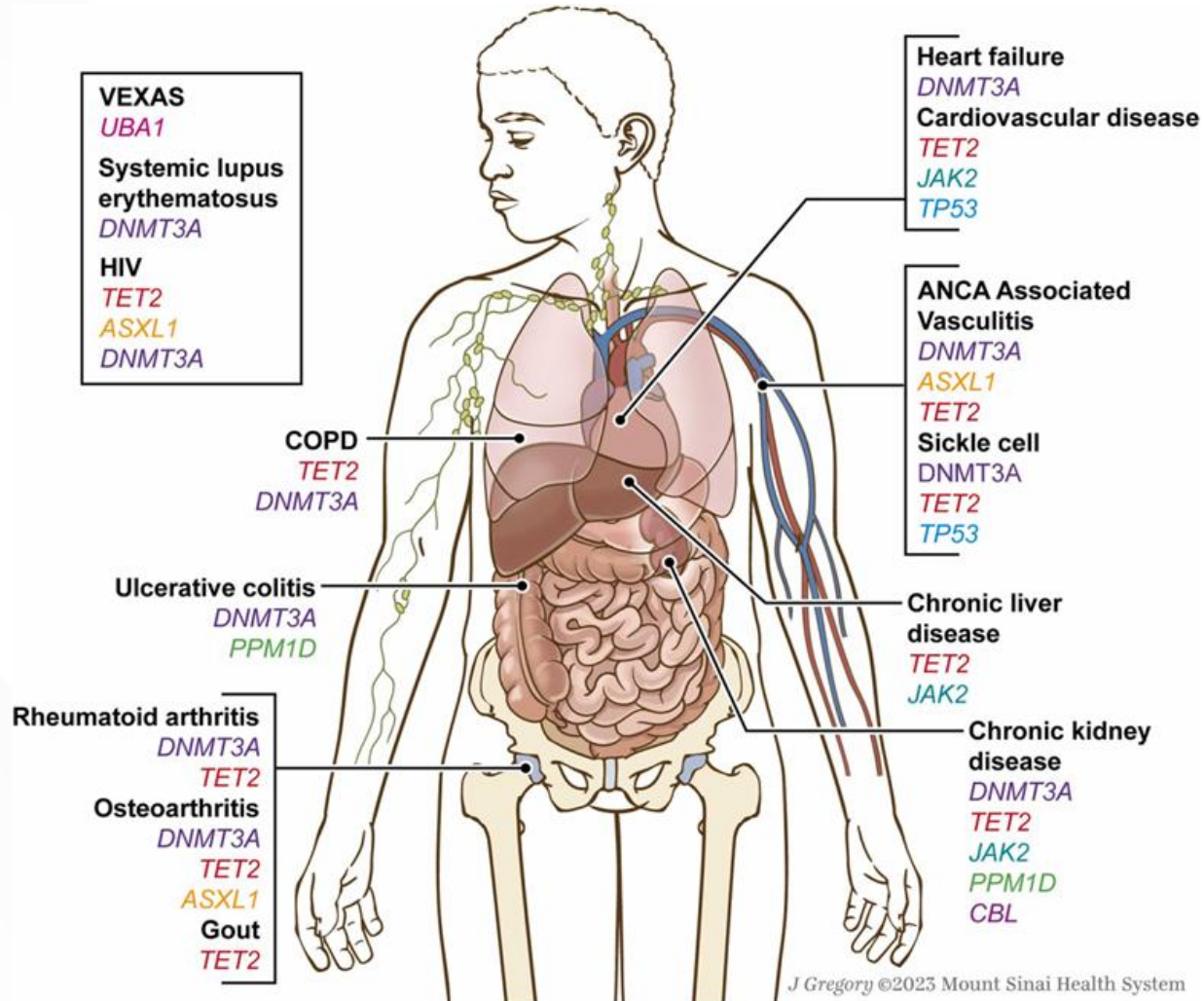


	CHRS CCUS vs LR-MDS	
CCUS Risk Category	HR	P-value
Low-Risk	0.35 (0.20-0.60)	< 0.001
Intermediate-Risk	0.63 (0.43-0.92)	0.017
High-Risk	0.65 (0.38-1.12)	0.119



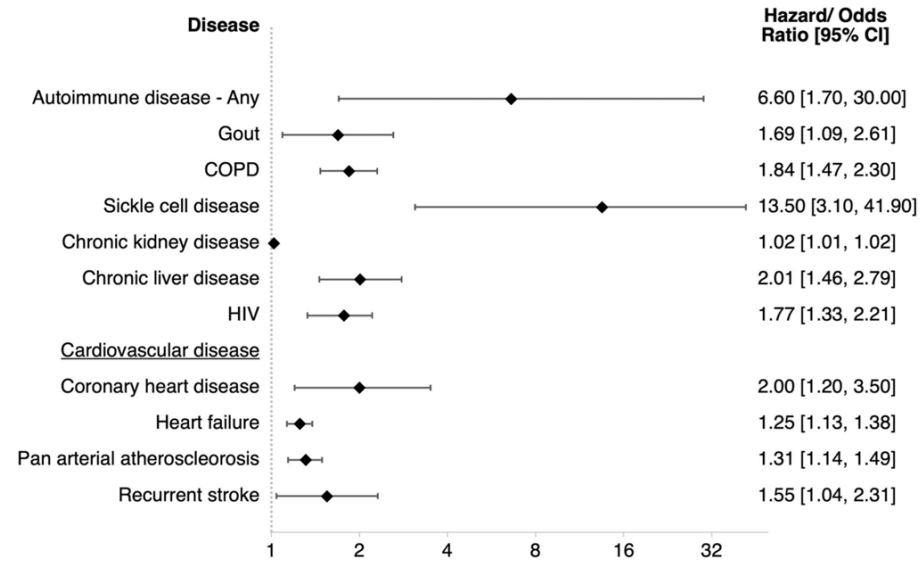
	CCRS CCUS vs LR-MDS	
CCUS Risk Category	HR	P-value
Low-Risk	0.45 (0.29-0.71)	< 0.001
Intermediate-Risk	0.53 (0.34-0.82)	0.004
High-Risk	0.64 (0.40-1.03)	0.068

Implications Beyond Myeloid Malignancies

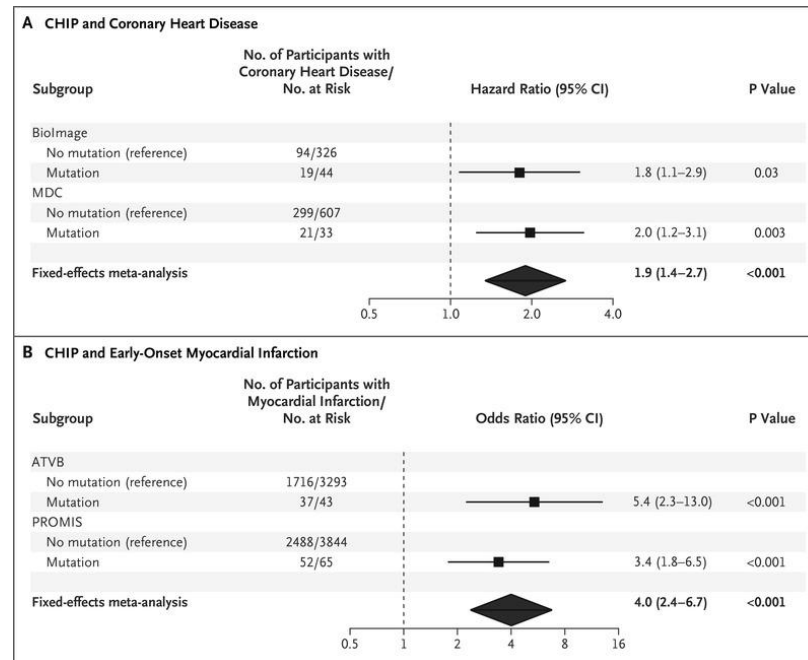


Non-malignant Implications of CH

All- Cause Mortality Increased



Atherosclerotic Cardiovascular disease is a well studied area



PESA Study: Progression of Early Subclinical Atherosclerosis

Longitudinal study (>20 years)
Large: N~4200 (~1500 women)
Middle-aged: 40-54 yrs at enrollment
Asymptomatic: Free of clinical CVD

DEEP PHENOTYPING

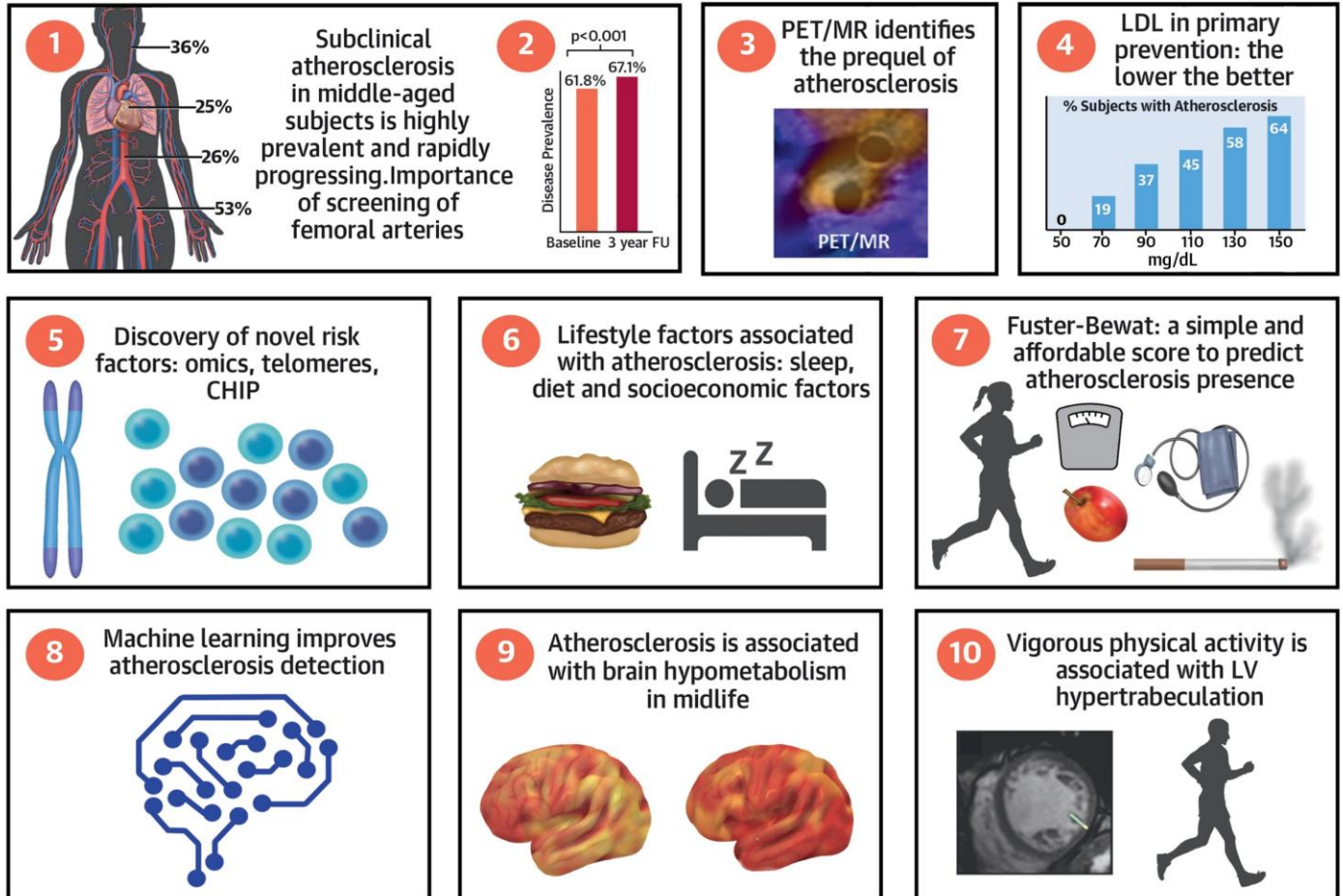
>4000 parameters related to:

- Cardiometabolic risk factors
- Lifestyle (diet, sleep pattern, physical activity, tobacco,...) & psychosocial stress
- Hematological & inflammatory parameters
- Leukocyte telomere length & attrition rate

MULTI-OMICS

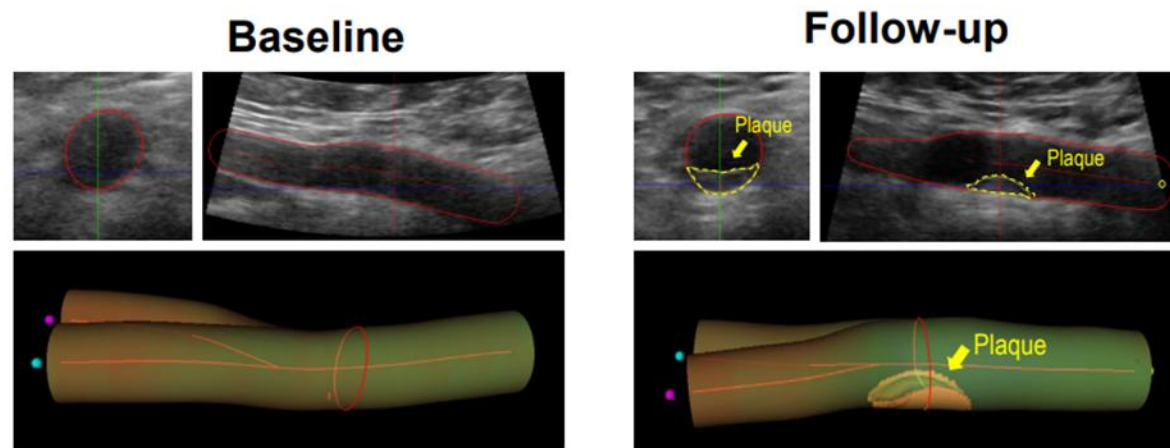
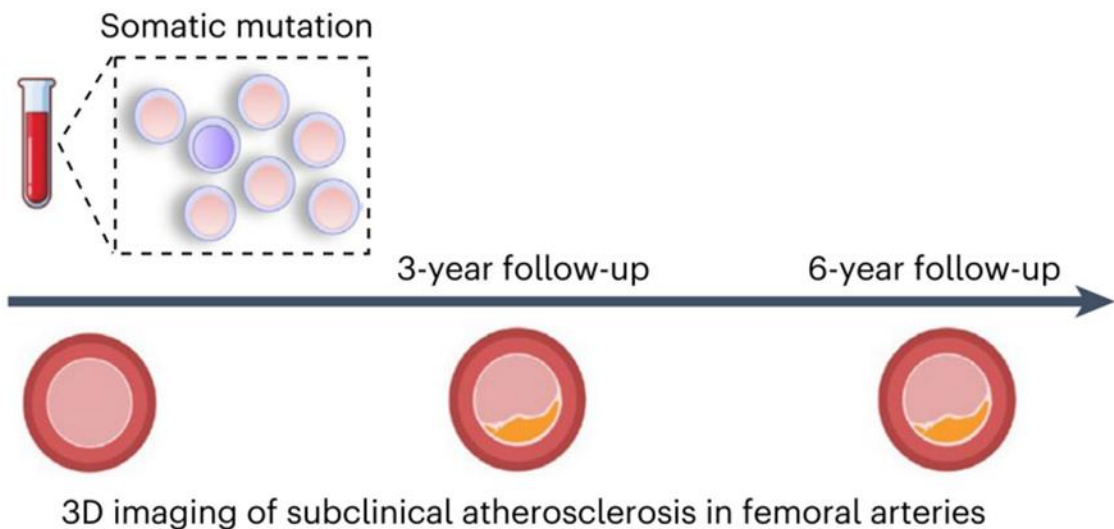
- Genomics
- Transcriptomics (mRNA and miRNA seq)
- Proteomics
- Metabolomics
- Methyloomics

CENTRAL ILLUSTRATION: The 10 Most Important Findings of the PESA Study: Key Messages From 10 Selected Contributions of PESA



Ibanez, B. et al. J Am Coll Cardiol. 2021;78(2):156-79.

CHIP is associated with **de novo subclinical atherosclerosis**



De novo atherosclerosis in femoral arteries at 3-year follow-up				
	Yes/No		OR [95% CI]	p-value
No CHIP (Ref.)	183/1,651			
CHIP mutations	76/437		1.56 (1.13–2.13)	0.006
CHIP mutations (VAF 0.2–2%)	52/332		1.37 (0.95–1.95)	0.081
CHIP mutations (VAF ≥2%)	24/105		2.16 (1.27–3.55)	0.003

*Adjusted for age, sex, CVRFs, and cumulative systemic burden of atherosclerosis

De novo atherosclerosis in femoral arteries at 3-year follow-up				
	Yes/No		OR [95% CI]	p-value
No CHIP (Ref.)	183/1,651			
<i>DNMT3A</i>	50/297		1.52 [1.04 ; 2.18]	0.025
<i>TET2</i>	31/222		1.85 [0.98 ; 3.29]	0.045
Other mutations	19/75		2.05 [1.24 ; 3.28]	0.004

Odds ratio

Colchicine?

Targeted
inhibitors?

CH

Targeted anti-
inflammatory
agents?

Metformin?

Micronutrient
supplementation?



Thank you!

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