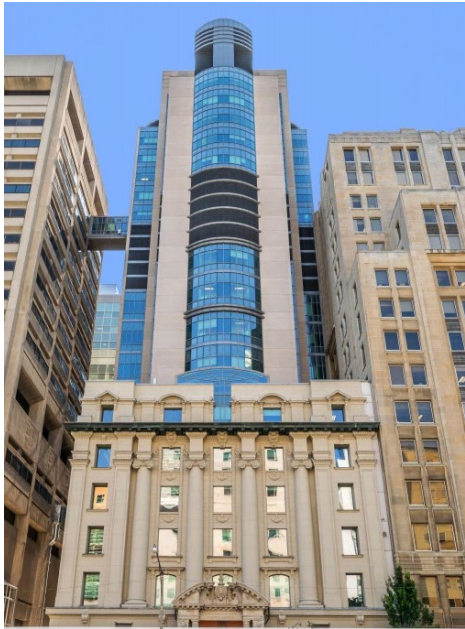


Clonal Hematopoiesis: What is it? Why it matters? And what can we do about it?



Steven Chan M.D., Ph.D.

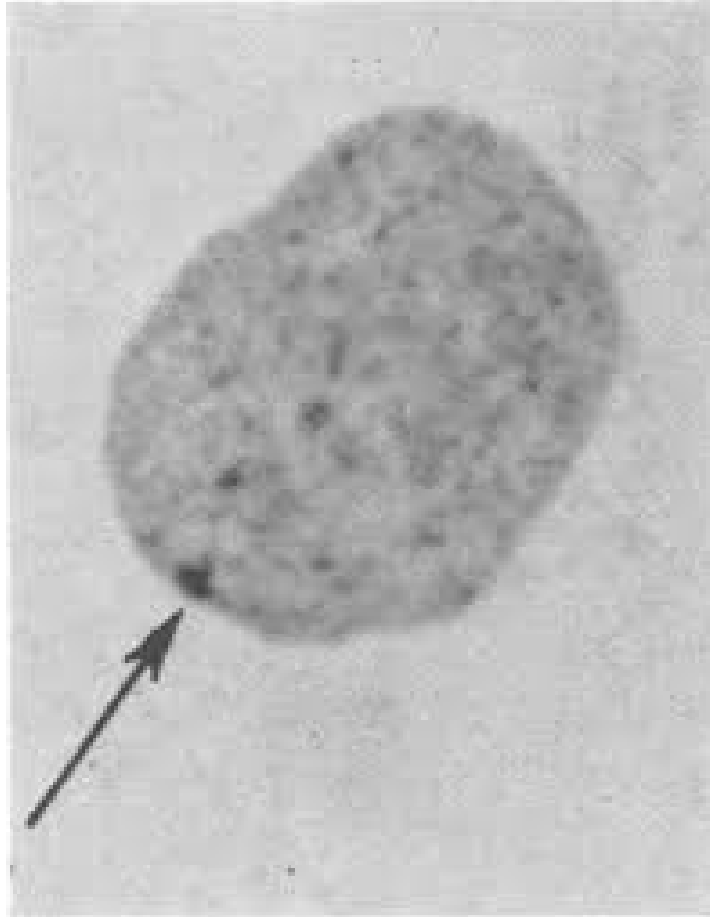
Senior Scientist & Staff Physician
Princess Margaret Cancer Centre

Associate Professor in Medicine
University of Toronto

July 16, 2024

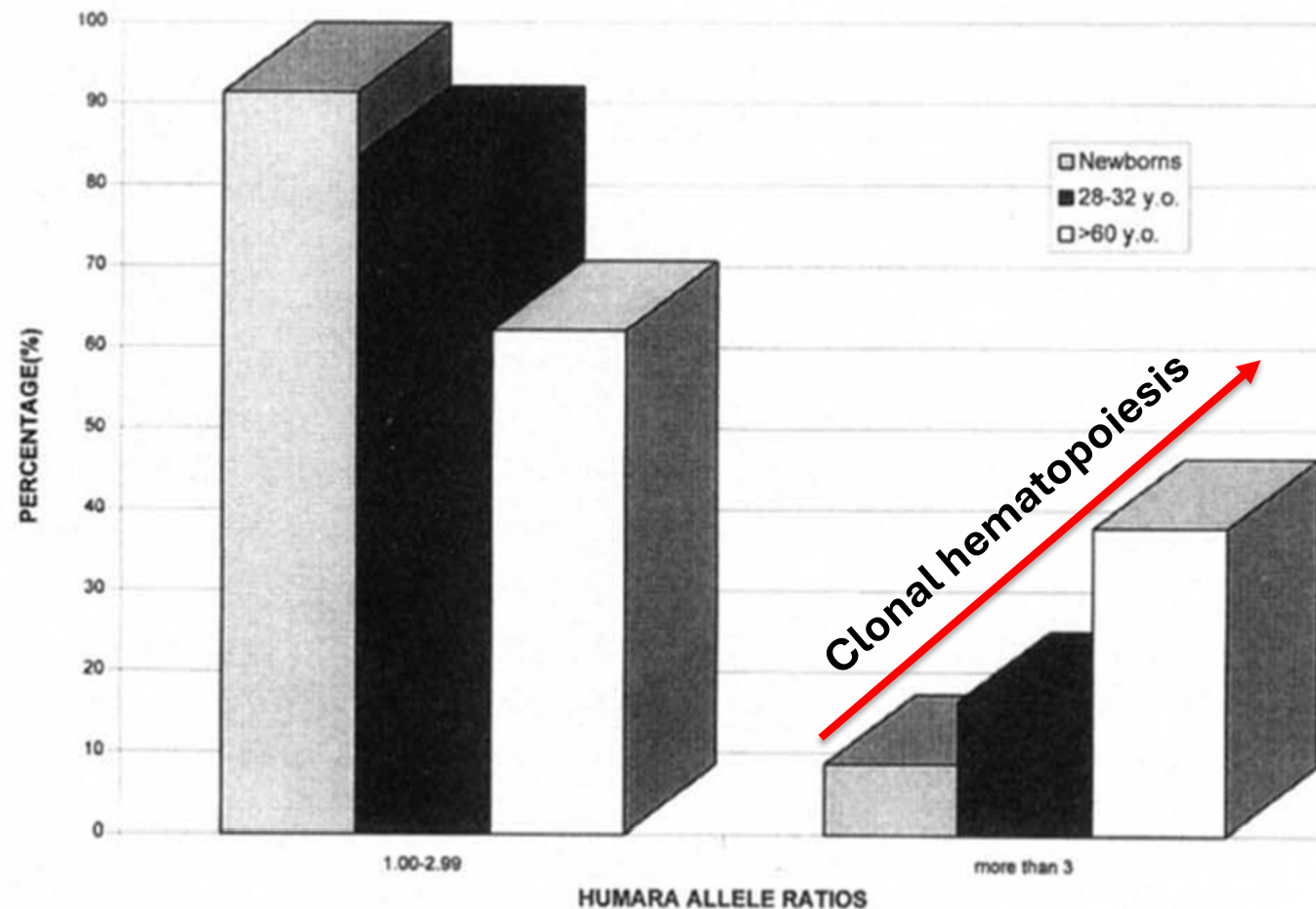


Barr Body

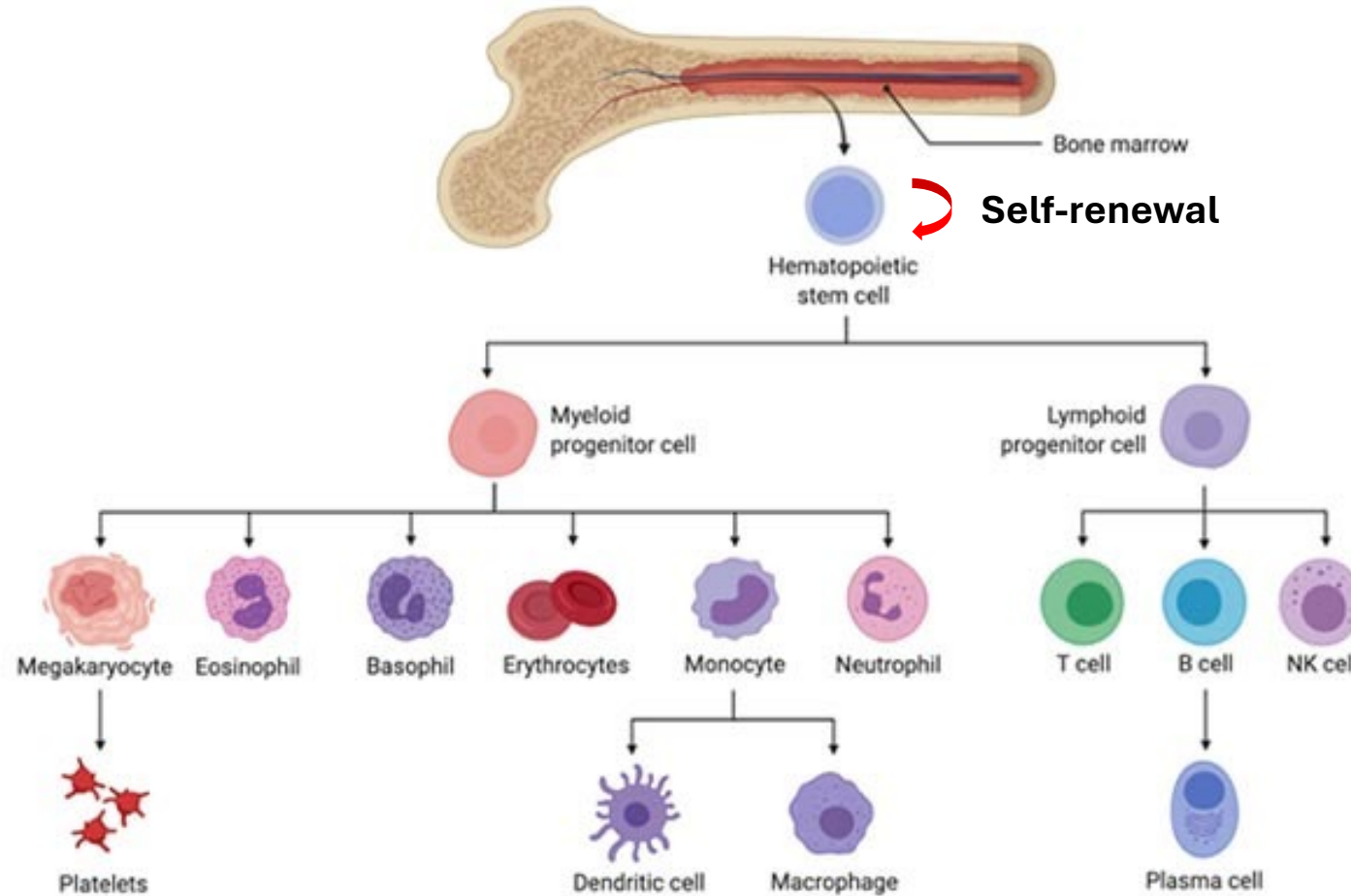


Nonrandom X-Inactivation Patterns in Normal Females: Lyonization Ratios Vary With Age

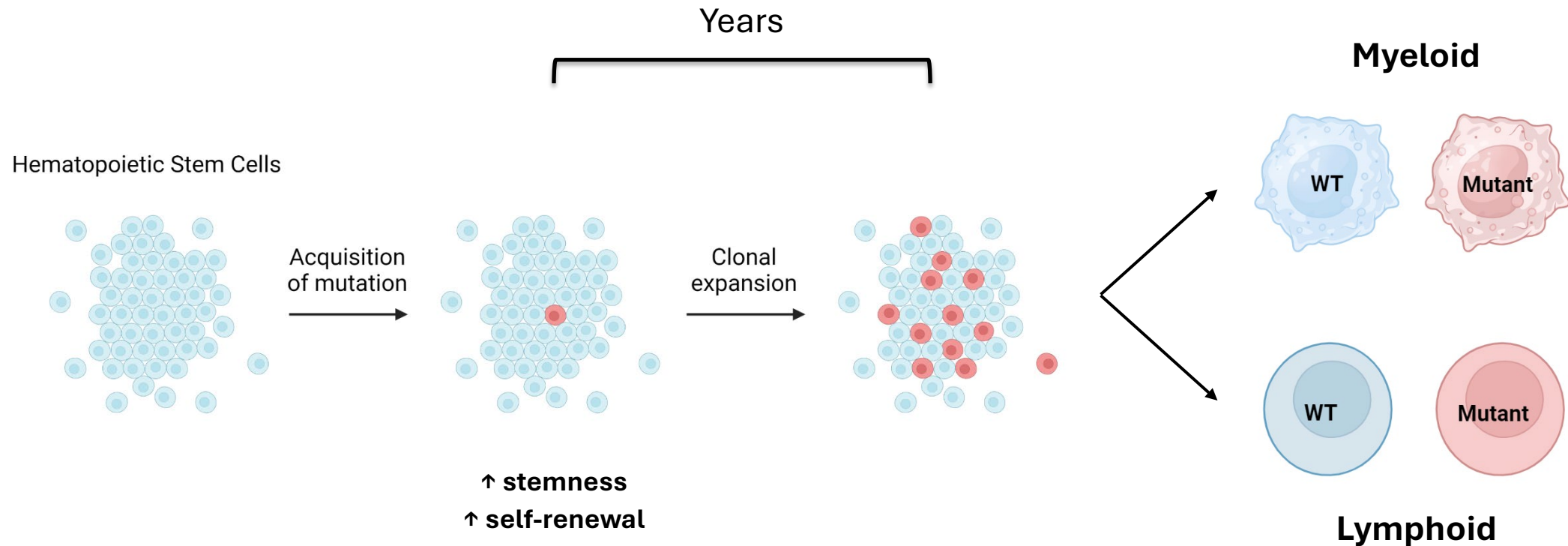
By Lambert Busque, Robert Mio, Johanne Mattioli, Elise Brais, Normand Blais, Yves Lalonde, Marlon Maragh,
and D. Gary Gilliland



Hematopoiesis

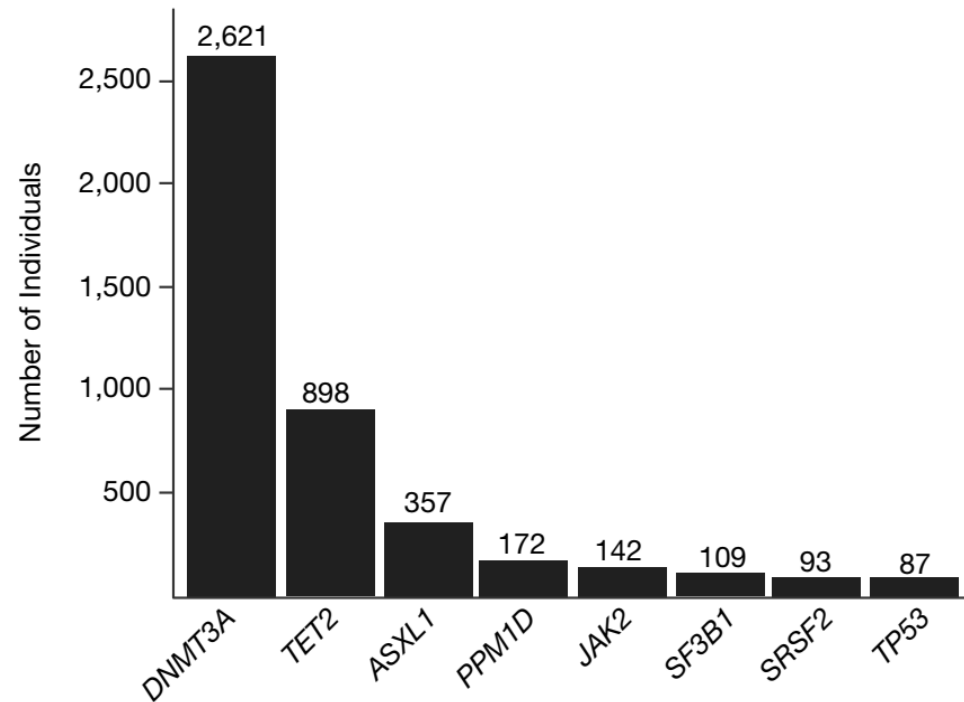


Clonal Hematopoiesis (CH): What is it?



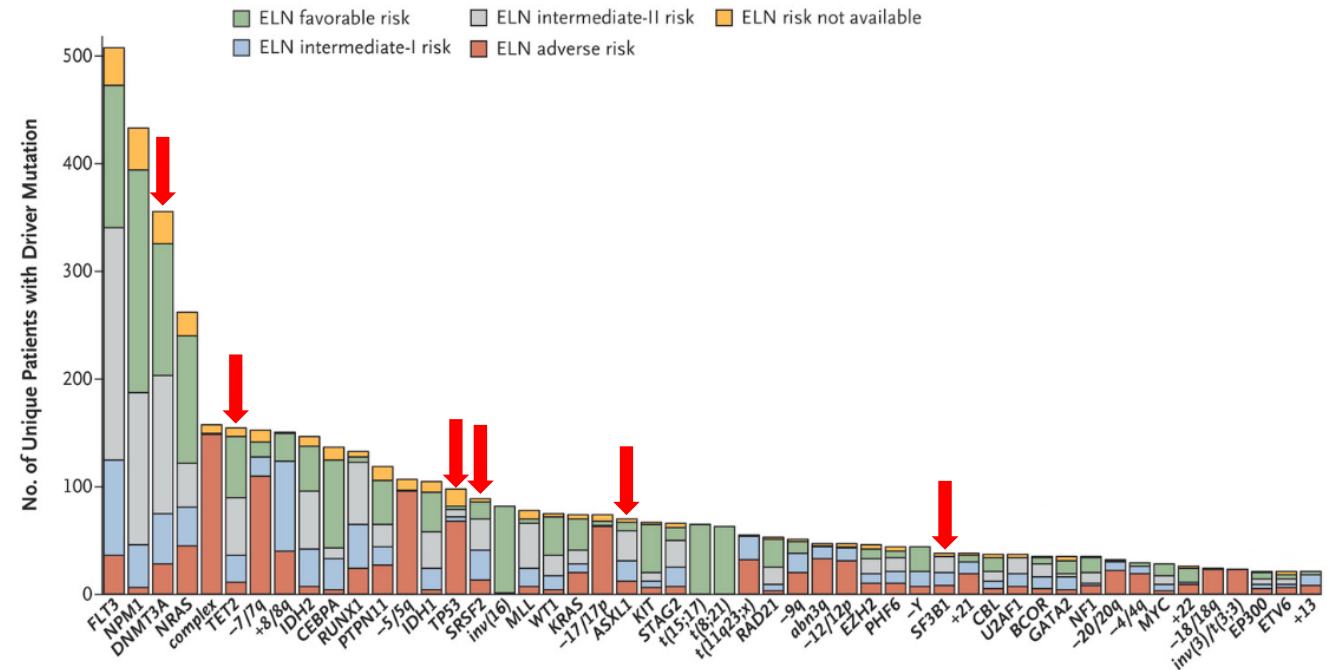
Clonal Hematopoiesis (CH): Mutations

Clonal Hematopoiesis



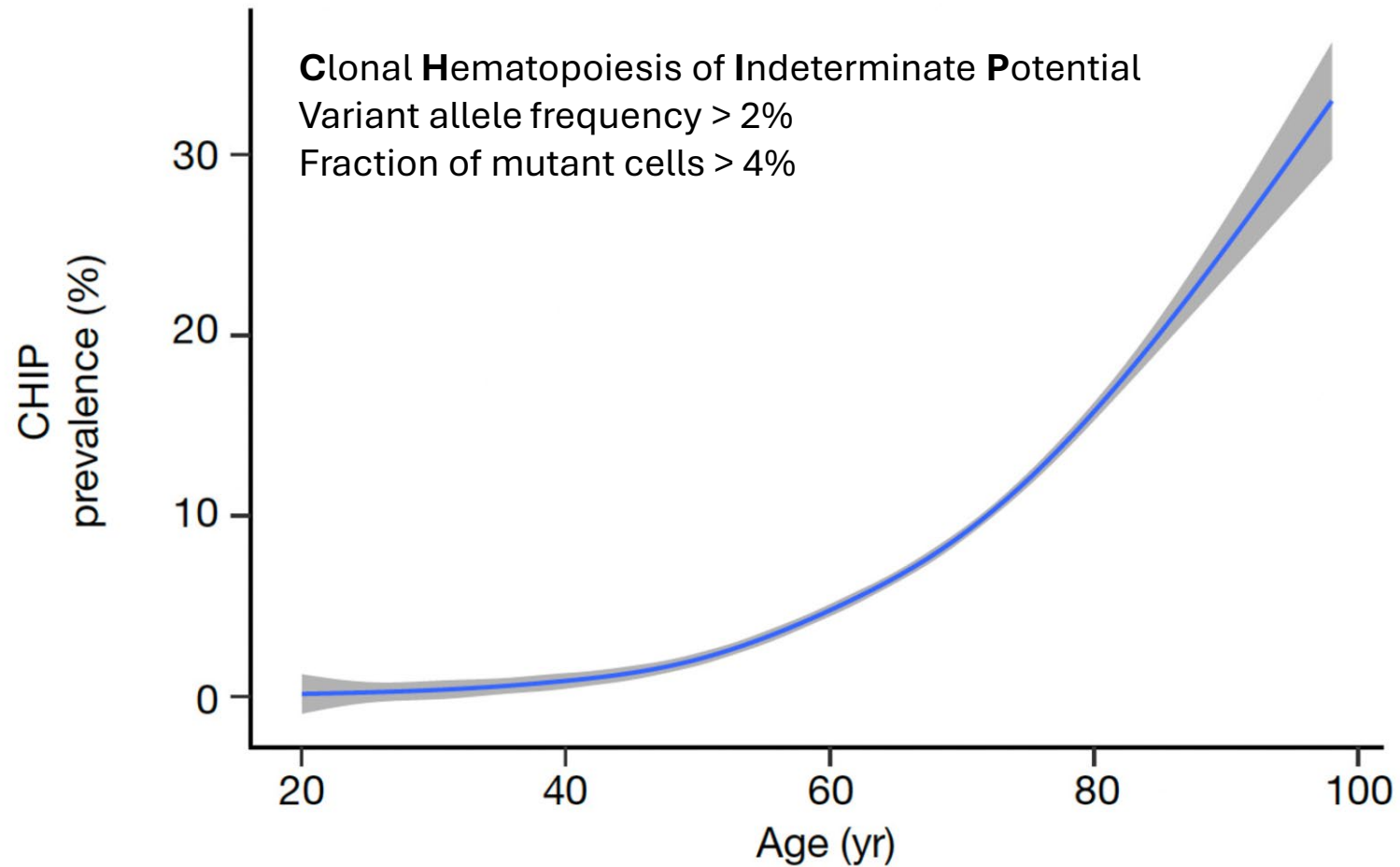
Bick et al. 2020. *Nature*

Acute Myeloid Leukemia

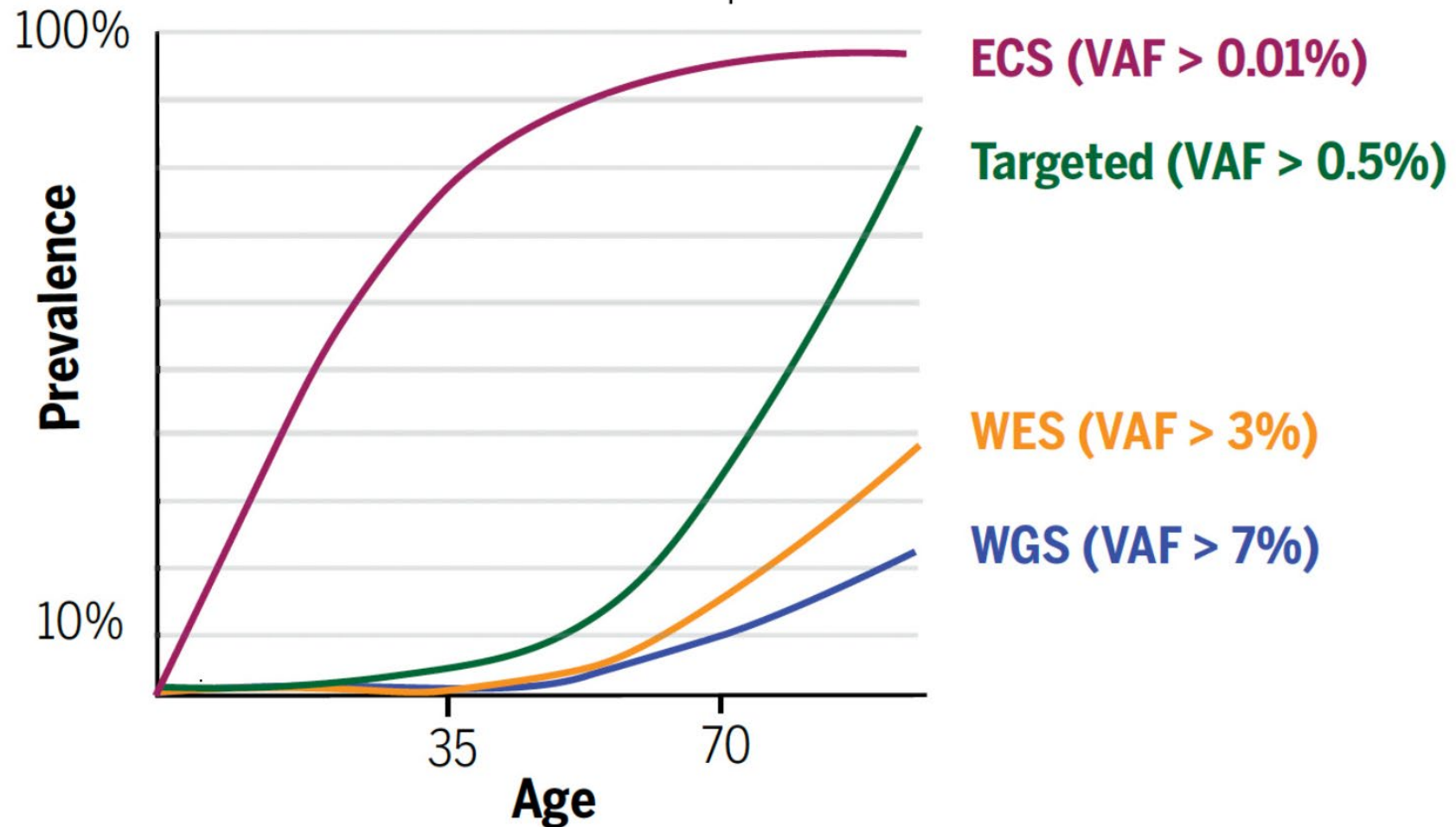


Papaemmanuil et al. 2016. *NEJM*

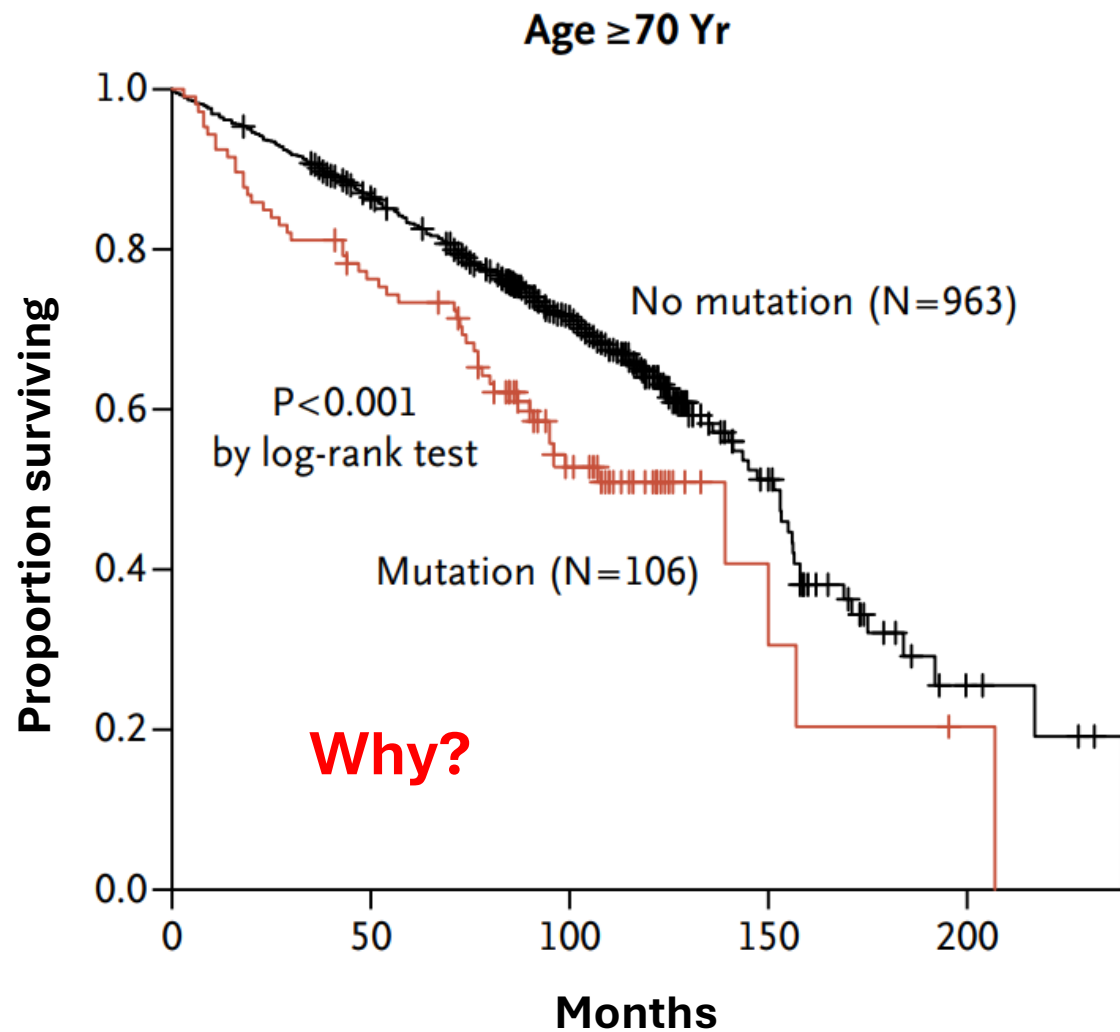
Clonal Hematopoiesis (CH): Prevalence



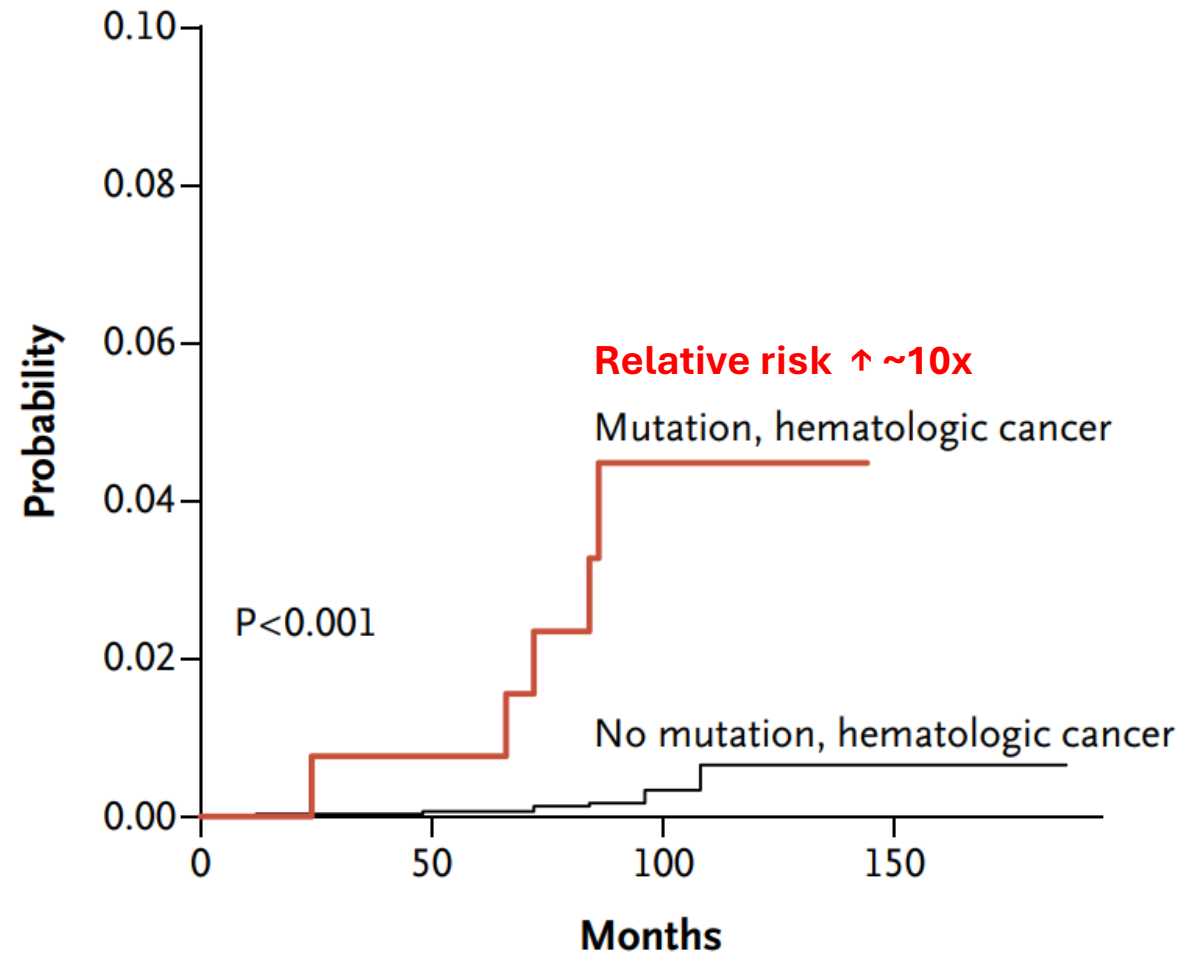
Clonal Hematopoiesis (CH): Prevalence



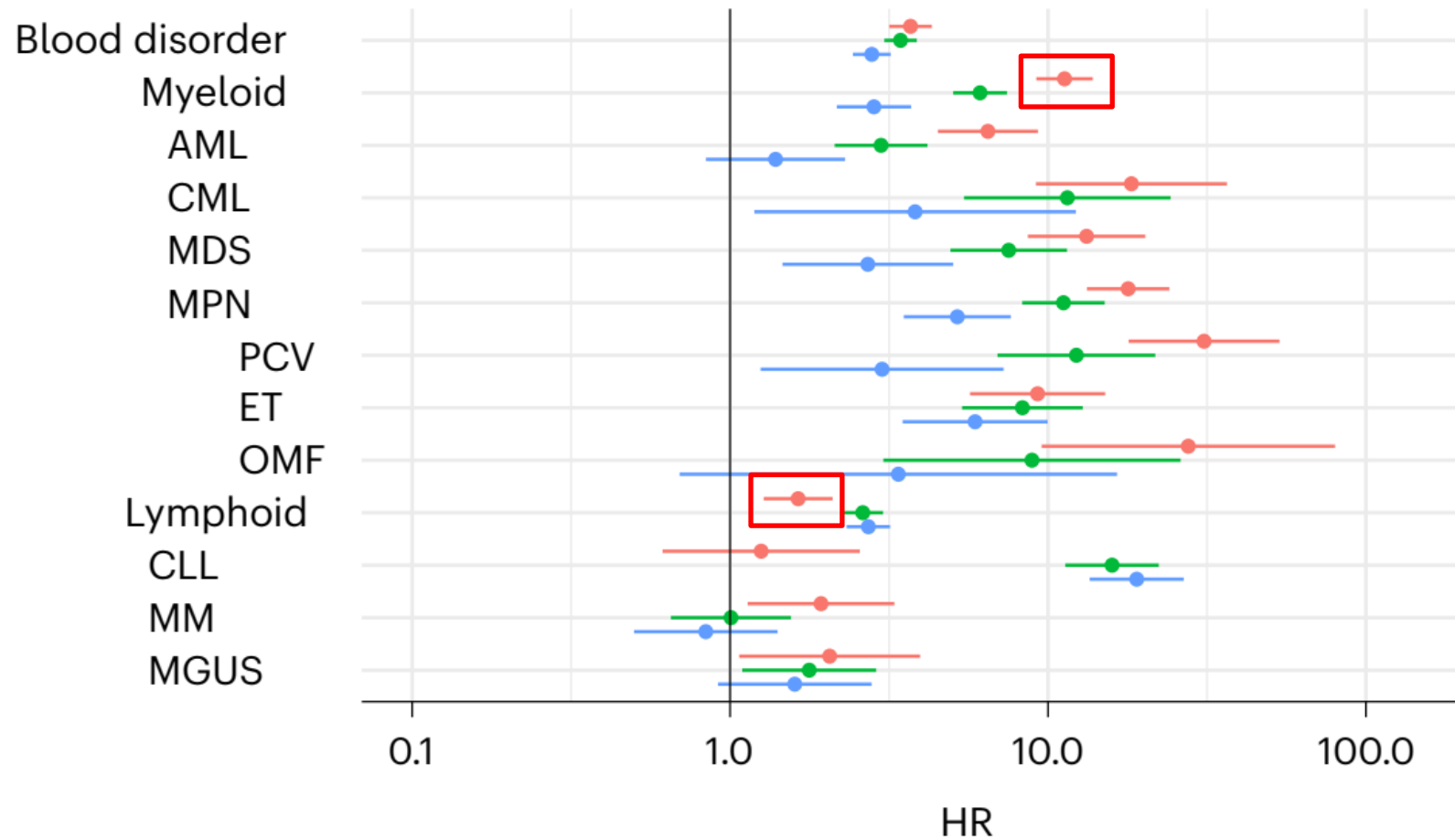
Impact of CHIP on overall survival



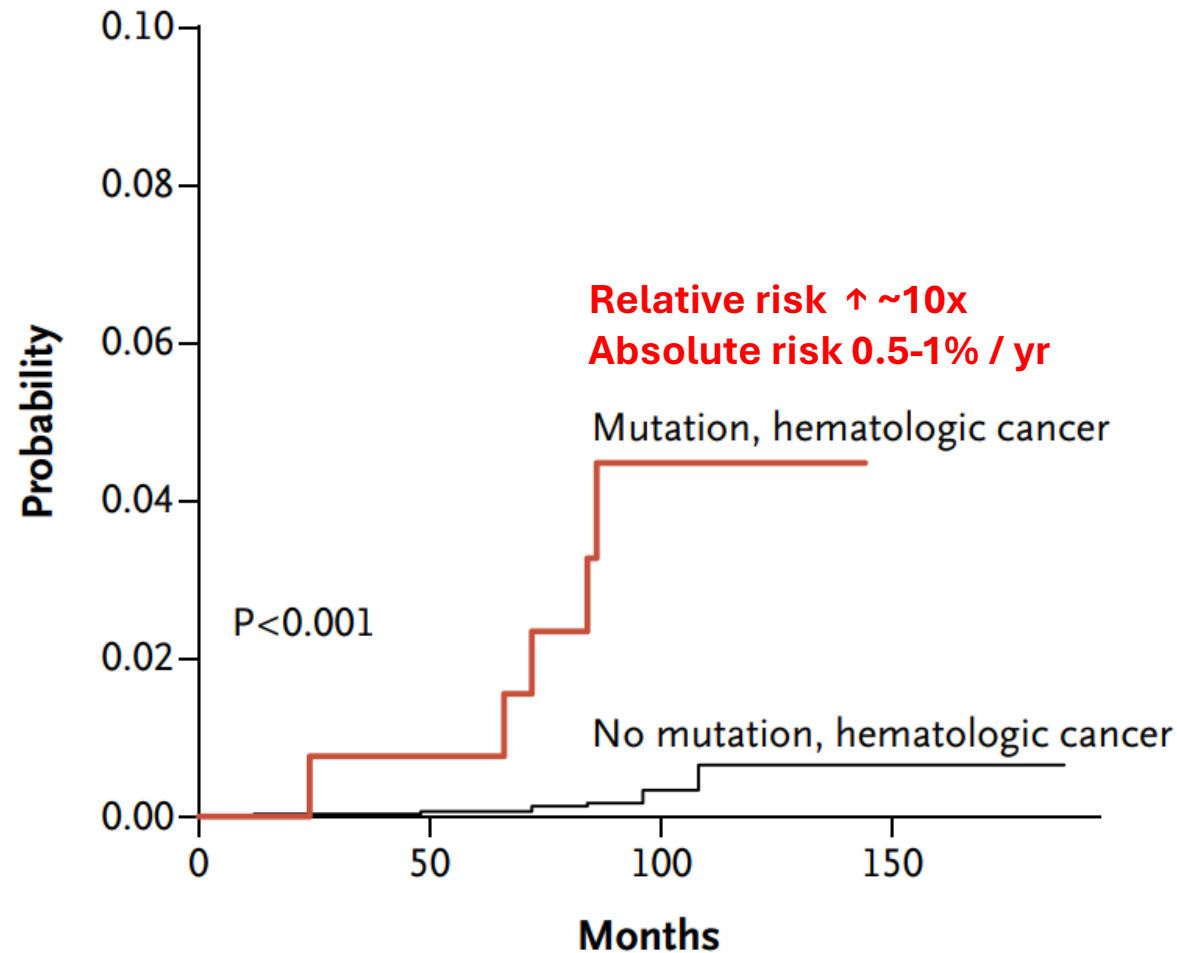
Impact of CHIP on risk of hematologic cancer



Impact of CHIP on risk of hematologic cancer

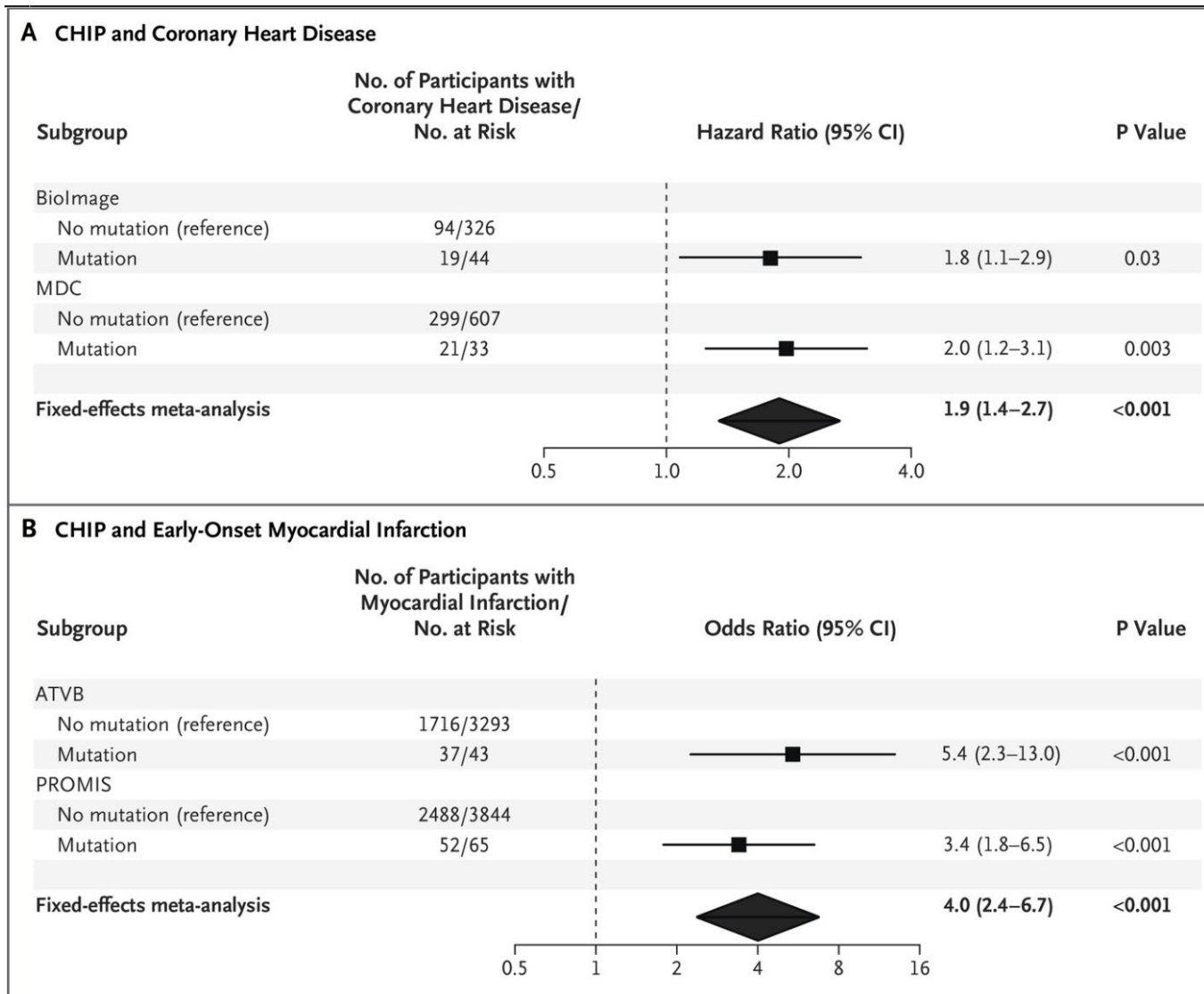


Impact of CHIP on risk of hematologic cancer

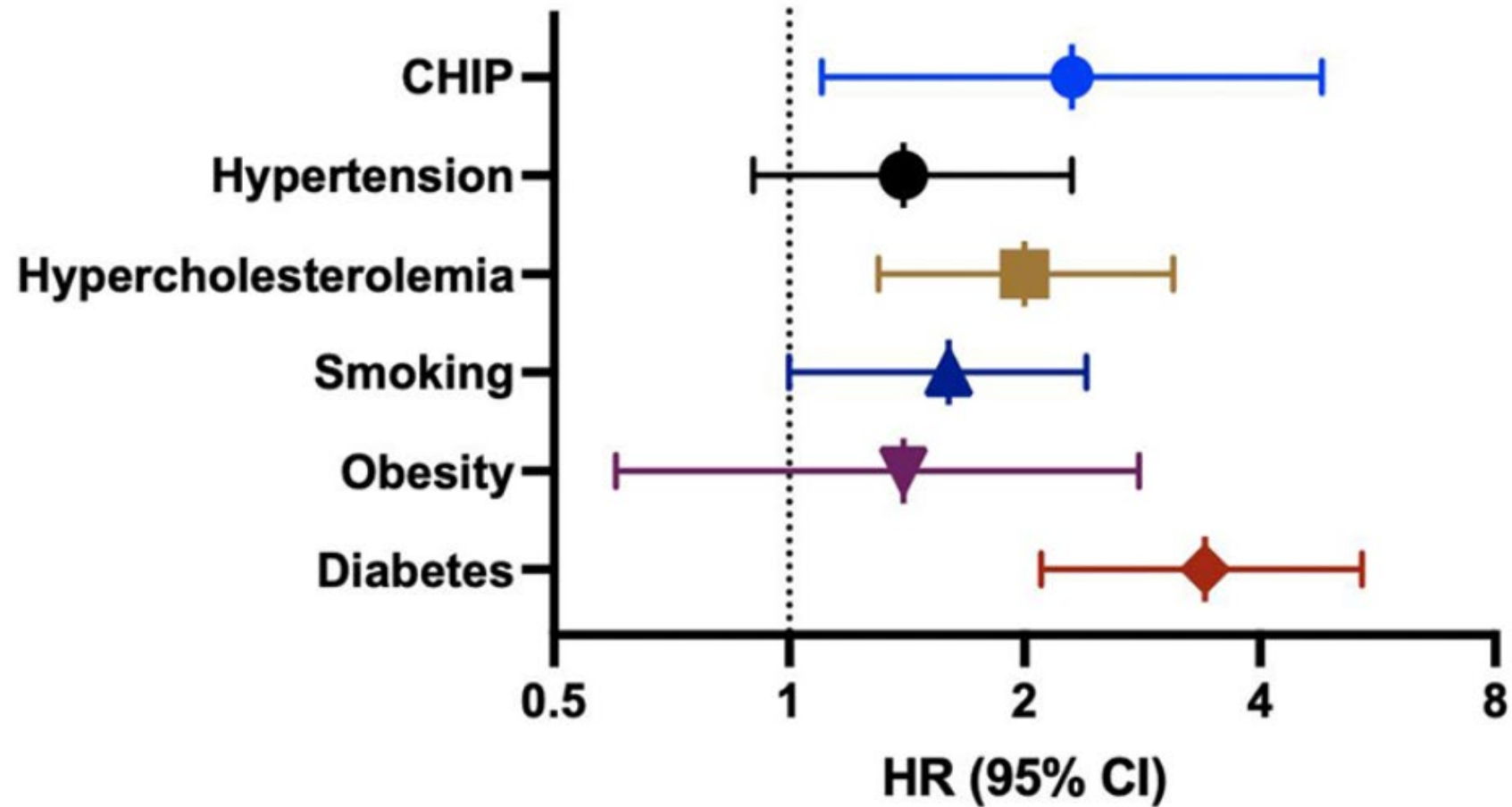


“Death from hematologic neoplasms alone could not account for the observed increase in mortality, since only 1 person with a mutation died from a hematologic cancer.”

Impact of CHIP on risk of CHD and MI



Impact of CHIP on risk of CHD and MI



Impact of CH on the risk of non-malignant diseases

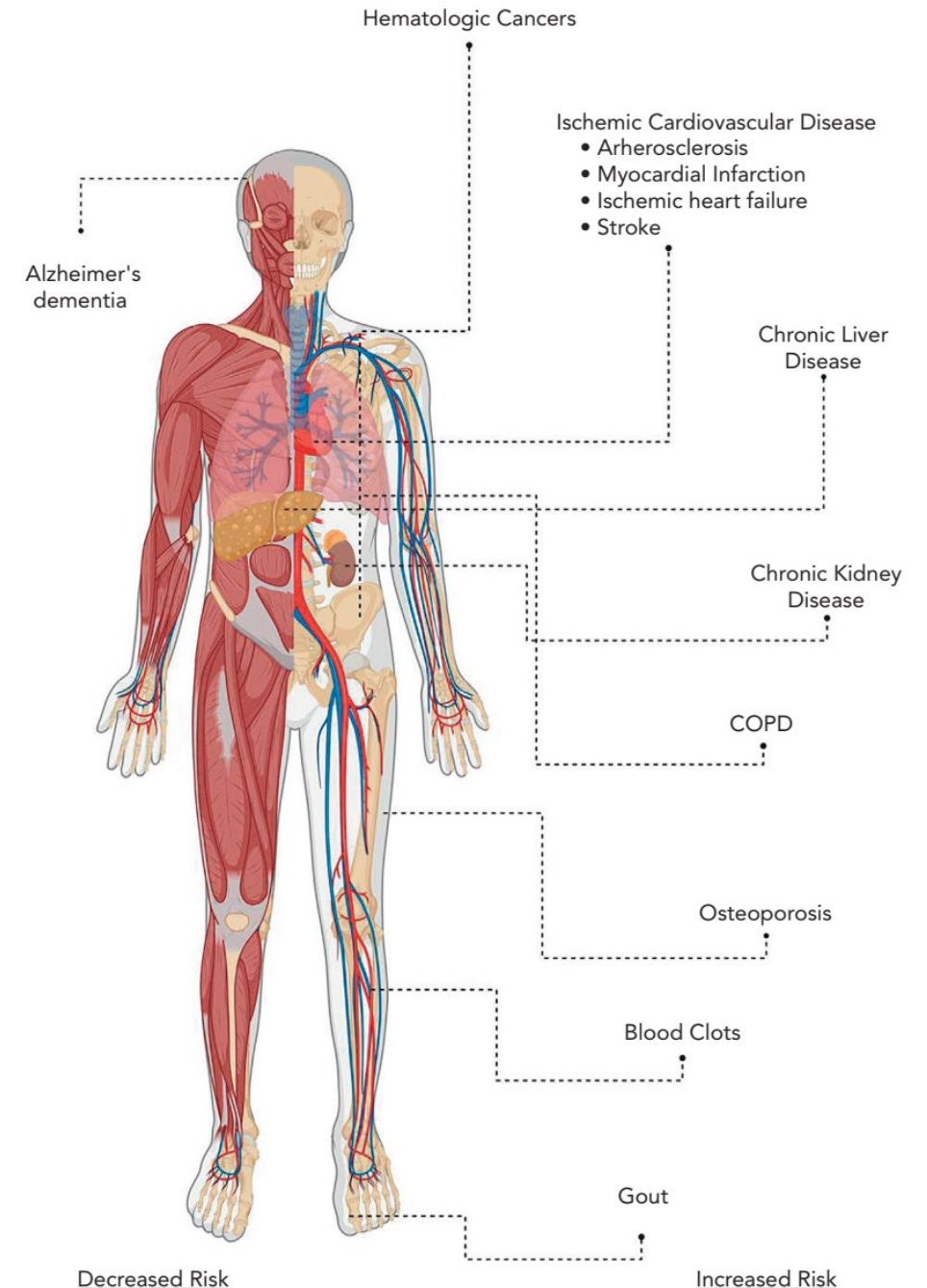
Increase in risk

- Ischemic cardiovascular disease
- Chronic obstructive pulmonary disease
- Chronic liver disease
- Chronic kidney disease
- Osteoporosis
- Blood clots
- Gout
- Type 2 diabetes

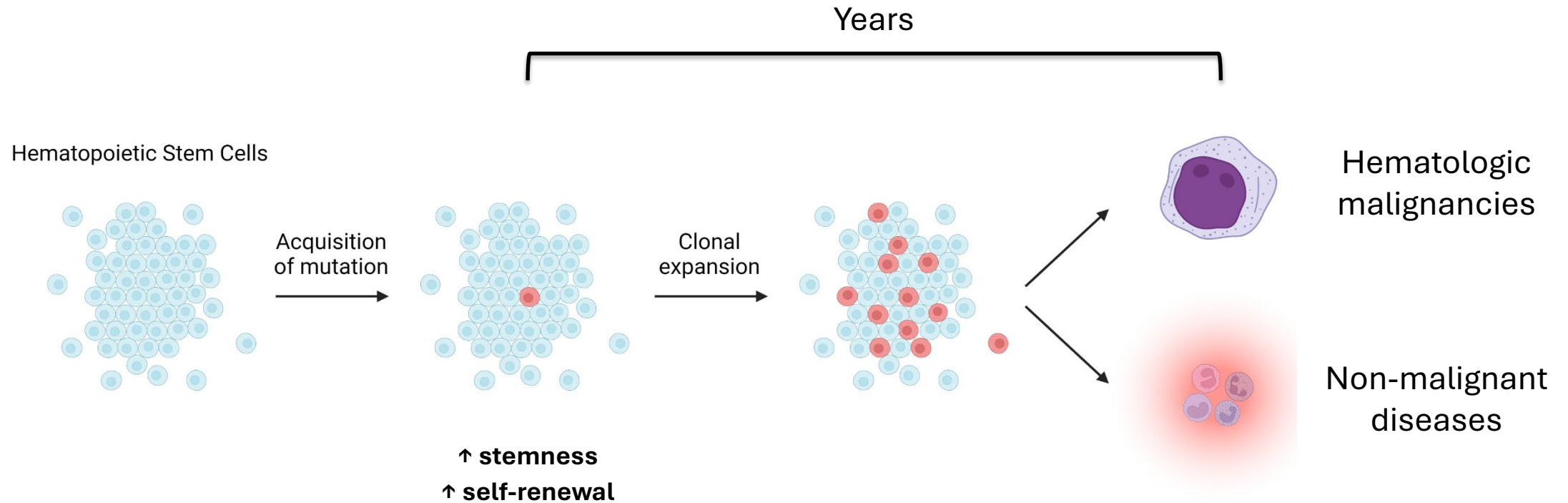
Decrease in risk

- Alzheimer's dementia

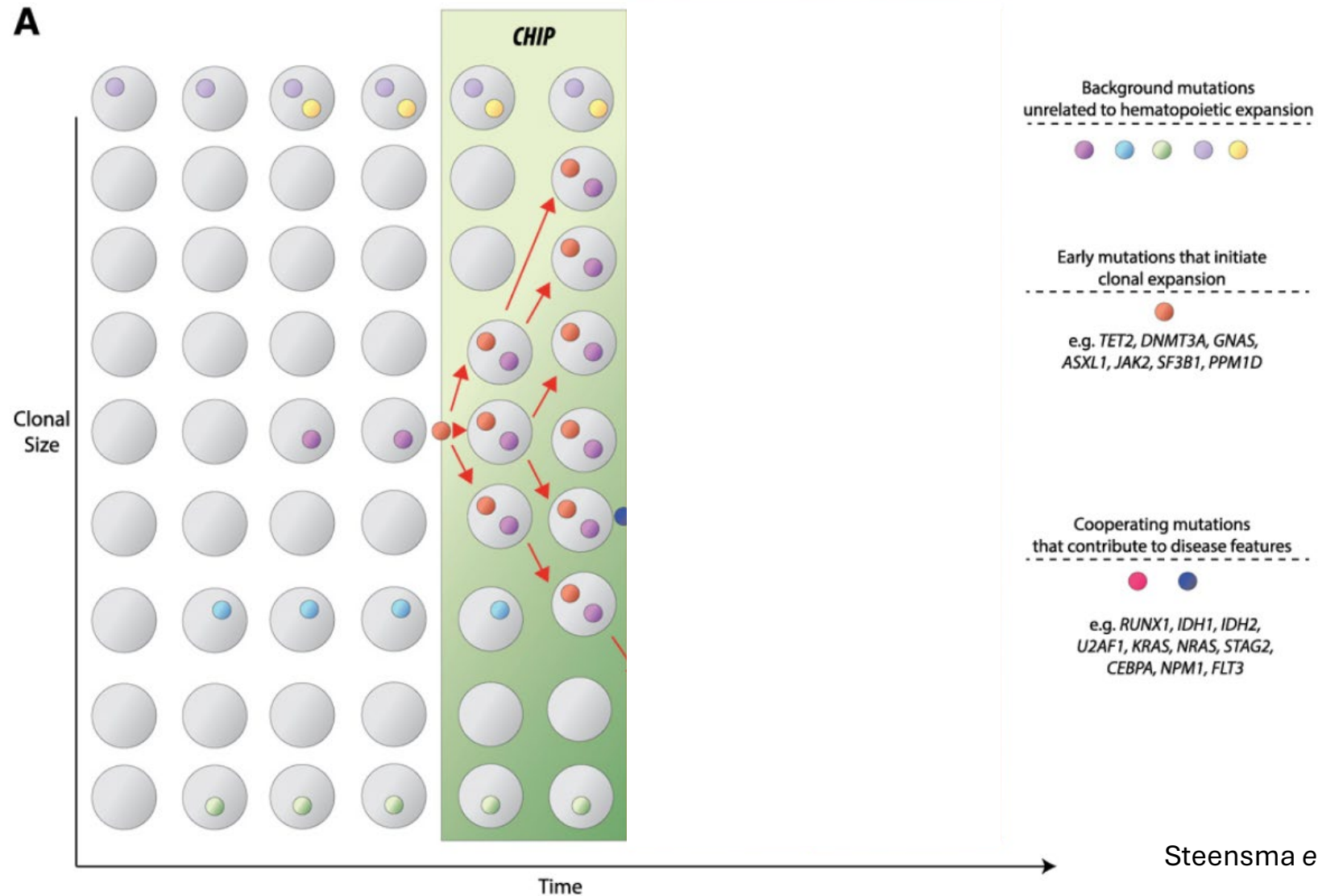
Weeks et al. 2023. *Blood*



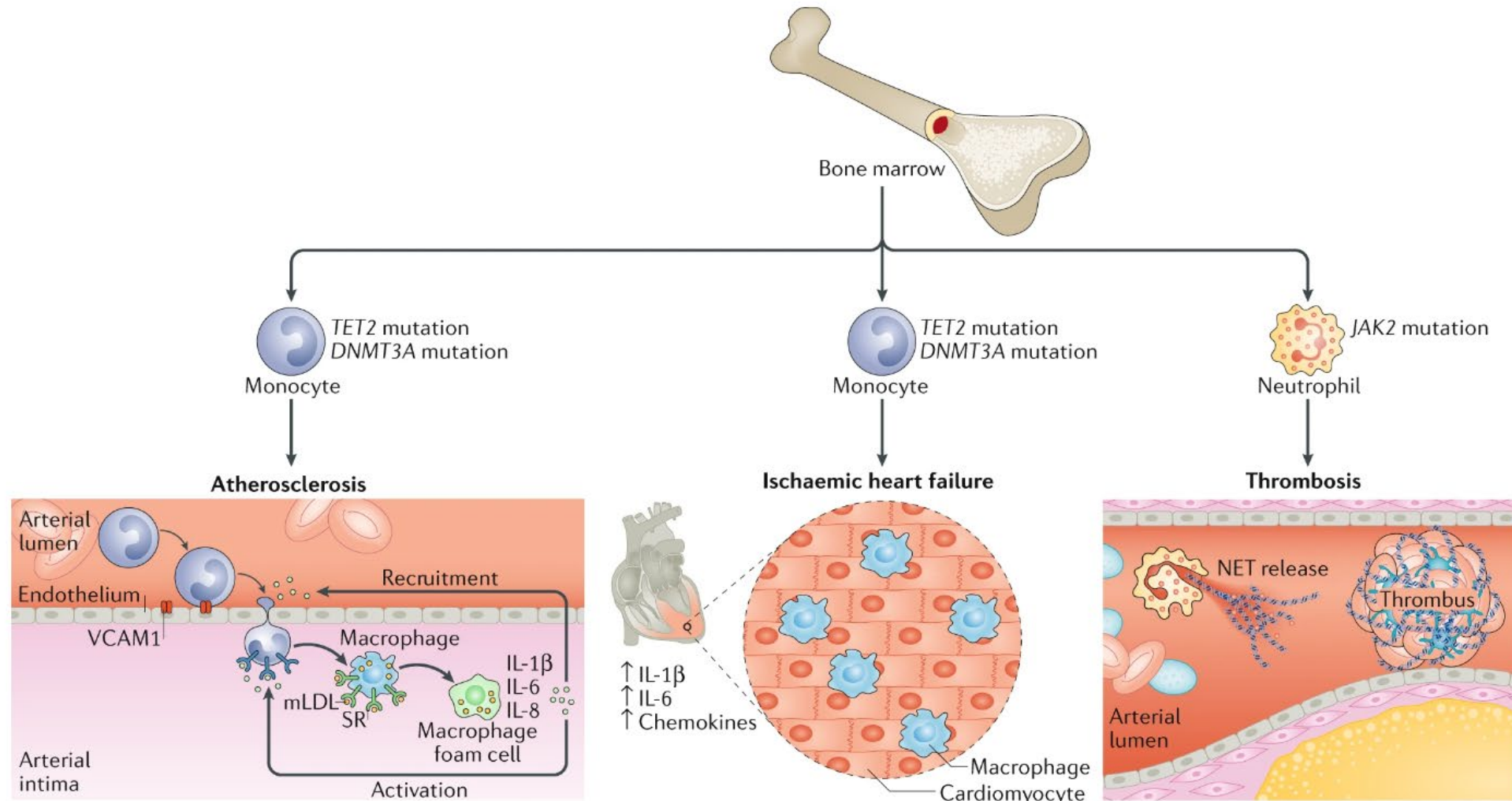
Impact of CH on human health



How does CH increase risk of blood cancers?

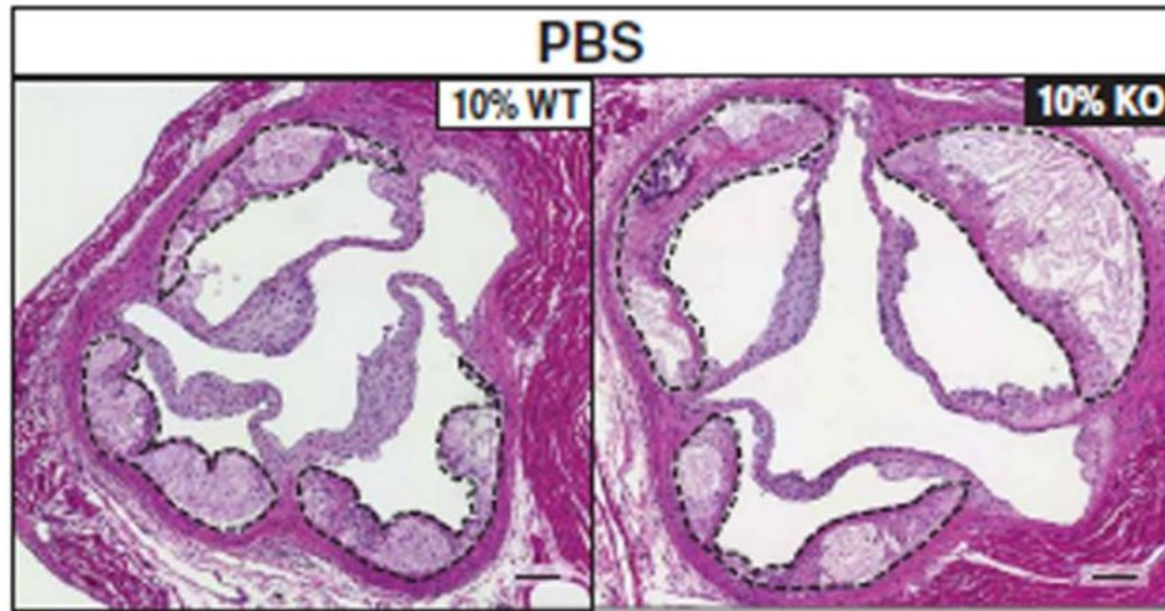


Impact of CH on the function of myeloid cells



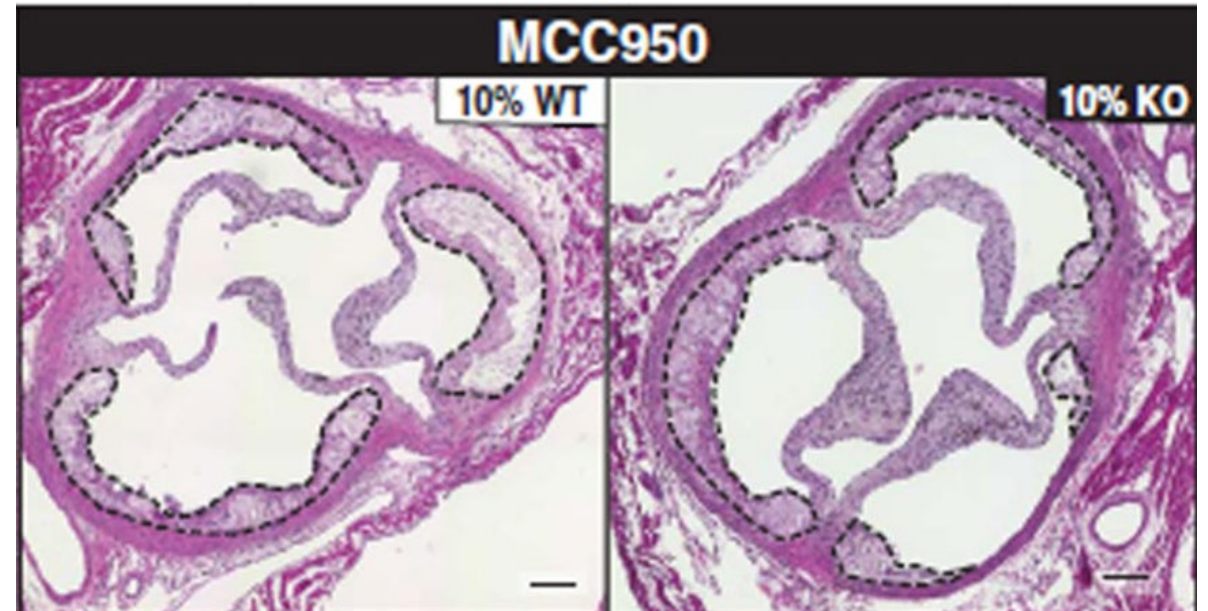
CHIP-related inflammation exacerbates atherosclerosis

NLRP3 inflammasome inhibitor



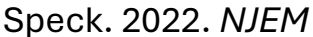
Tet2-WT

Tet2-KO

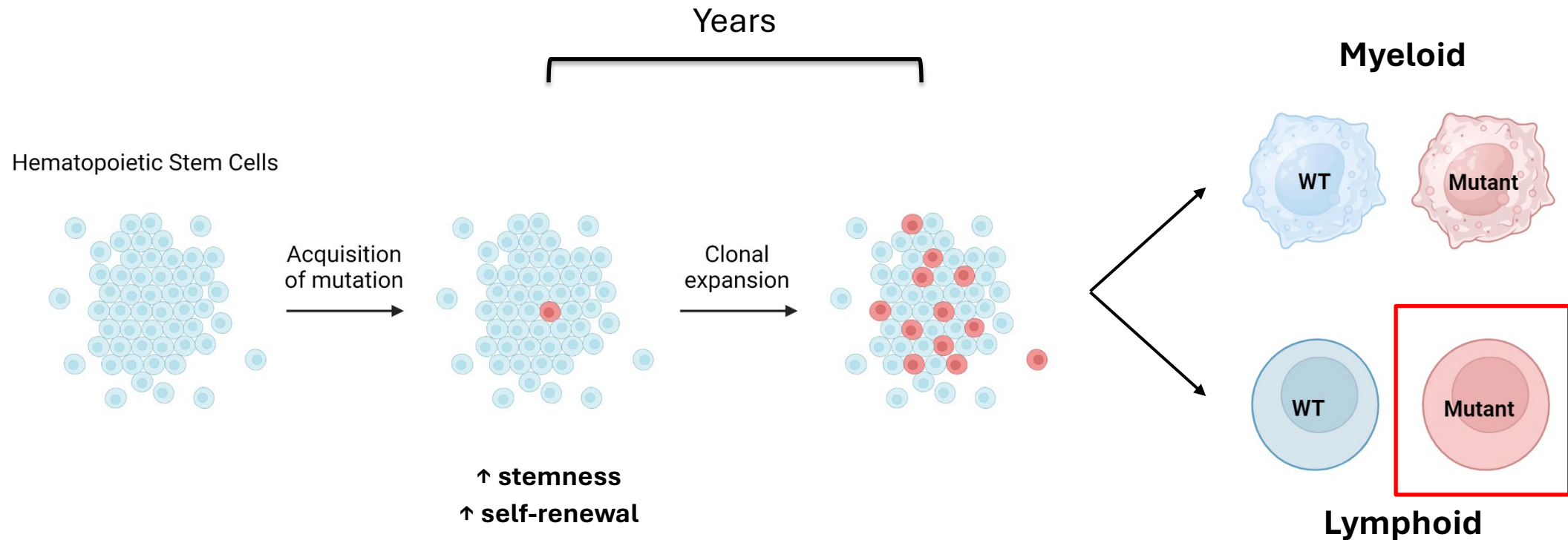


Tet2-WT

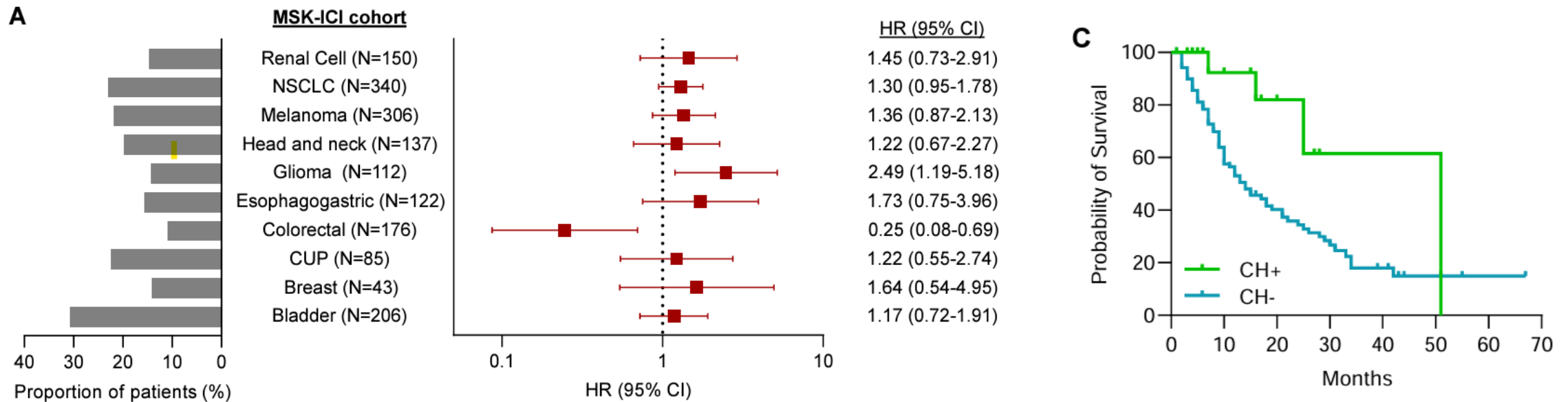
Tet2-KO



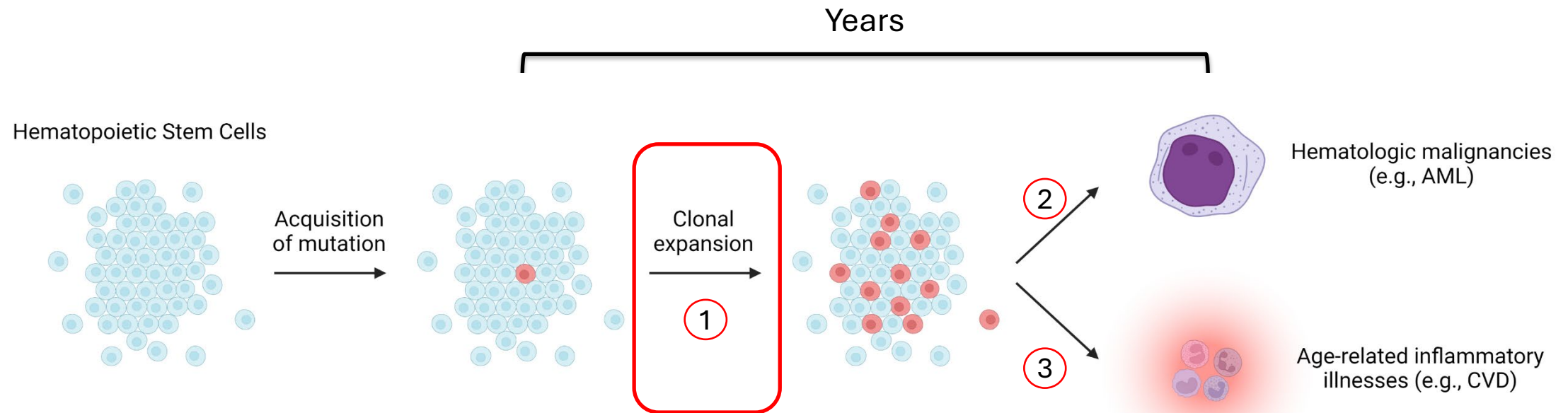
What is the impact of CH on lymphoid cells?



CH impacts response to immune checkpoint inhibitors

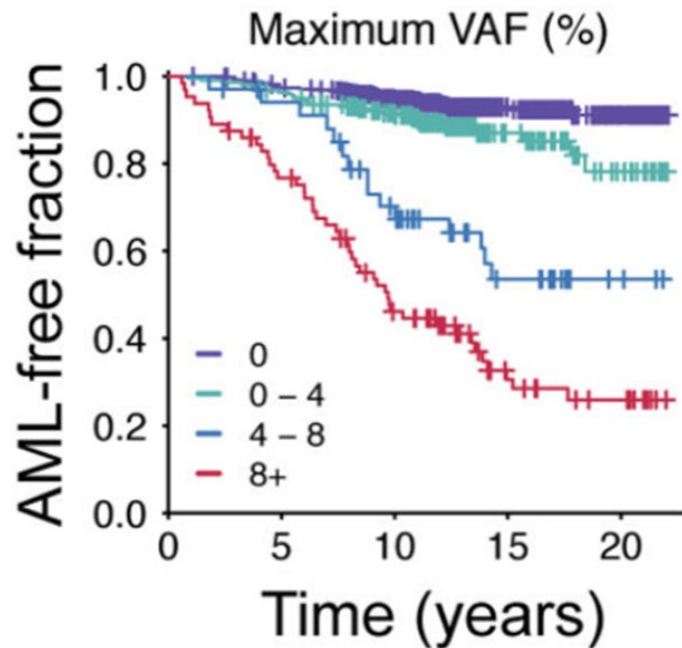


Clonal Hematopoiesis (CH): What can we do about it?

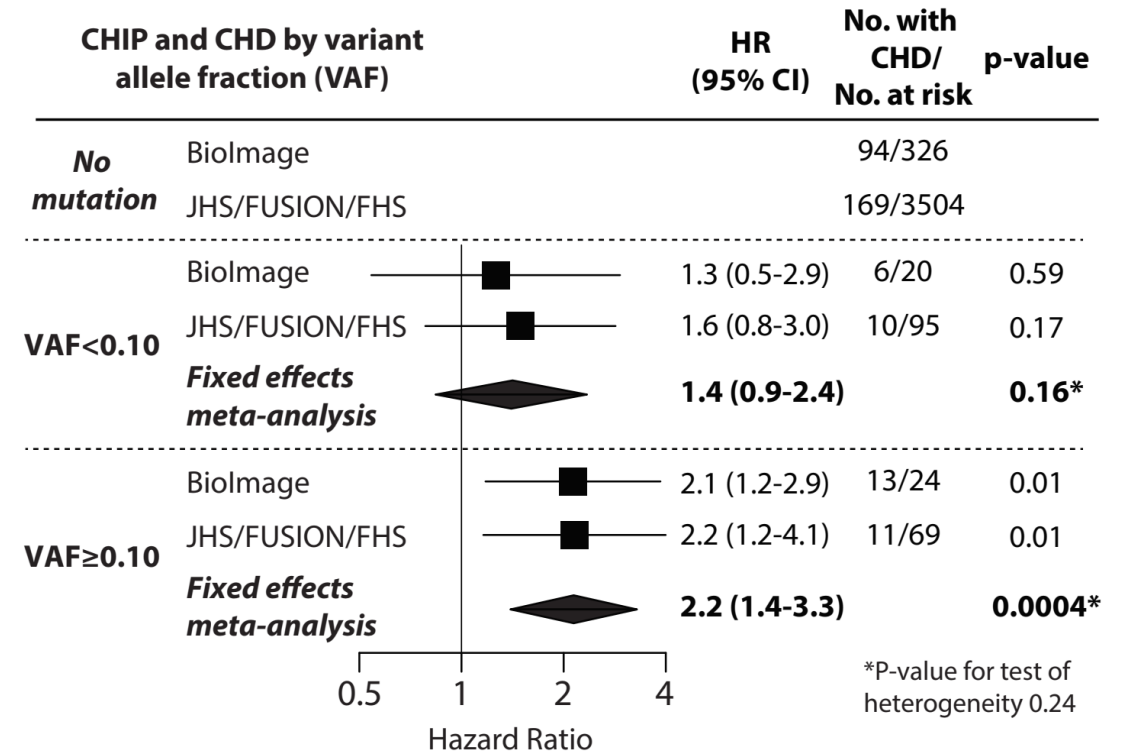


1. Suppress clonal expansion
2. Suppress the mechanisms that drive malignant transformation of CH clones
3. Suppress CH-related inflammation

A higher clone size is associated with an increased risk of AML and coronary heart disease (CHD)



Abelson et al. 2018. *Nature*

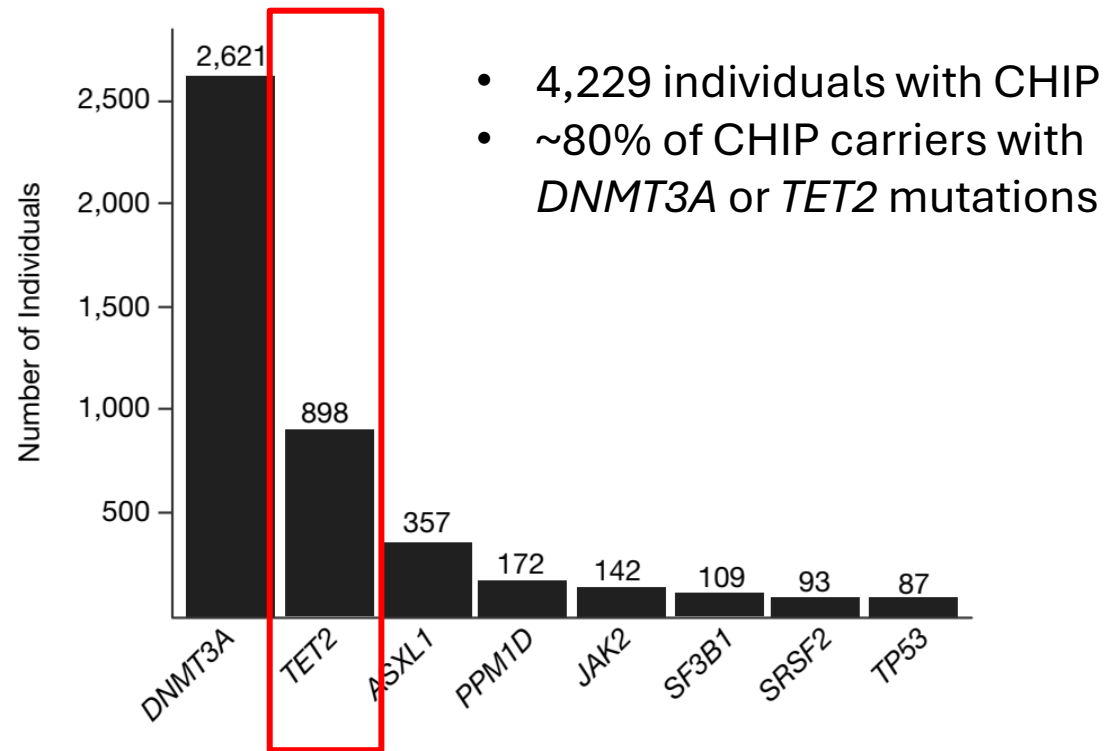


Jaiswal et al. 2017. *NEJM*

Suppression of clonal expansion may prevent CHIP-related illnesses.

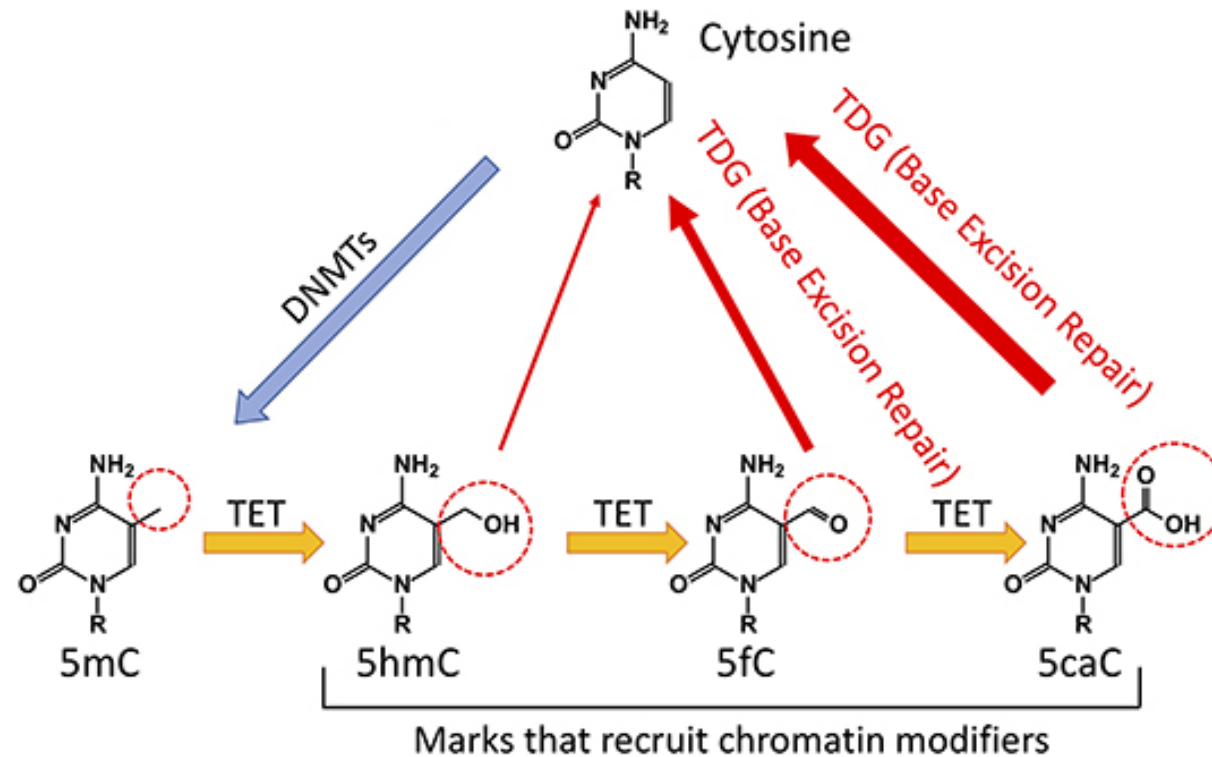
***DNMT3A* and *TET2* are the two most frequently mutated genes in CH**

NHLBI TOPMed Project



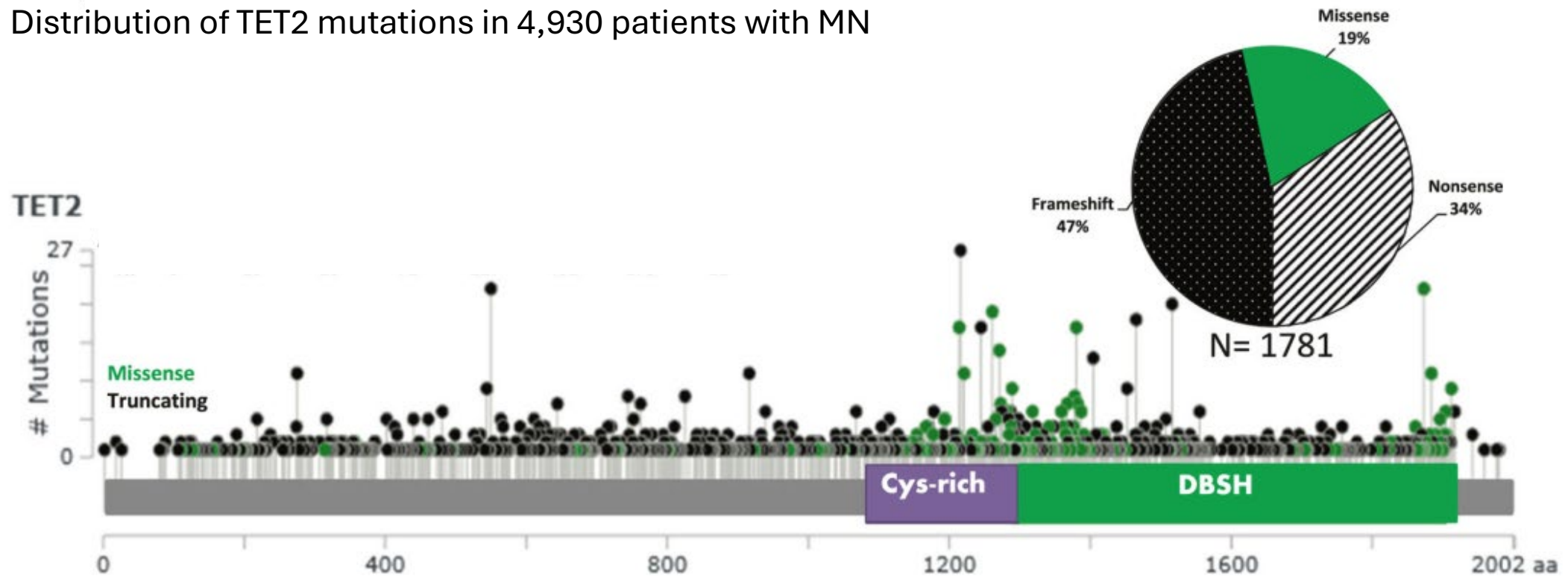
Bick et al. 2020. *Nature*

TET2 catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine



***TET2* mutations lead to a loss of function**

Distribution of TET2 mutations in 4,930 patients with MN



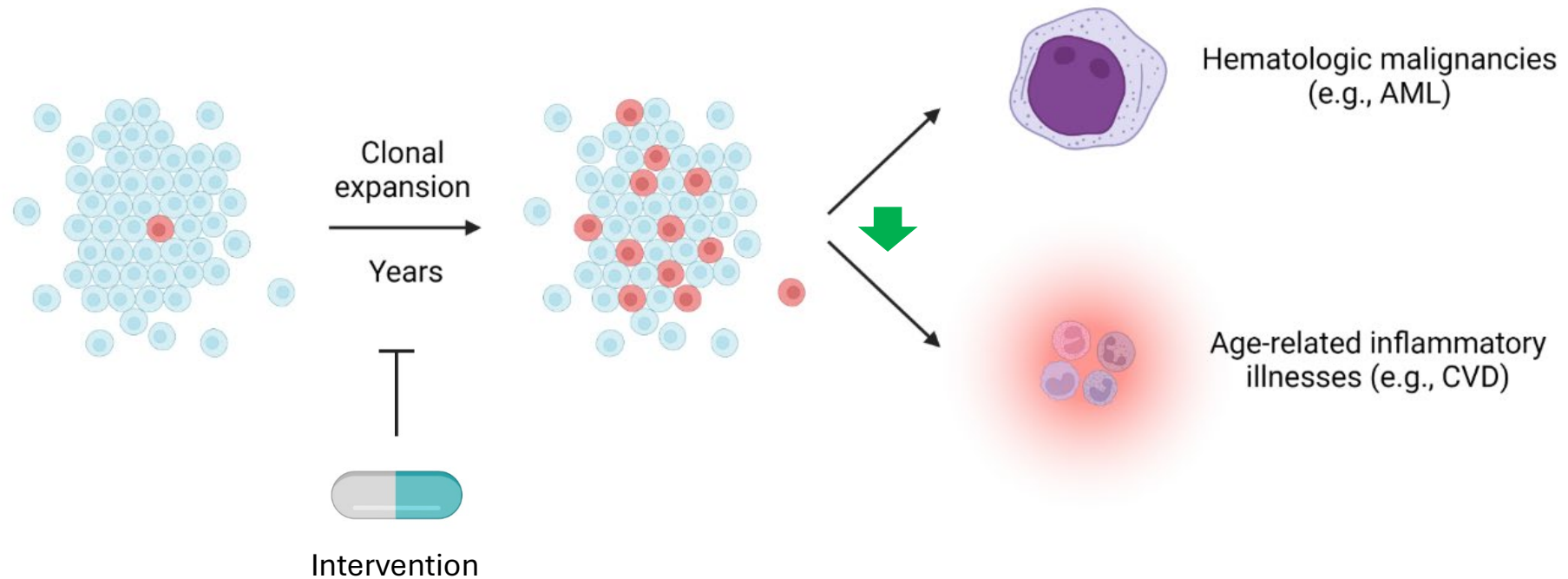
Hirsch et al. 2018. *Leukemia*

Summary – Targeting *TET2* mutations

- TET2-deficient HSPCs are preferentially dependent on DOT1L activity.
- TET2 deficiency causes aberrant H3K79 hypermethylation at the *Mpl* locus and a consequent increase in *Mpl* gene expression.
- *Tet2*^{KO} HSPCs are dependent on heightened TPO-R signaling to maintain their competitive advantage.
- Pharmacologic inhibition of JAK2 suppresses the clonal expansion of *Tet2*^{KO} HSPCs.
- Inhibition of DOT1L activity and TPO-R/JAK2 signaling are potential therapeutic strategies to suppress the expansion of *TET2*-mutated clones.

What's next?

Prevention Clinical Trials



1. How do we identify patients with CH?
2. Which subset of CH carriers do we target?
3. What are the appropriate endpoints?