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O que acontece antes do  
diagnóstico de SMD?  
ICUS? CCUS? CMUS? CCMUS?

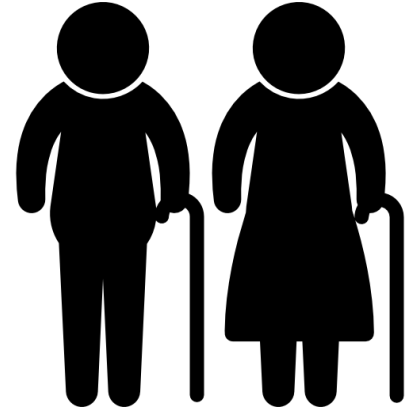


Silvia M.M. Magalhães  
Universidade Federal do Ceará  
2024

# AGING HEMATOPOIESIS

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- **cellularity**
- **immunesenescence** reduced production of lymphocytes  
relative increase in myeloid cell production (myeloid skewing)
- ***inflammaging***
- age-related predisposition to acquire **somatic mutations** in cancer related genes (VAF  $\geq 2\%$ ) in the absence of disease



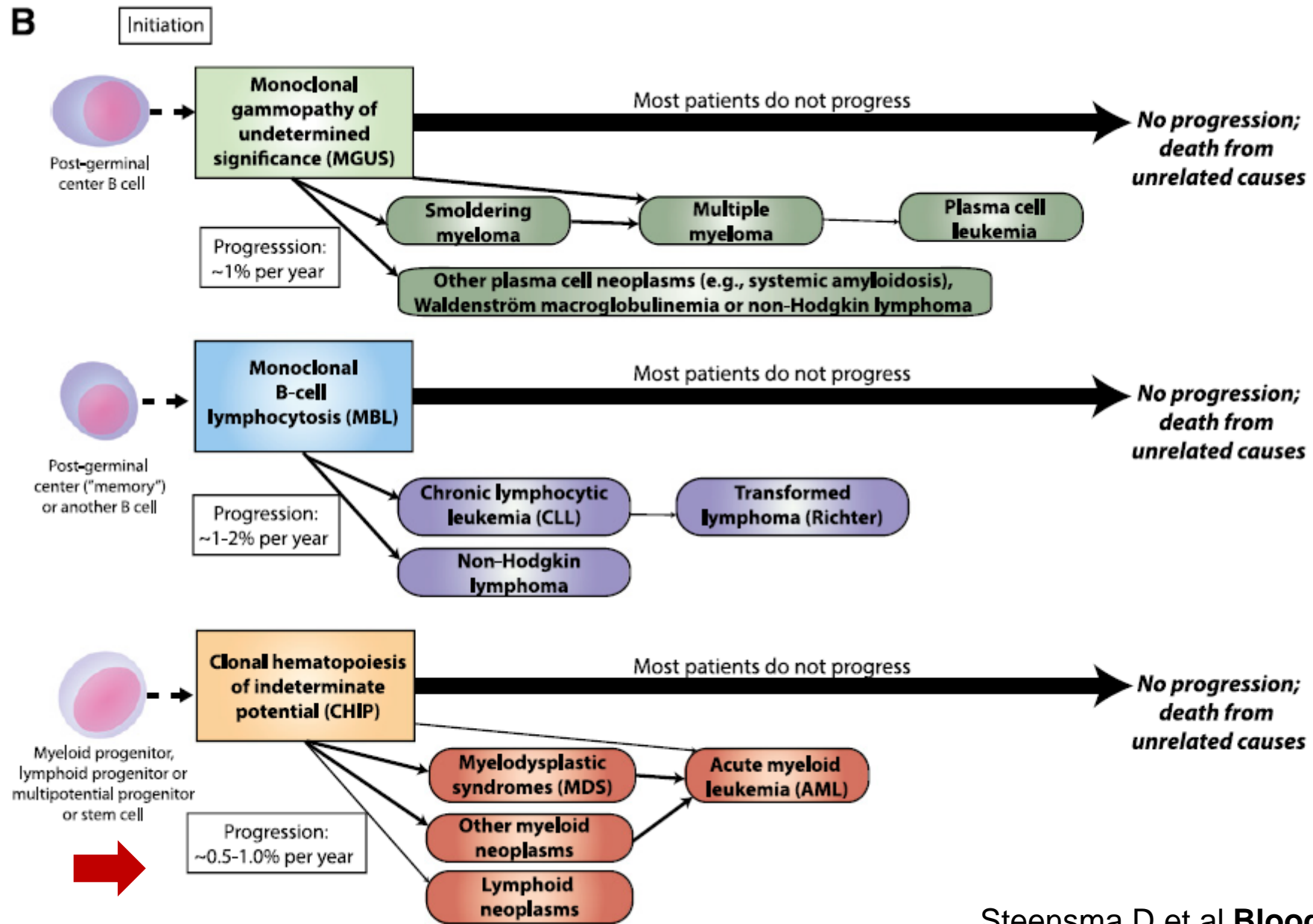
# CLONAL HEMATOPOIESIS

Presence of mutation in myeloid neoplasm related genes at a variant allele fraction (VAF)  $\geq 2\%$  in the absence of diagnosed blood disorder

## CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP)

Steensma DP, 2015



**B**

# CLONAL HEMATOPOIESIS

2014

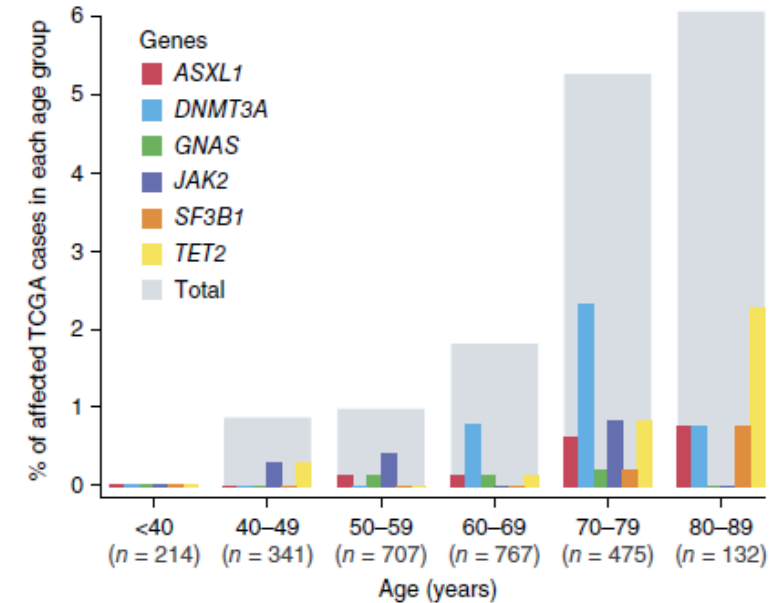
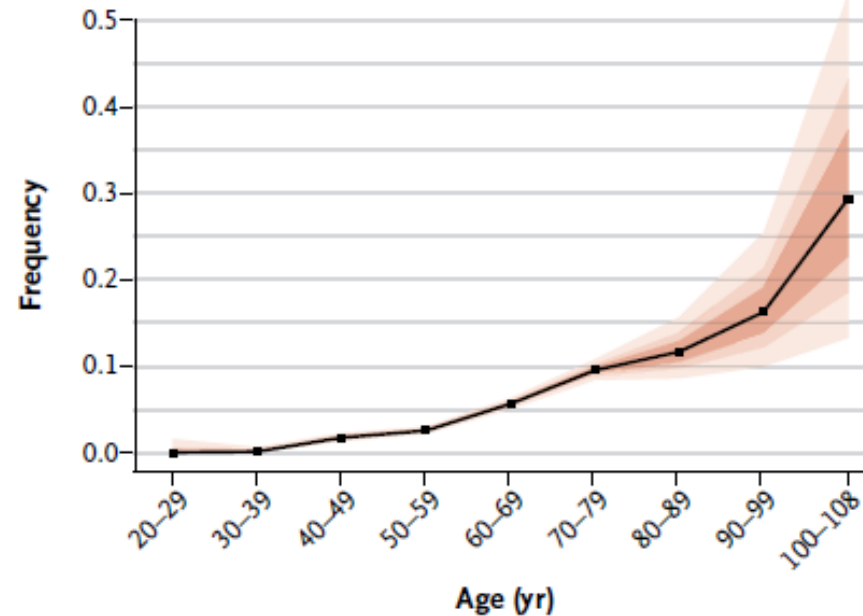
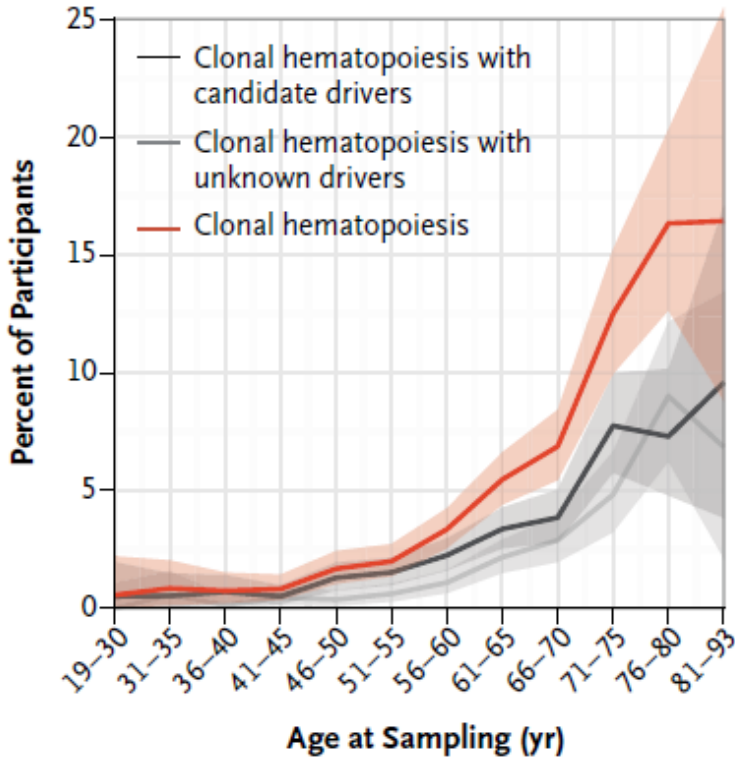
## SOMATIC MUTATIONS LEADING TO CLONAL OUTGROWTH OF HEMATOPOIETIC CELLS

Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. **Genovese G** et al **N Engl J Med**. 2014; 371: 2477.

Age-related clonal hematopoiesis associated with adverse outcomes. **Jaiswal S** et al **N Engl J Med**. 2014; 371: 2488.

Age-related mutations associated with clonal hematopoietic expansion and malignancies. **Xie M** et al **Nat Med**. 2014; 20 : 1472.

# PREVALENCE OF CLONAL HEMATOPOIESIS DURING AGING



DTA

Genovese G et al **N Engl J Med** 2014; 371:2477-8.

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

Xie M et al **Nat Med** 2014; 20:1472.


# ILL OR JUST OLD?

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# Association of clonal hematopoiesis mutations with clinical outcomes: A systematic review and meta-analysis

Malgorzata K. Nowakowska<sup>1</sup>  | Taebeom Kim<sup>2</sup> | Mikayla T. Thompson<sup>3</sup> |  
Kelly L. Bolton<sup>4</sup> | Anita Deswal<sup>5</sup> | Steven H. Lin<sup>6</sup> | Paul Scheet<sup>2</sup> |  
Mackenzie R. Wehner<sup>7,8</sup> | Kevin T. Nead<sup>2,6</sup>



# CLONAL HEMATOPOIESIS AND CLINICAL OUTCOMES

association of clonal hematopoiesis mutations with meta-analyzed clinical outcomes

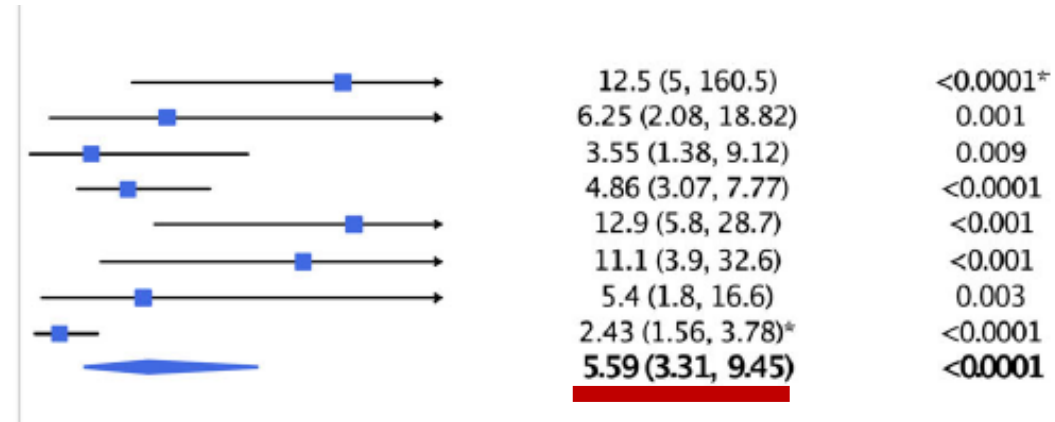
## Hematologic cancer

Abelson et al. 2018\*\*  
 Bick et al. 2020  
 Bick et al. 2020\*\*  
 Desai et al. 2018\*\*  
 Genovese et al. 2014\*\*  
 Jaiswal et al. 2014\*\*  
 Young et al. 2019\*\*  
 Zink et al. 2017\*\*

### Summary

Heterogeneity:  $Q = 18.73$ ,  $df = 6$ ,  $p = 0.0046$ ;  $I^2 = 0.68$

Acute myeloid leukemia  
 Myeloid leukemia  
 Myeloproliferative neoplasms  
 Acute myeloid leukemia  
 Hematologic cancer  
 Hematologic cancer  
 Acute myeloid leukemia  
 Hematologic cancer



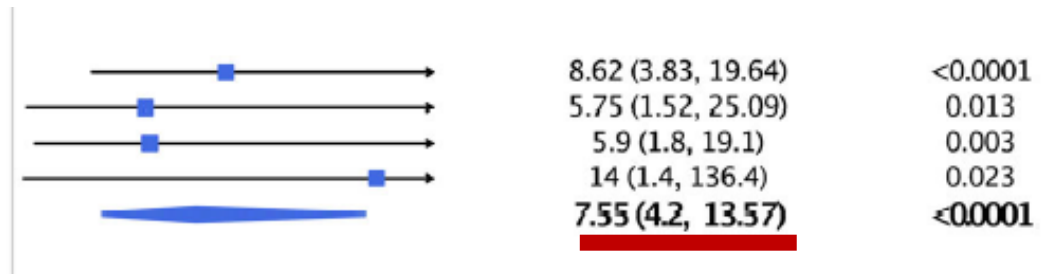
## Therapy-related myeloid neoplasm

Bolton et al. 2020\*\*  
 Gillis et al. 2017\*\*  
 Soerensen et al. 2020\*\*  
 Takahashi et al. 2017\*\*

### Summary

Heterogeneity:  $Q = 0.69$ ,  $df = 3$ ,  $p = 0.8749$ ;  $I^2 = 0$

Therapy-related myeloid neoplasm  
 Therapy-related myeloid neoplasm  
 Therapy-related myeloid neoplasm  
 Therapy-related myeloid neoplasm



# CLONAL HEMATOPOIESIS AND CLINICAL OUTCOMES

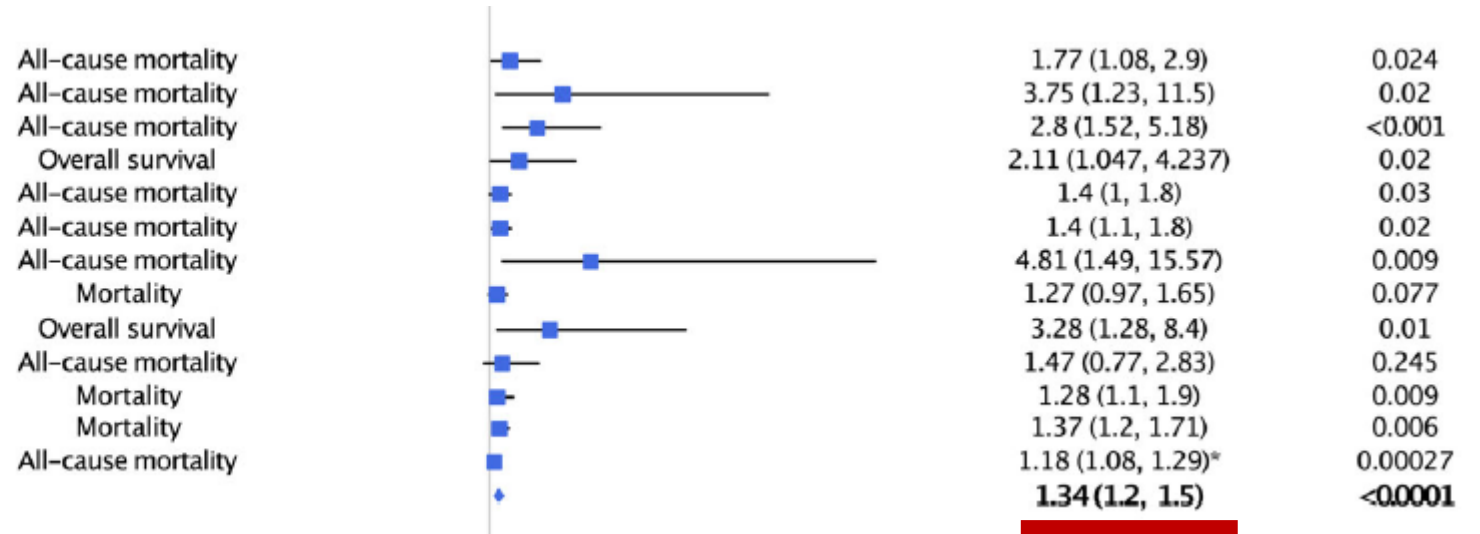
association of clonal hematopoiesis mutations with meta-analysed clinical outcomes

## Death

- Assmus et al. 2021\*\*
- Boucai et al. 2018\*\*
- Cremer et al. 2020
- Dorsheimer et al. 2019
- Genovese et al. 2014\*\*
- Jaiswal et al. 2014\*\*
- Mas-Peiro et al. 2020
- Nachun et al. 2021
- Okamura et al. 2021\*\*
- Pascual-Figal et al. 2021\*\*
- Rossi (Health & Anemia) et al. 2021\*\*
- Rossi (Monzino) et al. 2021\*\*
- Zink et al. 2017\*\*

## Summary

Heterogeneity:  $Q=13.82$ ,  $df=8$ ,  $p=0.0866$ ;  $I^2=0.42$



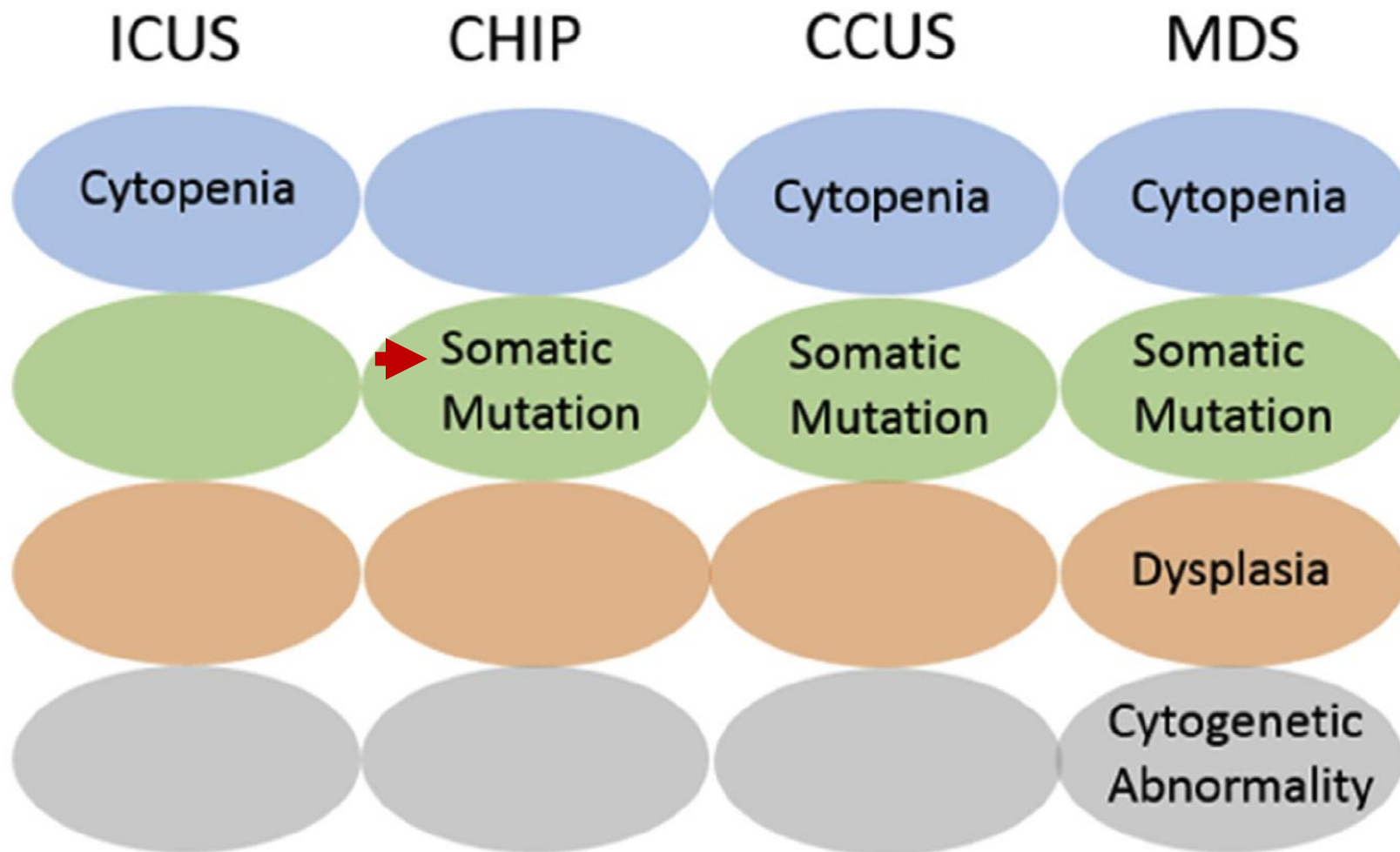
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# INDOLENT MYELOID HEMATOPOIETIC DISORDERS

ICUS CHIP CCUS CMUS CCMUS

cause  
contributor  
biomarker  
just correlated with age





→ More frequent somatic mutations:  
DNMT3A, TET2, ASXL1

GroarkeEM et al **Clin Geriatr Med** 2019;35: 285.

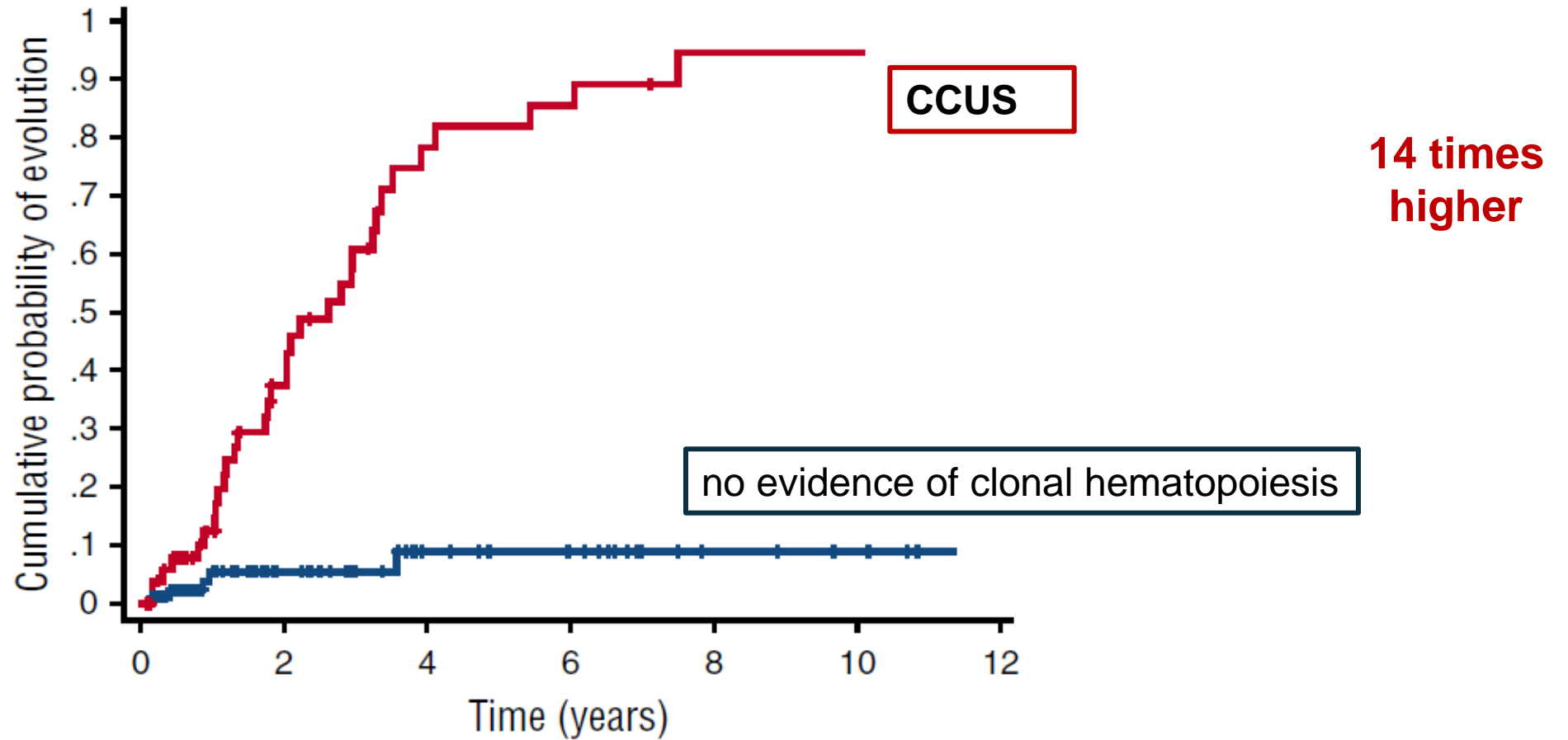


# CYTOPENIAS



cytopenias in older persons: a challenge in clinical practice

# CUMULATIVE PROBABILITY OF PROGRESSION TO MYELOID NEOPLASM ACCORDING TO MUTATION STATUS



Premalignant **clonal cytopenias** are classified similarly in the **ICC** and **WHO**

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**CMUS/CCMUS**

ICC, 2022

**clonal monocytosis of indeterminate significance**

presence of persistent **monocytosis** ( $\geq 0.5 \times 10^9/L$  of the WBC)

associated with a **somatic mutation** in the myeloid neoplasm related genes. If **cytopenia** is present it is called clonal cytopenia and monocytosis of undetermined significance (CCMUS).

This term has been coined in the new International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemia, 2022



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nature genetics

Article

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# Multiparameter prediction of myeloid neoplasia risk

By analyzing differences between ‘pre-MN’ and controls, a ‘MN-predict’ web application generated time-dependent predictions with the input of **basic blood tests** and **genetic** data

Many individuals that develop myeloid neoplasms can be identified years in advance and provides a framework for disease-specific prognostication

454,340 UKB participants

Gu M et al **Nature Genetics** 2023; 55: 1523

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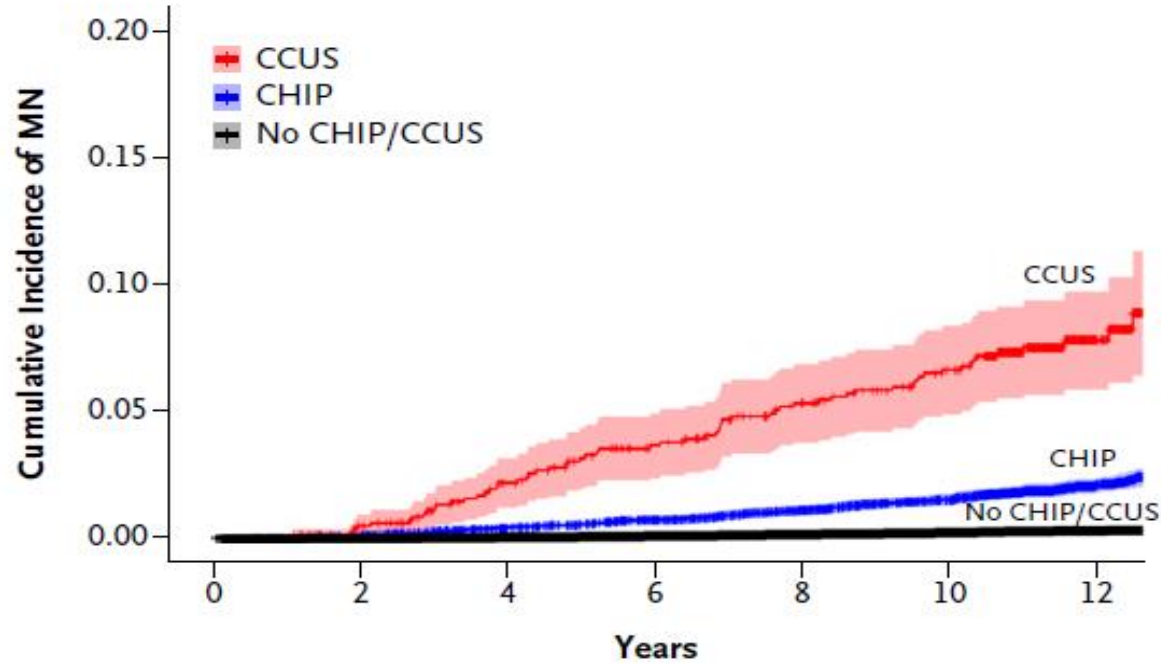
ORIGINAL ARTICLE

# Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis

Healthy UK Biobank participants n= 438,890 in separate derivation and validation cohorts

Weeks LD et al **NEJM Evid** 2023; 2(5): 101056/EVIDoa2200310.

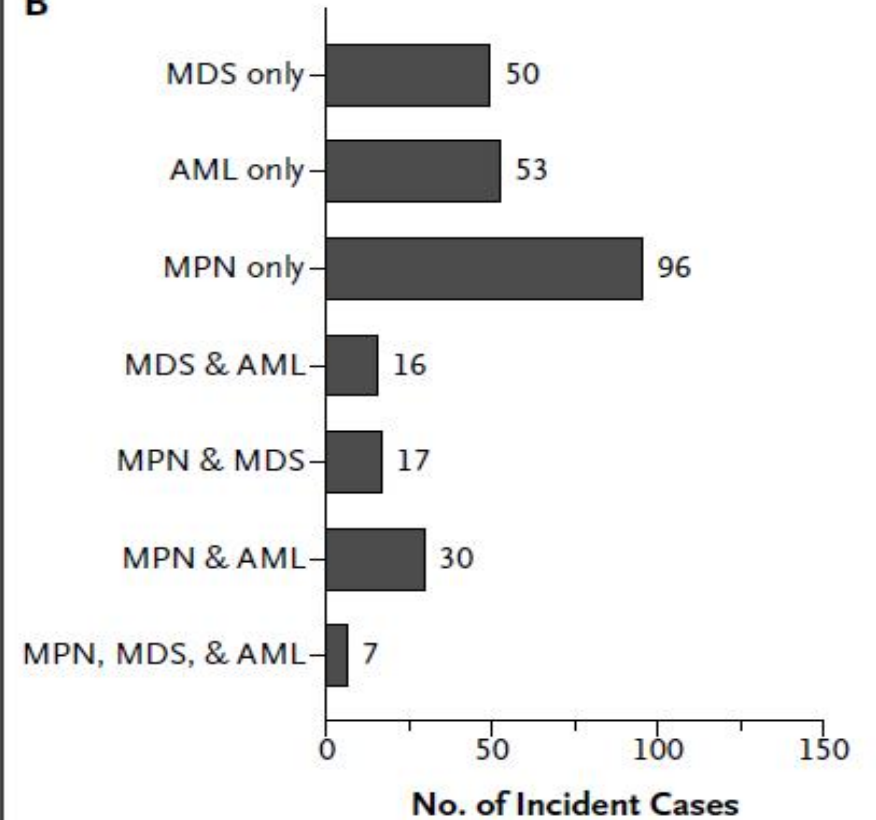
A



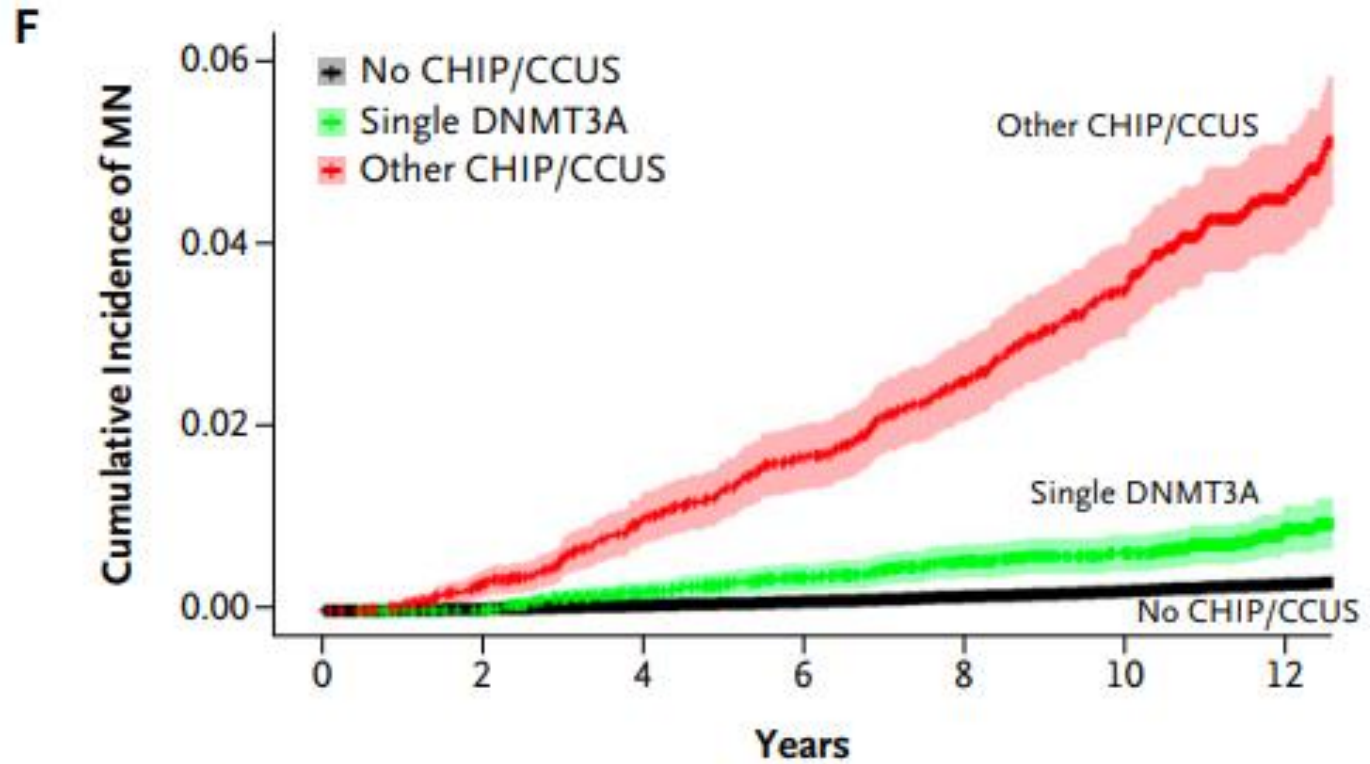
**Number at Risk**

Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254

B



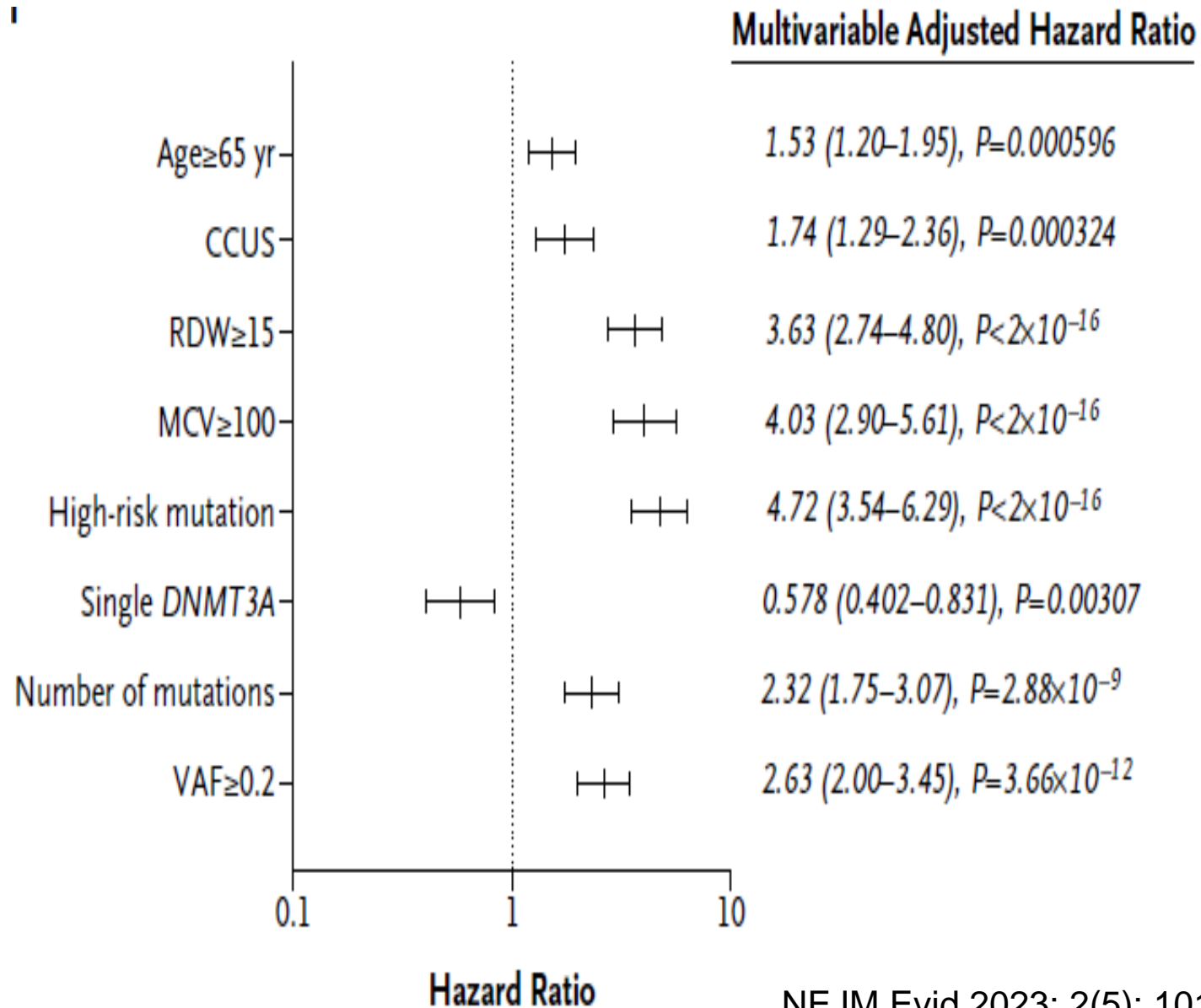
N=11,337  
 MN events: 269  
**(2.37%)**



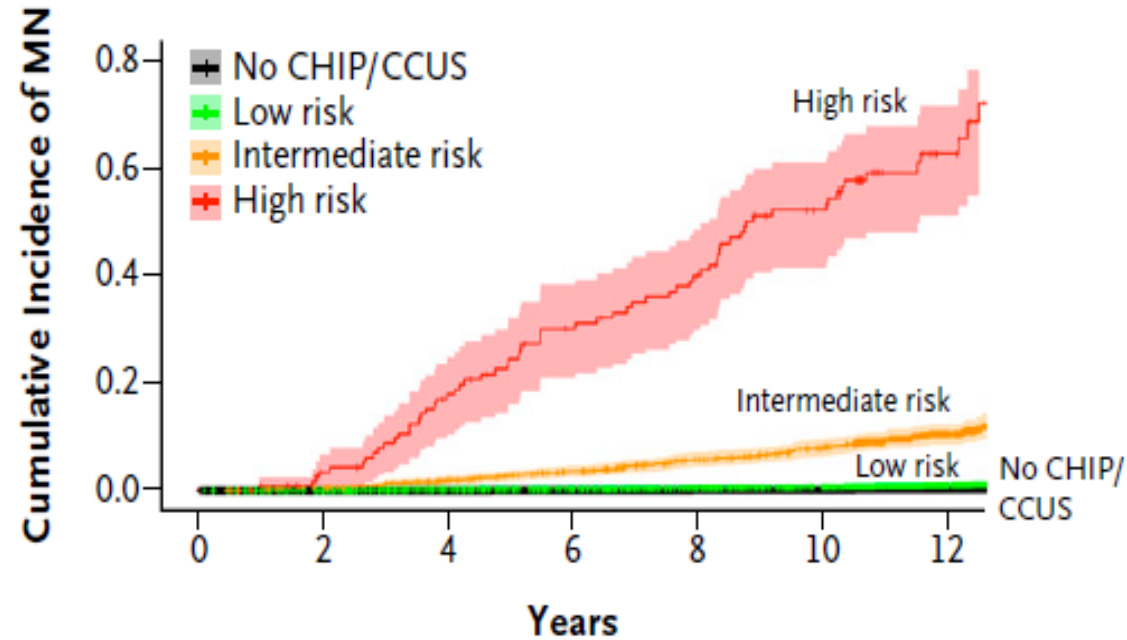
**Number at Risk**

Time (yr)	0	2	4	6	8	10	12
Single DNMTA	6,235	6,200	6,114	6,042	5,948	5,835	2,476
Other CHIP/CCUS	5,102	5,041	4,922	4,809	4,668	4,517	1,945
No CHIP/CCUS	182,407	181,674	180,407	178,734	176,774	174,453	72,254

# ADJUSTED MULTIVARIABLE COX REGRESSION



# CLONAL HEMATOPOIESIS RISK SCORE - CHRS

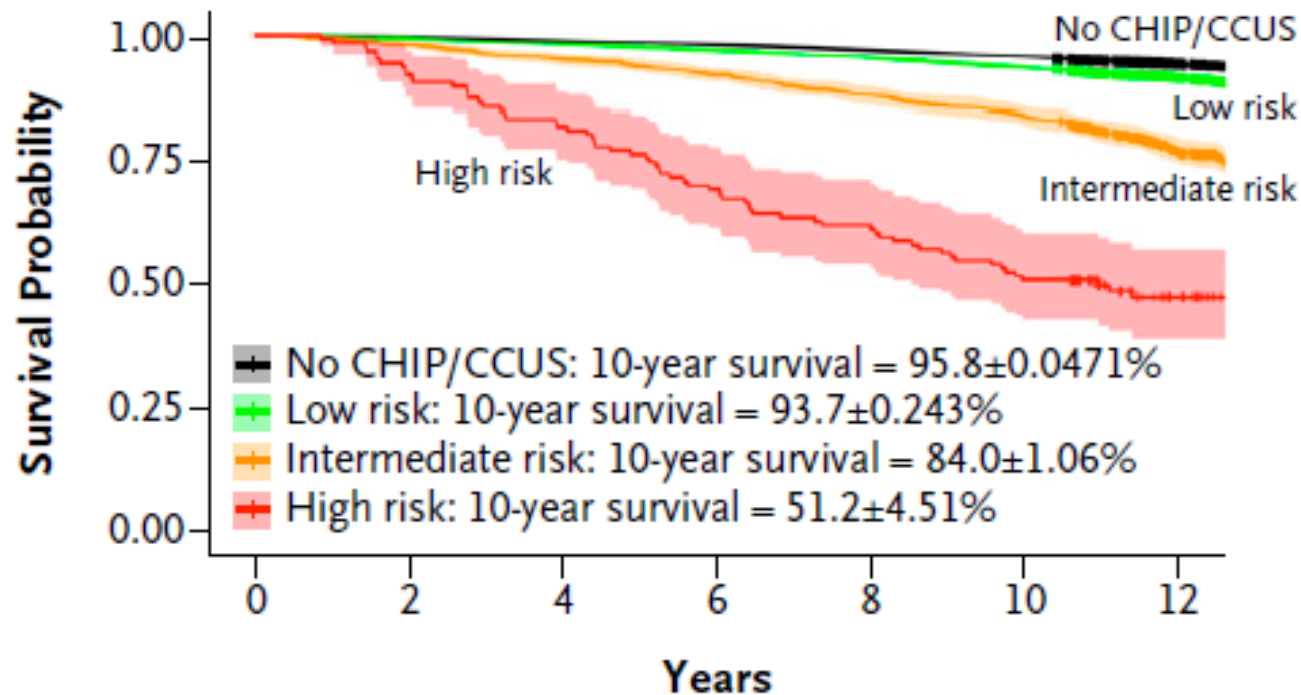


Number at Risk							
Time (yr)	0	2	4	6	8	10	12
High risk	123	109	90	72	60	43	15
Int. risk	1,196	1,174	1,125	1,080	1,016	961	336
Low risk	10,018	9,958	9,821	9,699	9,540	9,348	3,772
No CHIP/CCUS	182,406	181,674	180,407	178,734	176,174	174,455	72,254

**C-INDEX DERIVATION COHORT:** 0.807 ± 0.016

**C-INDEX VALIDATION COHORT:** 0.799 ± 0.015

# CLONAL HEMATOPOIESIS RISK SCORE - CHRS



## Number at Risk

Time (yr)	0	2	4	6	8	10	12
High risk	123	113	101	86	76	63	25
Int. risk	1,196	1,176	1,141	1,101	1,051	1,005	354
Low risk	10,018	9,963	9,830	9,717	9,567	9,386	3,793
No CHIP/CCUS	182,406	181,706	180,486	178,864	76,967	174,688	72,376

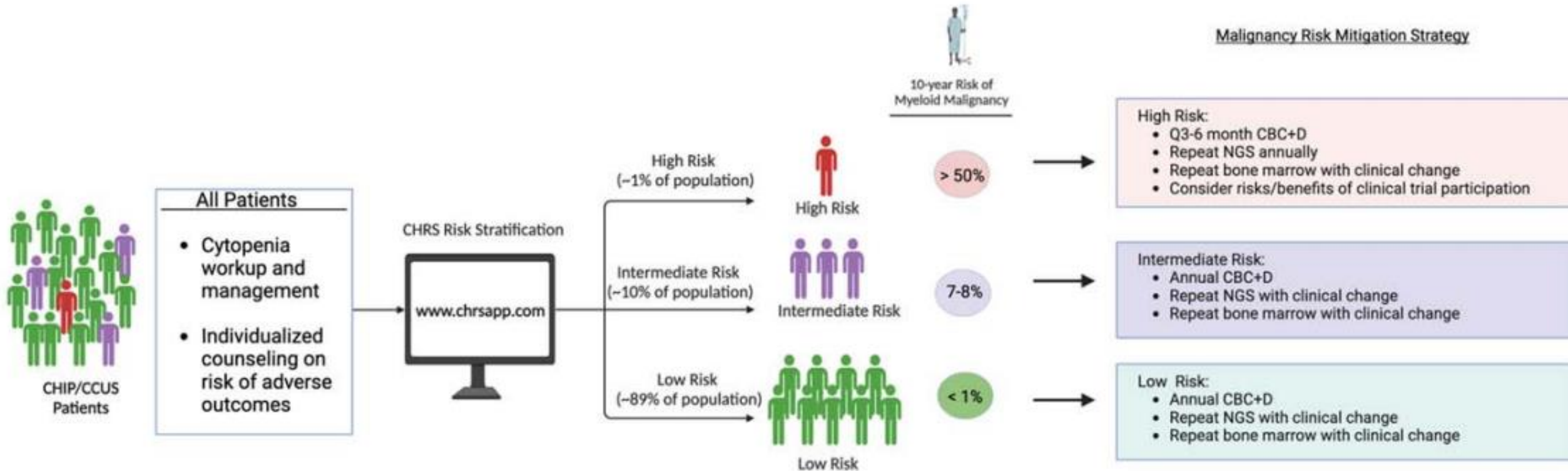


# SUMMING UP

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- The CHRS model permits risk assessment using objective data obtained at a single time point from two peripheral blood tests: an NGS panel and a complete blood count.
- Early cancer detection programs: aid in clinical decision-making and research, allowing prioritization of **intensive surveillance** and therapeutic intervention in the minority of patients who are most likely to progress to overt MN.

# CURRENT MANAGEMENT STRATEGIES FOR CLONAL HEMATOPOIESIS



Weeks L et al **Blood** 2023; 142: 2235.

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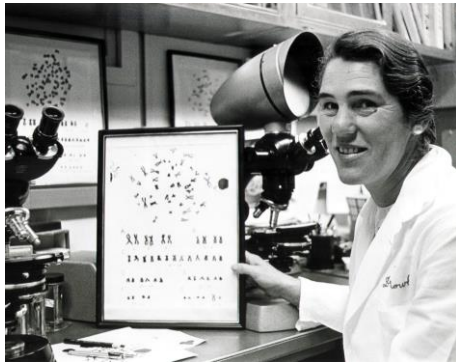
# WHAT IS THE ROLE OF MOLECULAR TESTING IN MDS DIAGNOSIS



The molecular events necessary to transition from **clonal hematopoiesis** to the clinically significant cytopenias seen in MDS remain unclear

# “PRELEUKEMIA”

... “a crucial question to be asked...  
will they develop leukemia”?



# CONCLUSIONS

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- The prevalence of CH increases dramatically with age. Somatic mutations that drive clonal expansion of blood most frequently involve DNMT3A, TET2, or ASXL1.
- CH is a **pre-malignant state**: the somatic mutations detected in CH are the initiating mutations for hematologic malignancies, and CH is a strong predictor for the development of blood cancers.
- CH is associated with non-malignant disorders such as CVD and increased overall mortality.
- Clinical relevance is greater with **higher VAF** thresholds

# CONCLUSIONS

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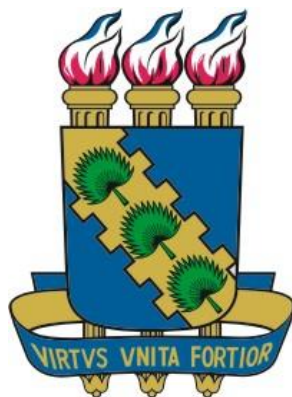
- Current evidence does not support the use of somatic mutations as presumptive evidence of MDS with exclusion of **SF3B1** in the presence of  $\geq 5\%$  ring sideroblasts.
- Detection of specific somatic mutations in the peripheral blood, in coordination with blood count parameters, can powerfully predict the development of hematologic malignancies and overall mortality.
- Tools for risk stratification are ongoing

# CONCLUSIONS

- Management strategies: there is no clear guideline on follow-up of **CH** individuals.
- **High risk** patients may be monitored more frequently and considered to be include in clinical trials: CHRS risk groups. Consider age-appropriate screening for non-malignant comorbidities
- Lack of evidence that early intervention in asymptomatic patients leads to a survival improvement

**The number of clinical outcomes associated with CH mutations is rapidly expanding.**





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