VANDERBILT UNIVERSITY

Clonal Hematopoiesis

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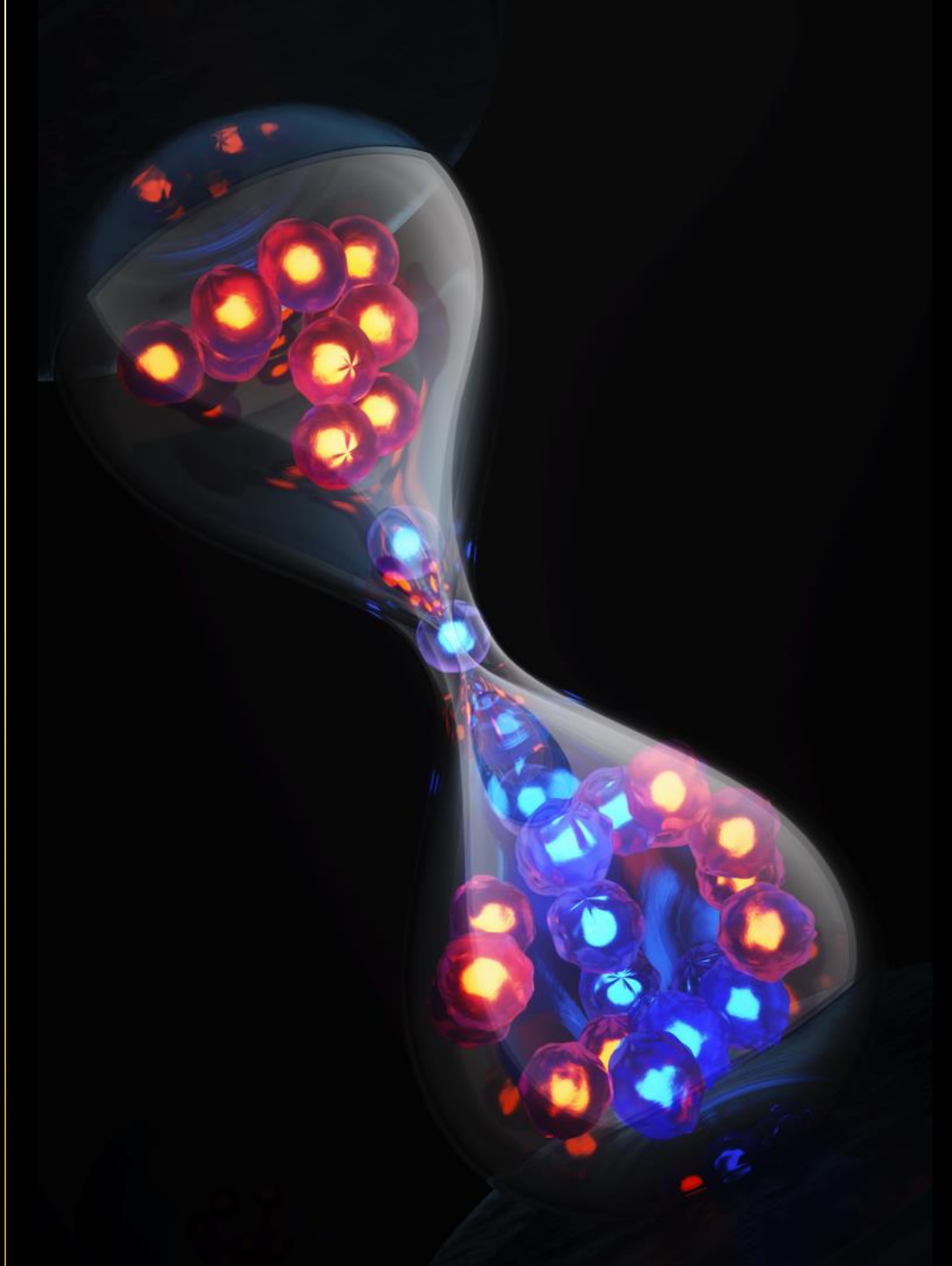
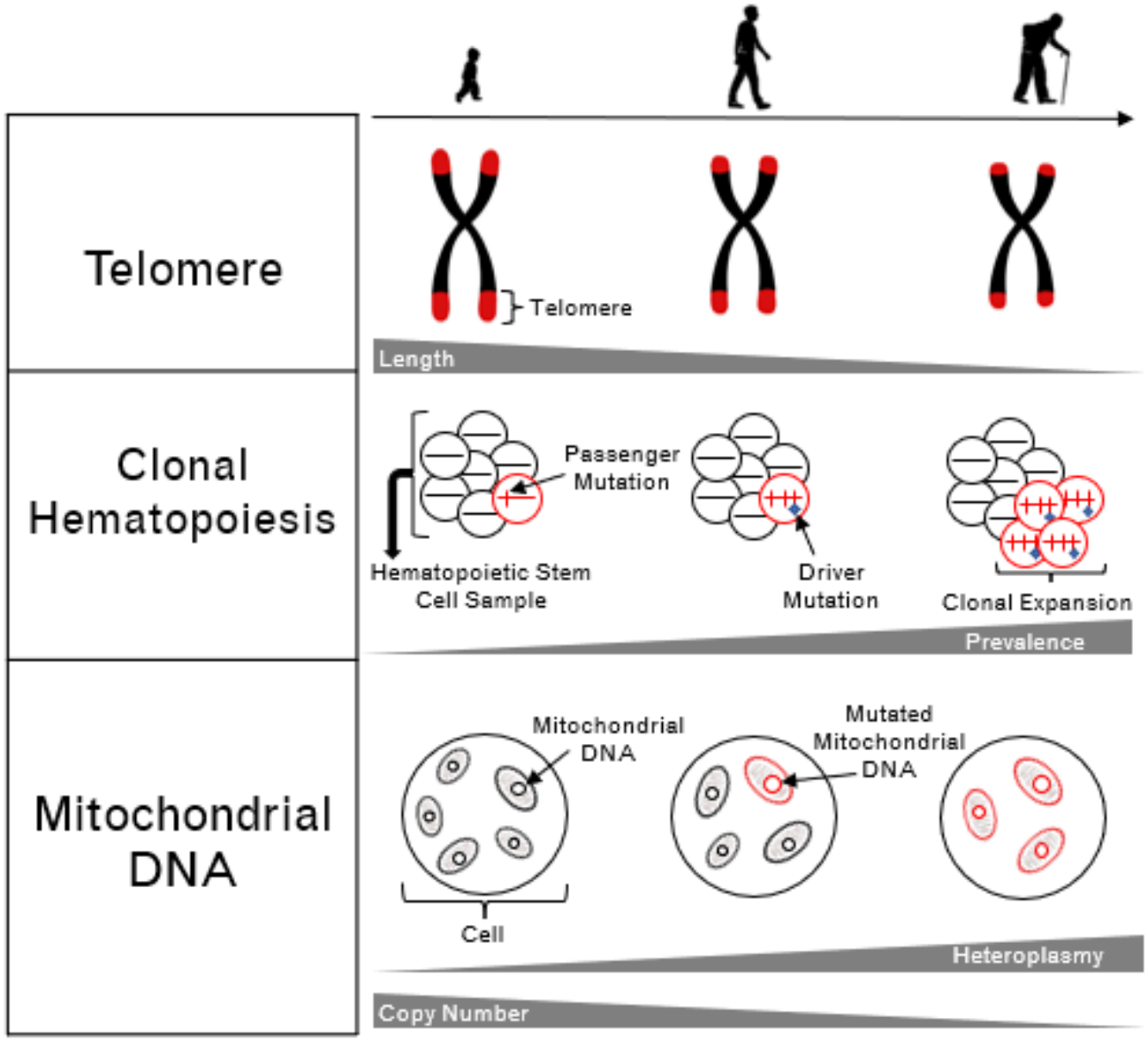


Disclosures

I am on the scientific Advisory Board of TenSixteen Bio.

Although some things never change … our genome does



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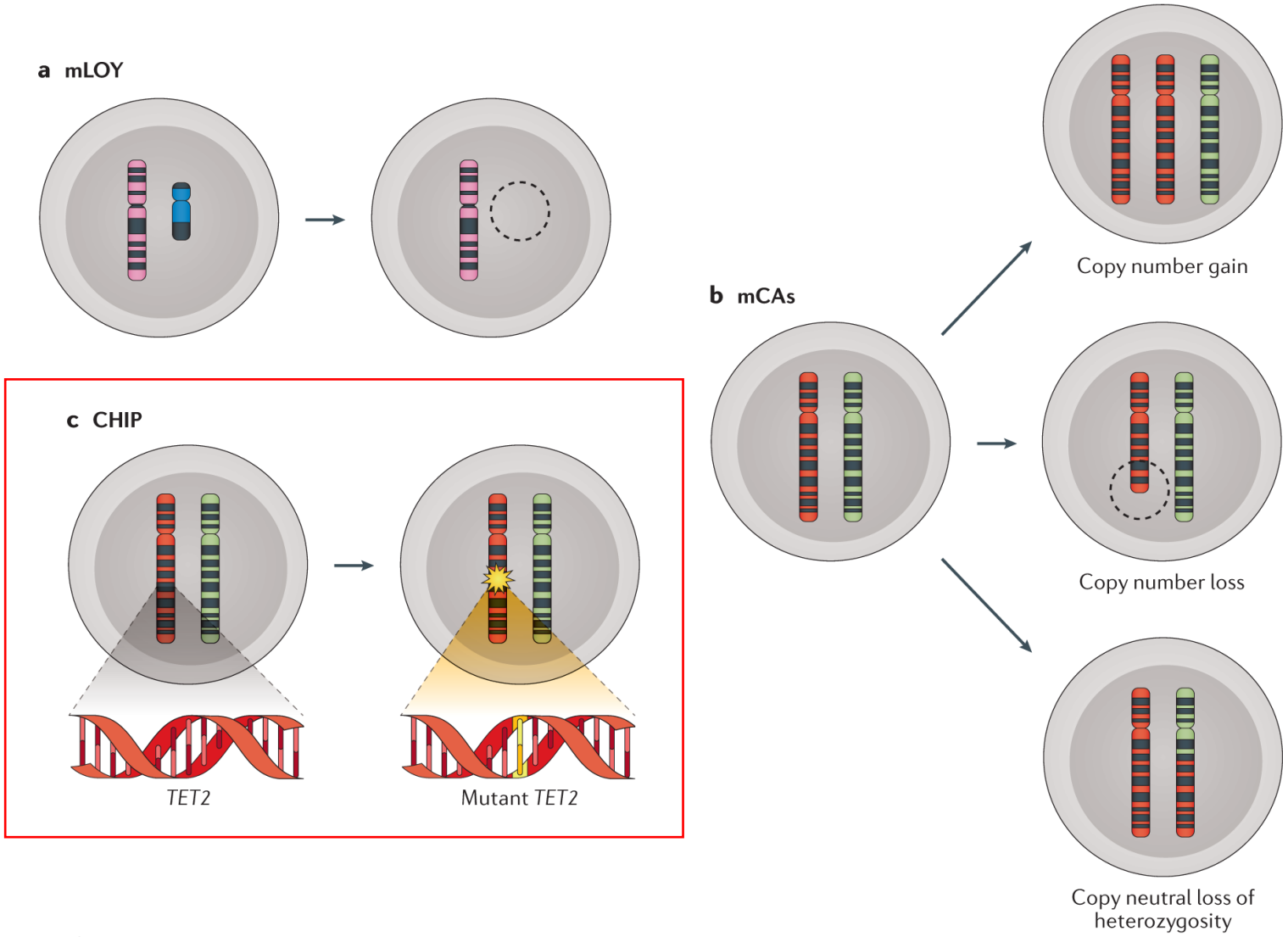
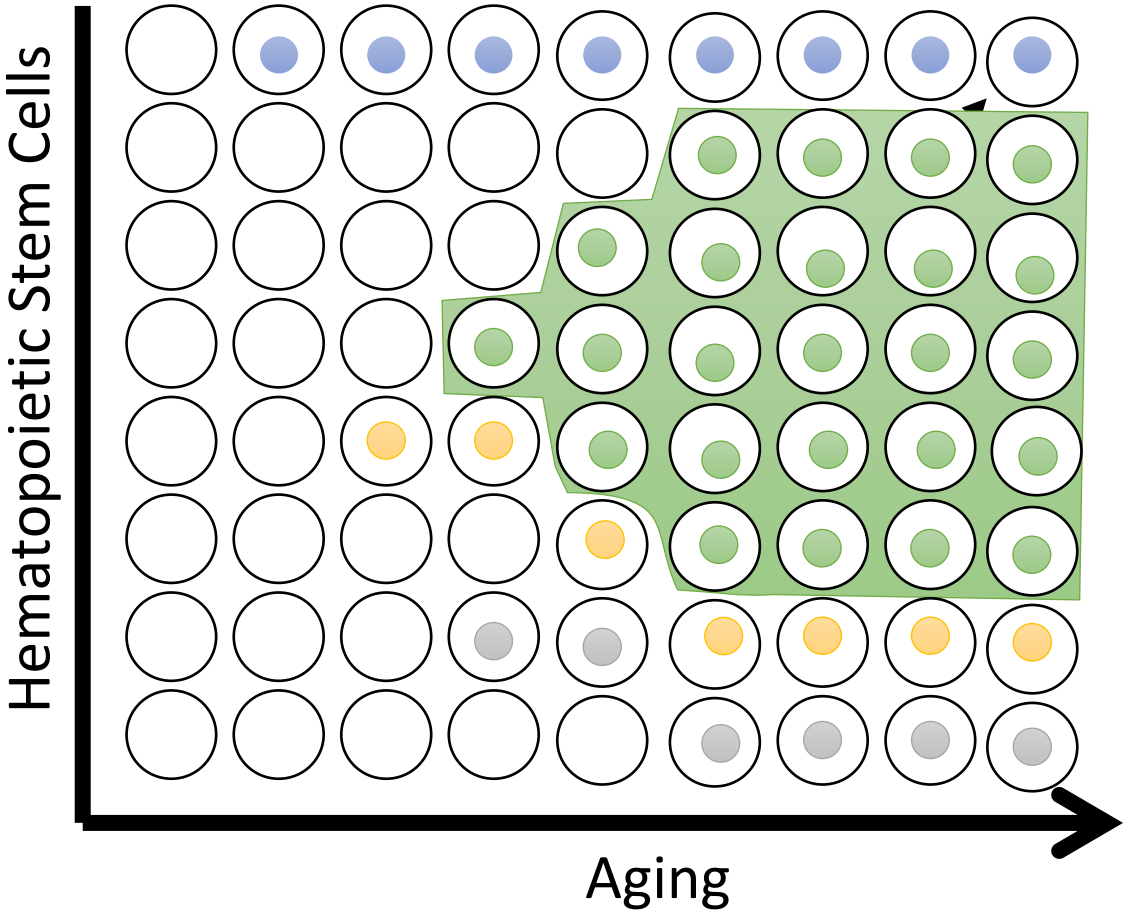


Silver, Bick, Savona, Nature Rev. Genetics 2021

WHO Classification of Haemato- lymphoid Tumours 5th edition



Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Myeloid driver mutation
- Variant Allele Fraction >2%
- No other blood abnormalities

WHO Classification of Haemato- lymphoid Tumours 5th edition

MODERN PATHOLOGY

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PDF [9 MB]

5TH EDITION OF THE WORLD HEALTH CLASSIFICATION OF TUMORS OF THE HEMATOPOIETIC AND LYMPHOID TISSUES

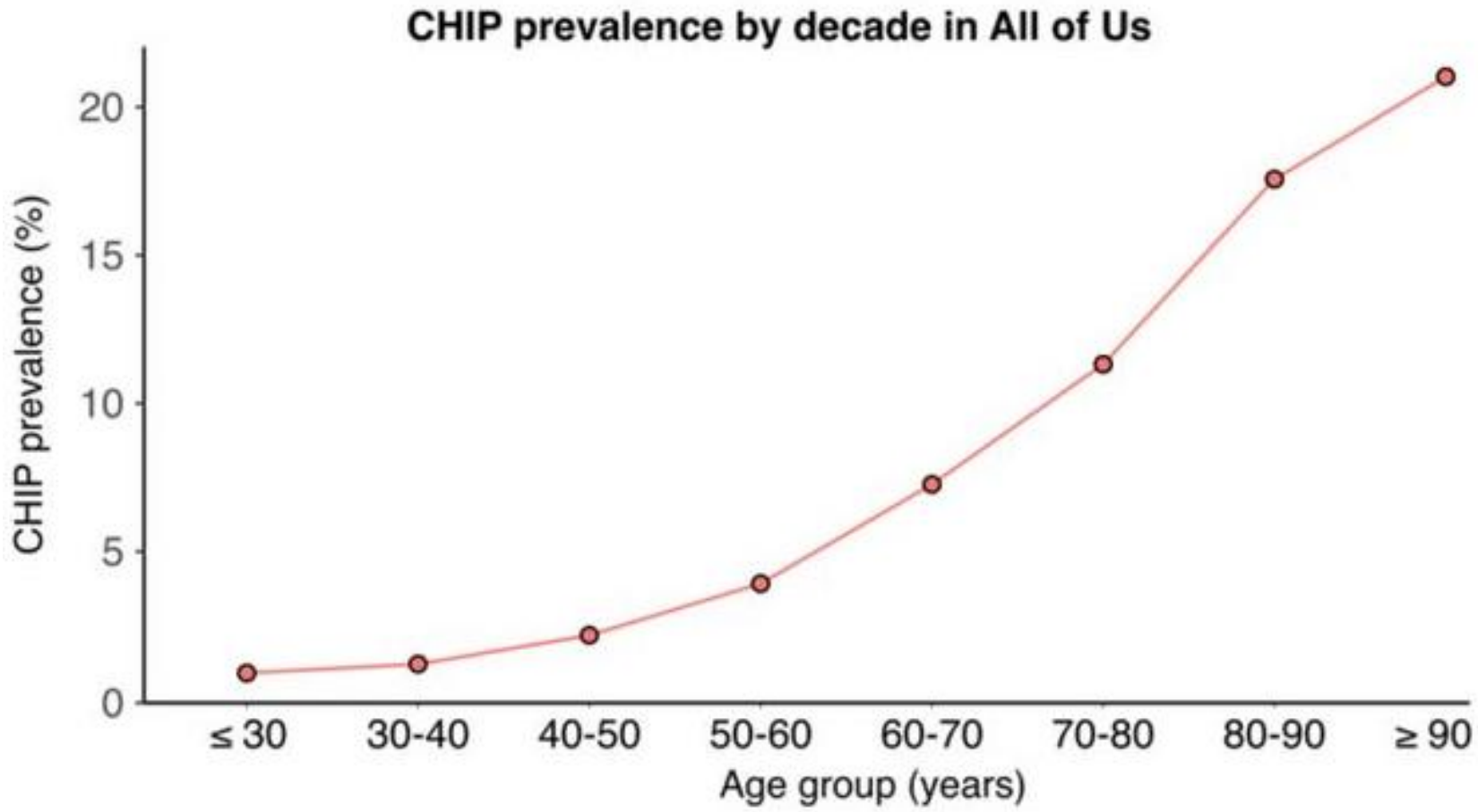
Sanam Loghavi • Rashmi Kanagal-Shamanna • Joseph D. Khoury • ... Reza Nejati • Mrinal M. Patnaik • on behalf of the WHO 5th Edition Classification Project • Show all authors

Published: December 01, 2023 • DOI: https://doi.org/10.1016/j.modpat.2023.100397

Aging

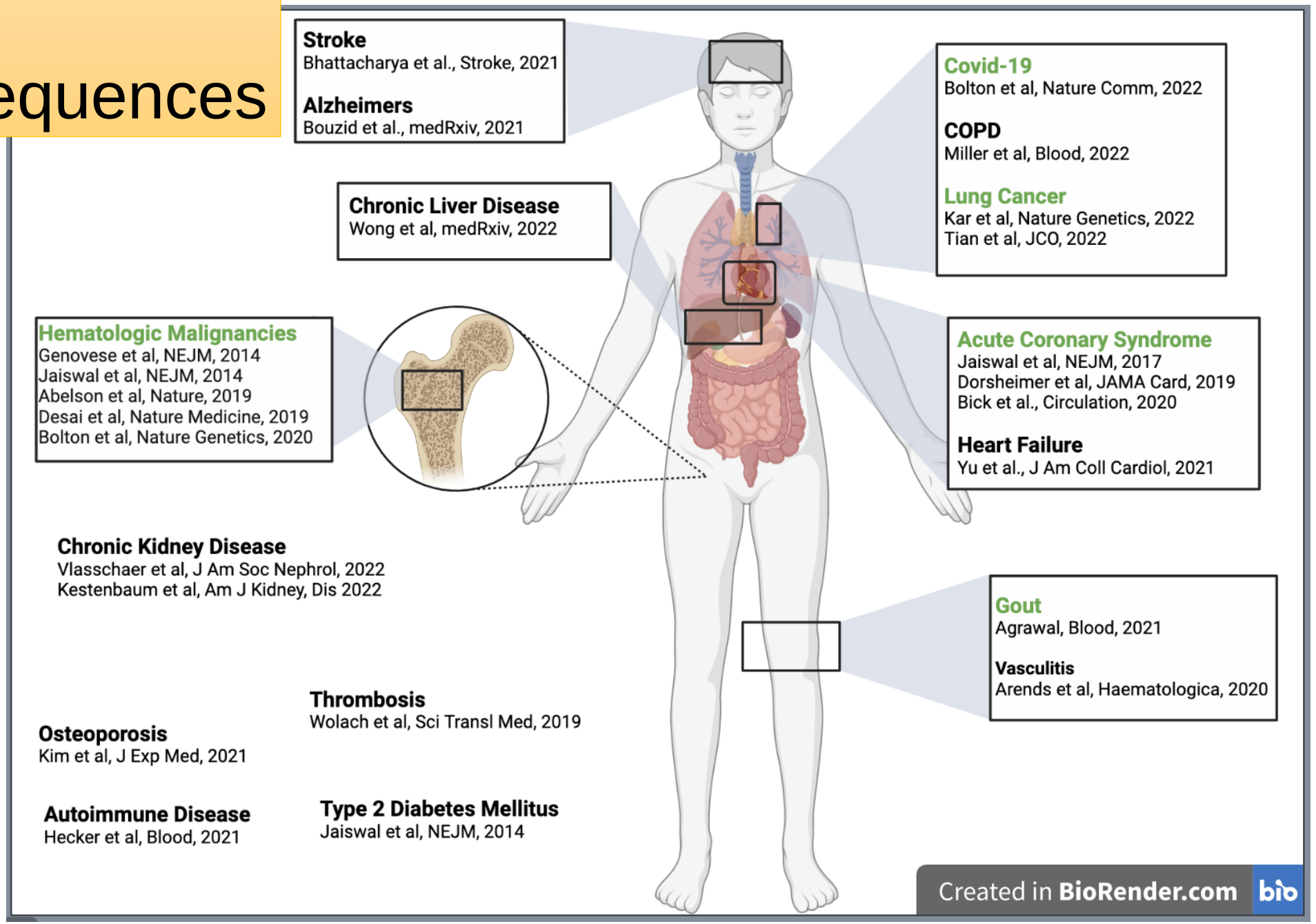
- CHIP + unexplained cytopenia

CHIP is common in the elderly



Vlasschaert […] Bick, Blood 2023

CHIP consequences



Beeler, Bick & Bolton, Nature Cardiovascular Research, 2022

nature genetics

Article

https://doi.org/10.1038/s41588-023-01555-z

Genetics and epidemiology of mutational barcode-defined clonal hematopoiesis

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Check for updates

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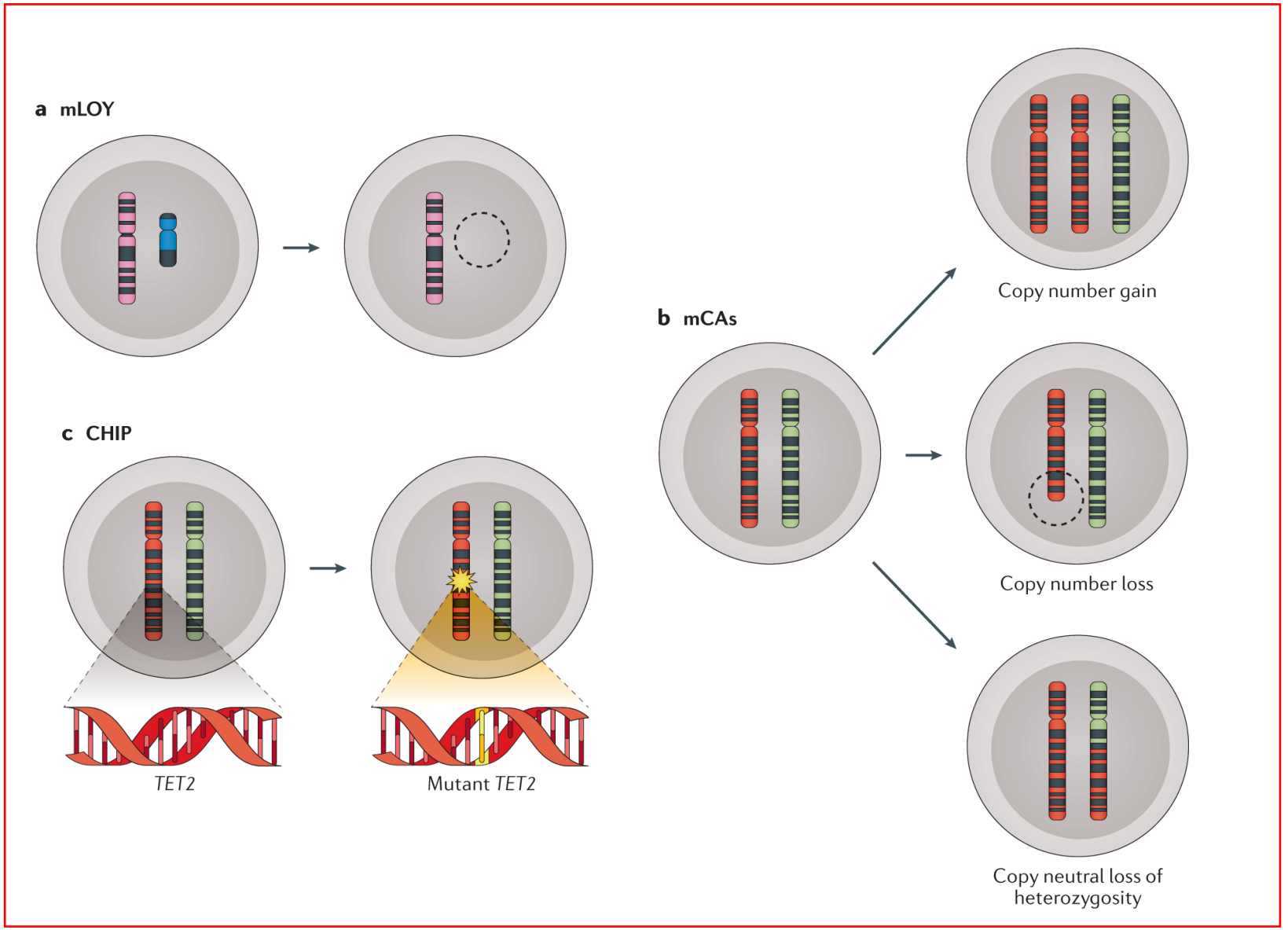
Smoking demonstrates a dosage-dependent impact on risk of CH. CH associates with several smoking-related diseases. Contrary to published claims, we find no evidence that CH is associated with cardiovascular disease. We provide evidence that CH is driven by genes that are commonly mutated in myeloid neoplasia and implicate several new driver genes.

deCODE CH

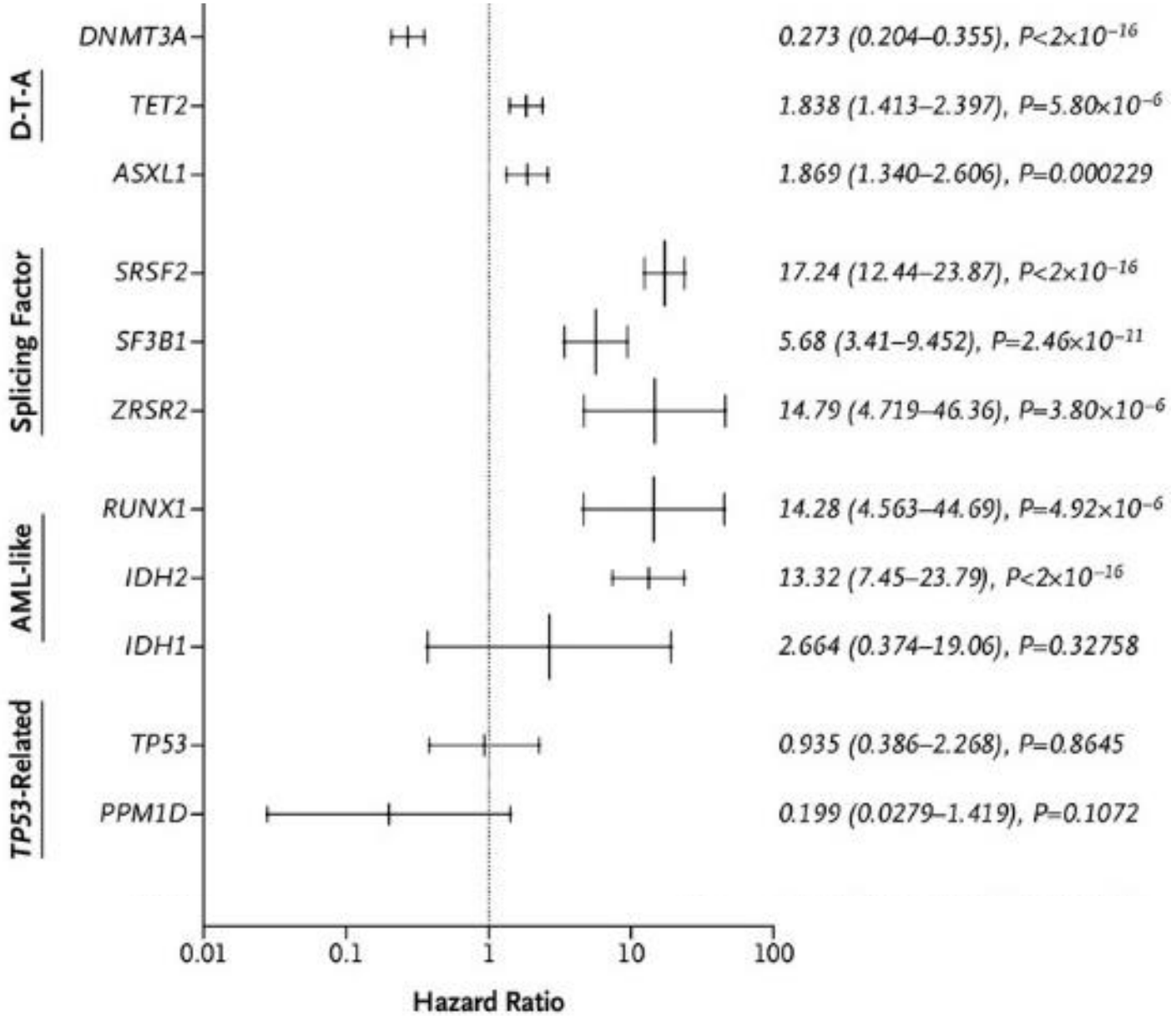

a mLOY
b mCAs
c CHIP
Copy number gain
Copy number loss
Copy neutral loss of heterozygosity
TET2
Mutant TET2

CHIP is associated with cardiovascular disease in the UK Biobank

Caitlyn Vlasschaert, Giulio Genovese, Yash Pershad, Siddhartha Jaiswal, Pradeep Natarajan, Alexander G. Bick

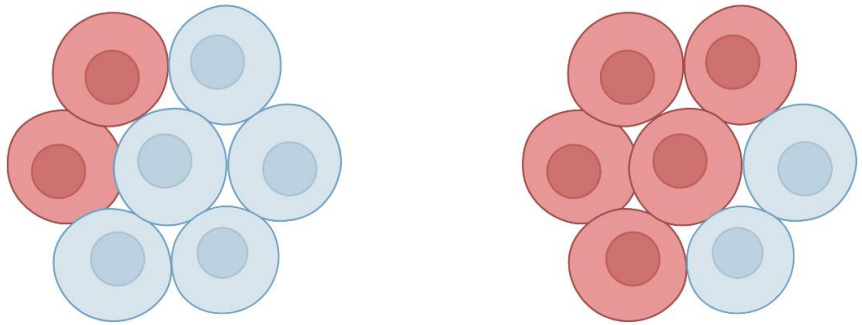
doi: https://doi.org/10.1101/2023.11.30.23299001

Myeloid Malignancy risk differs by CHIP gene

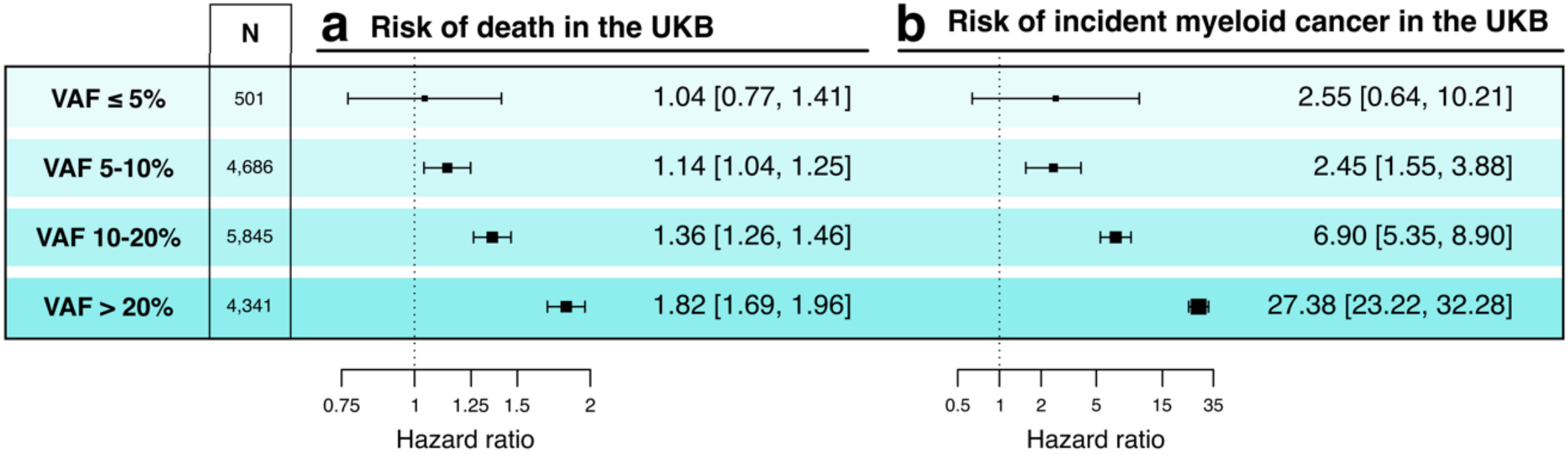


Weeks, NEJM Evidence 2023

Larger CHIP clones have worse outcomes

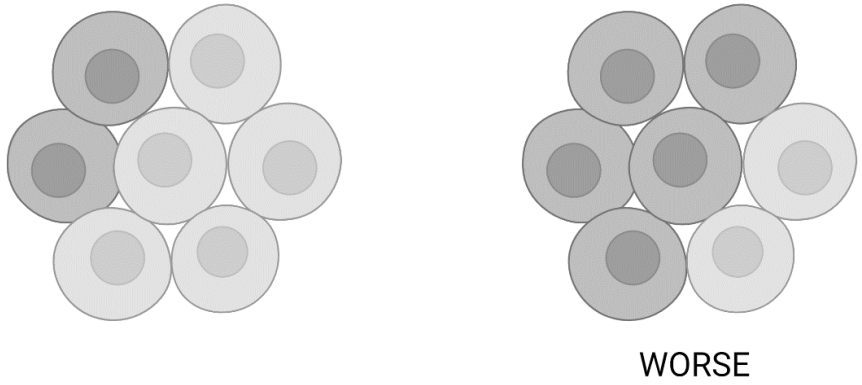


WORSE



Vlasschaert … Bick, Blood 2023

Larger CHIP clones have worse outcomes



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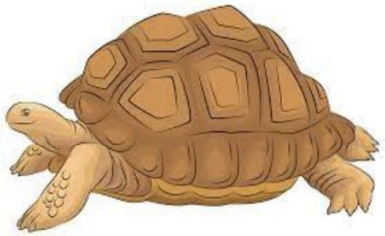
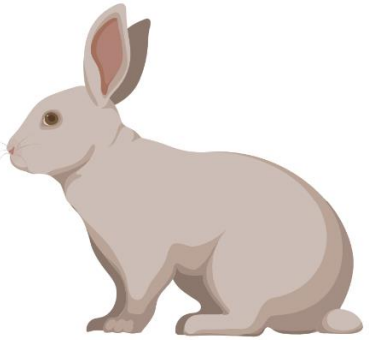




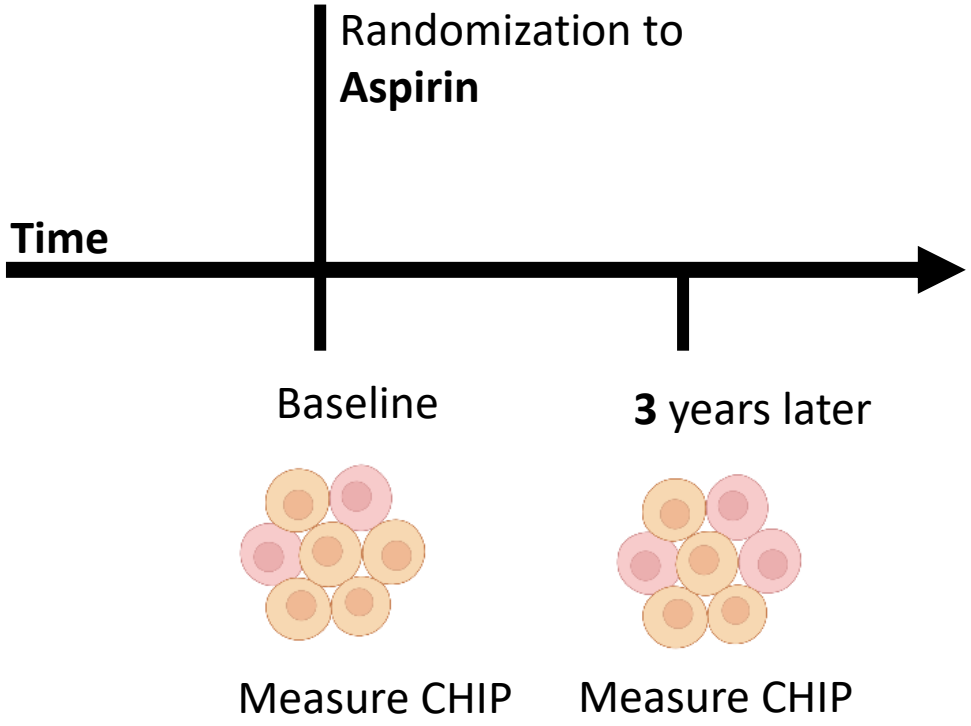
WORSE

Bigger clones have worse outcomes.

<u>Hypothesis:</u>

Faster growth is worse than slower growth.

ASPREE-CHIP study

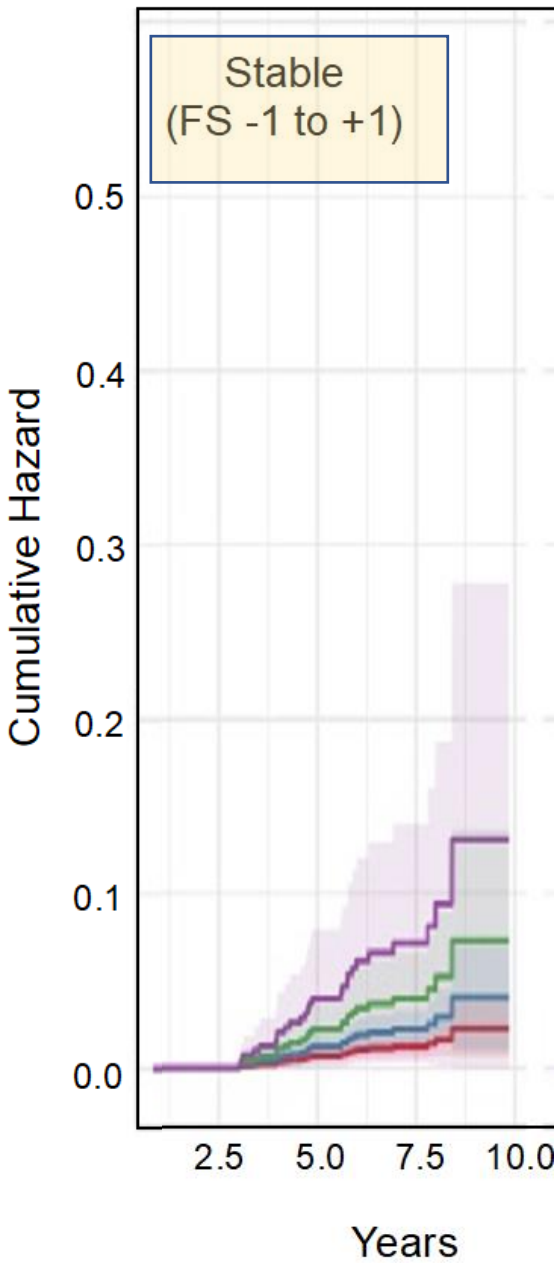


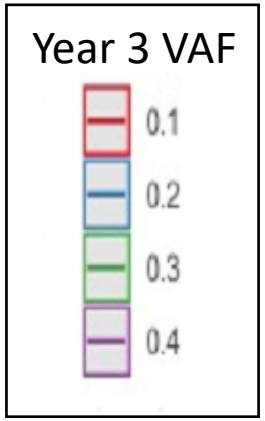
Participants: Community-dwelling age ≥70 or ≥65 US minorities
Intervention: randomization to 100mg aspirin daily or placebo
Main Outcomes and Measures: Disability-free survival, mortality, cancer and MACE

Median follow-up: 4.6 years
Observational f/u: 6.9 years

Zoe McQuilten, David Curtis
ASPREE-CHIP Investigators

ASPREE: Faster growth **is** worse than slower growth





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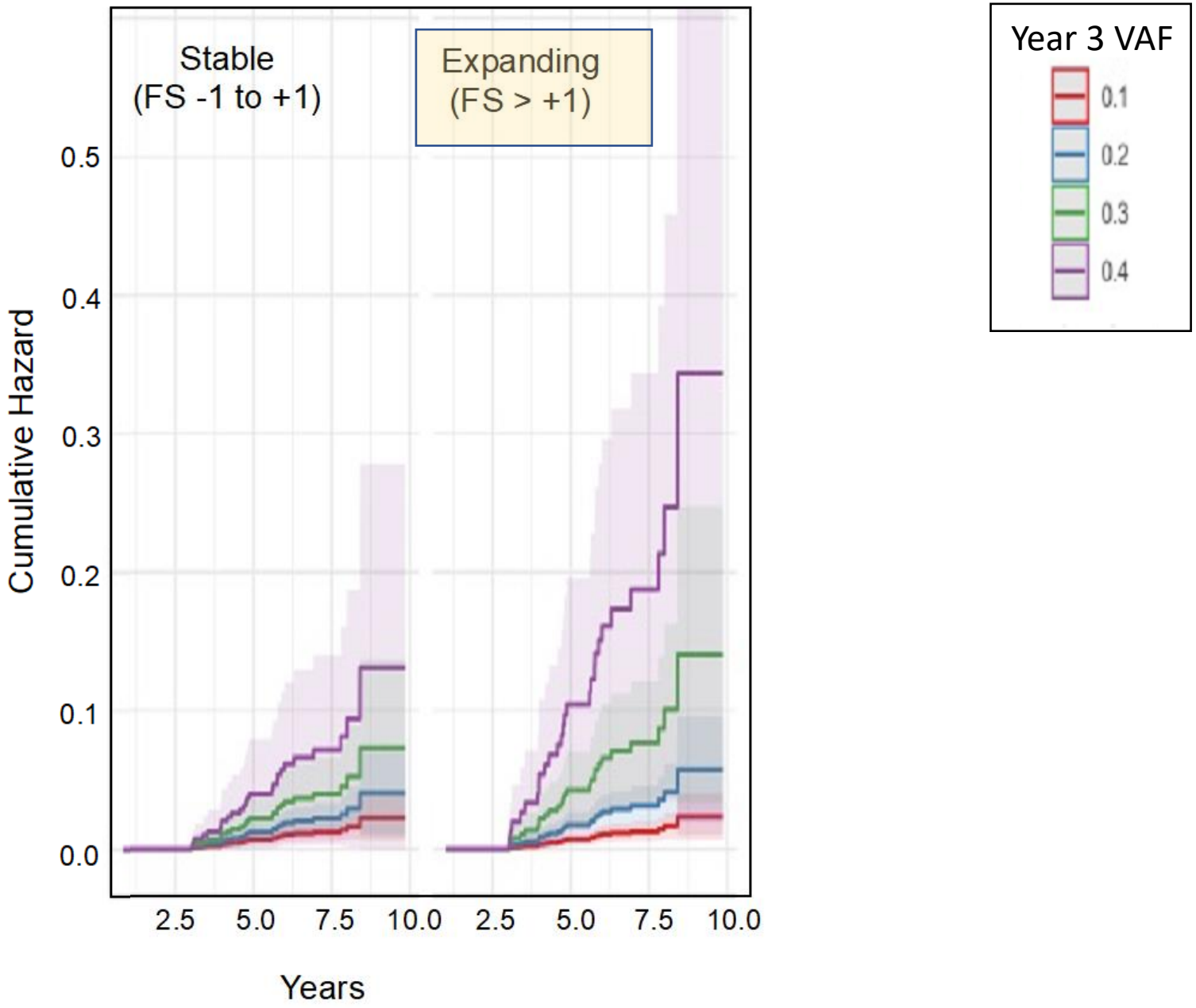

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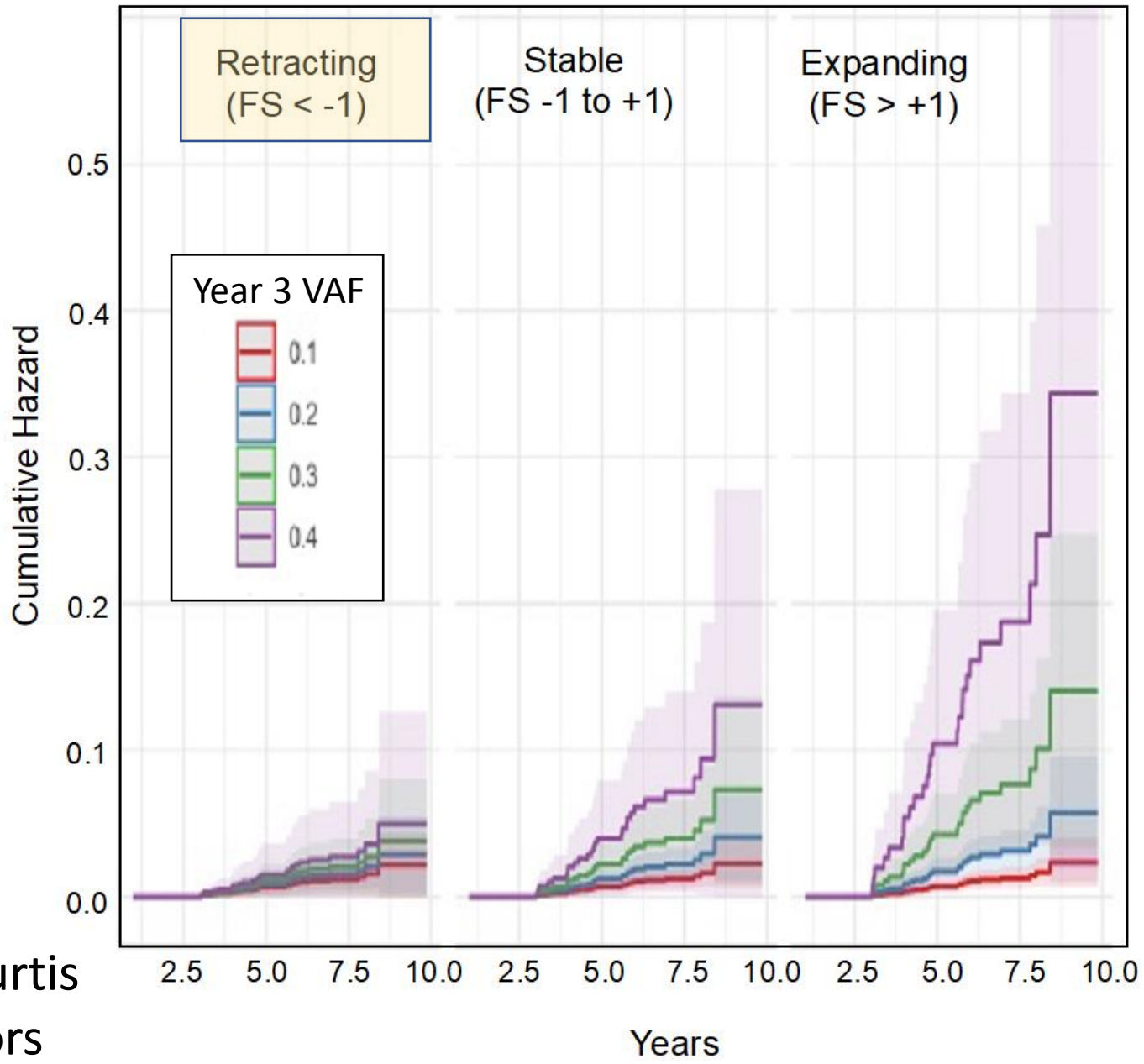


Zoe McQuilten, David Curtis
ASPREE-CHIP Investigators

What causes CHIP?

HSC Intrinsic

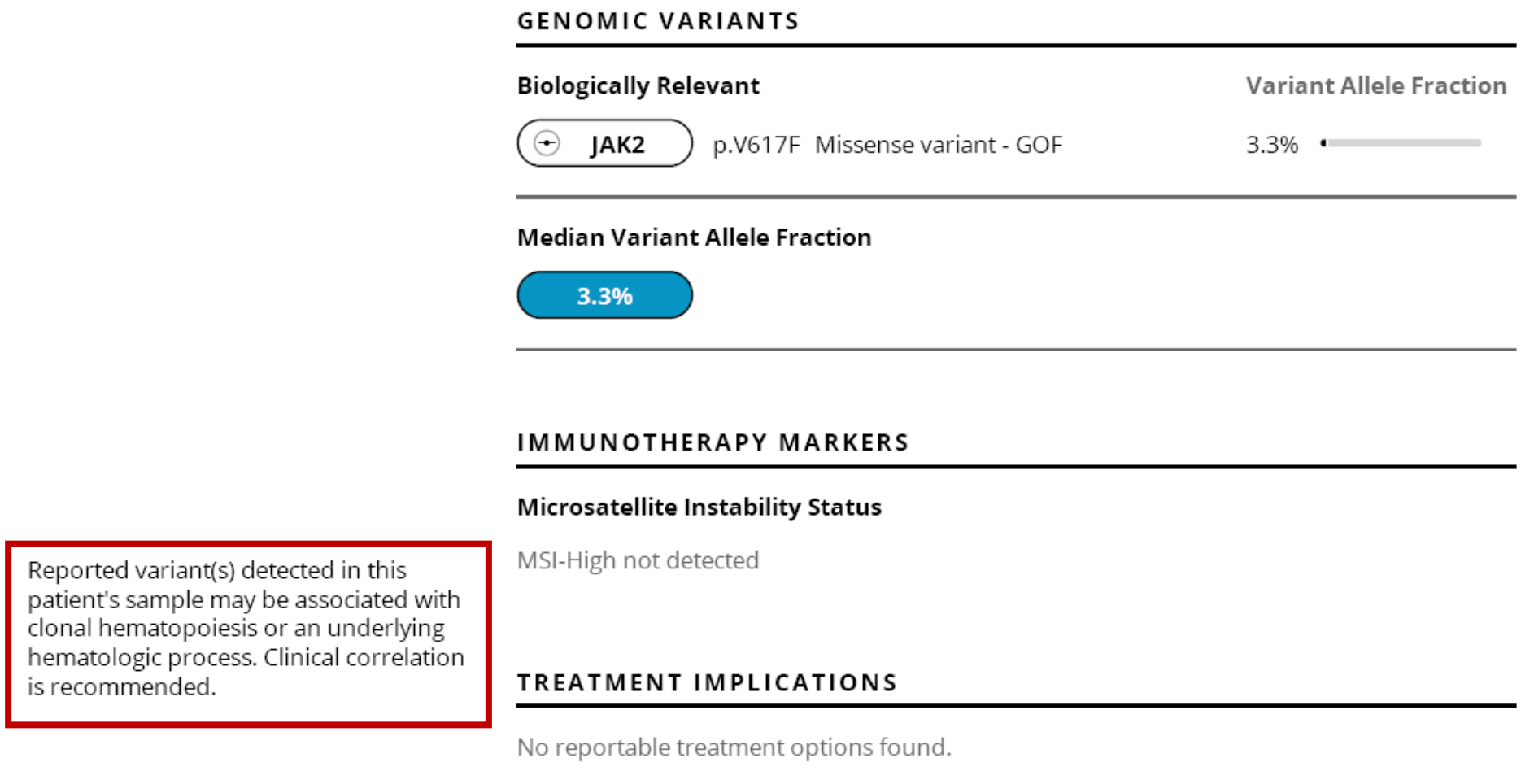
- DNA damage
  - Aging
  - Smoking
  - Radiation exposure
  - Telomere attrition
  - DNA mismatch repair
- **Germline genetics**

Selective pressures

- Chemotherapy
- Immune-mediated marrow depletion
- Inflammation, infection, stress […]

How are CHIP patients identified clinically?

Incidental finding from solid tumor genetic testing



GENOMIC VARIANTS

Biologically Relevant — Variant Allele Fraction

JAK2 p.V617F Missense variant - GOF 3.3%

Median Variant Allele Fraction

3.3%

IMMUNOTHERAPY MARKERS

Microsatellite Instability Status

MSI-High not detected

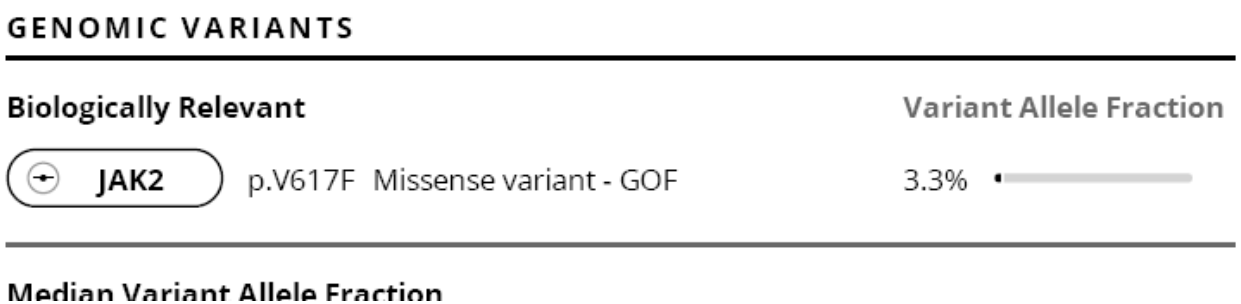
Reported variant(s) detected in this patient's sample may be associated with clonal hematopoiesis or an underlying hematologic process. Clinical correlation is recommended.

TREATMENT IMPLICATIONS

No reportable treatment options found.

How are CHIP patients identified clinically?

Incidental finding from solid tumor genetic testing



Myeloid NGS panel during cytopenia workup

TECHNICAL SUMMARY

Gene	Alteration	AMP Tier	Chr	Pos	Ref	Alt	Coverage	Allele Freq. or Fold Change
TET2	p.Gly1187Alafs*39	II	4	106164048	AG	A	14298	9%

Clonal Hematopoiesis Risk Score (CHRS)					
Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–	< 65y	≥ 65y	–	–

Weeks, NEJM Evidence 2023

Not secure | chrsapp.com

Clonal Hematopoiesis Risk Score (CHRS) Calculator

Patient Characteristics

CHIP or CCUS

Number of mutations

Maximum VAF

Mean corpuscular volume (MCV)

Red cell distribution width (RDW)

Age

About this calculator | CHRS Score and Clinical Outcomes | Population Data

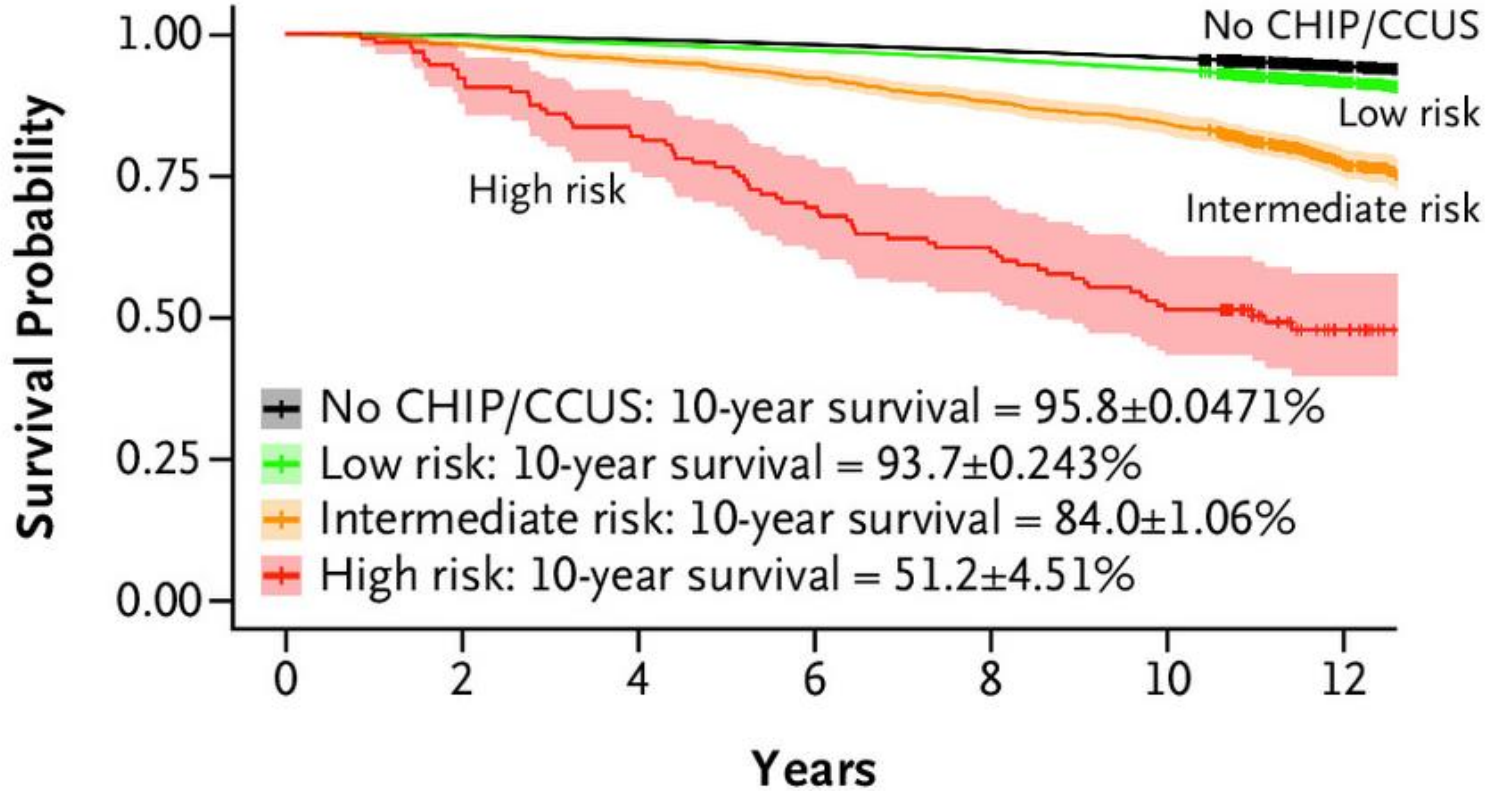
The clonal hematopoiesis risk score (CHRS) is a prognostic model for clonal hematopoiesis of indeterminat
uncertain significance (CCUS) which can be used to estimate 5- and 10- year cumulative risk of myeloid ma
data published in Weeks LD et al. 2023. *New England Journal of Medicine Evidence*. The CHRS was devel
Biobank and validated using patient cohorts from Dana-Farber Cancer Institute, Boston, MA, USA and Univ

Cytopenia definitions in CCUS:
- anemia: hemoglobin < 12g/dL for females, <13 g/dL for males
- thrombocytopenia: platelet count < 150 K/uL
- neutropenia: absolute neutrophil count < 1.8 K/uL

Using the CHRS calculator:

- Outcome predictions are made using data/variables obtained at the time of next generation sequenci
- Select a diagnosis of CHIP or CCUS.
- Select the number of pathogenic somatic variants (mutations) detected by peripheral blood or bone m
- For patients with only 1 mutation, indicate whether the mutated gene is *DNMT3A* (single *DNMT3A*). This field will default to 'Absent' for patients with multiple mutations.
- Indicate whether there are mutations in high risk genes (*SF3B1, SRSF2, ZRSR2, JAK2, TP53, RUN.* This field defaults to 'Absent' when single *DNMT3A* mutations is selected.
- Indicate if the maximum variant allele fraction (VAF) - for any mutation - is ≥ 0.2 (20%)
- Indicate whether mean corpuscular volume (MCV) is ≥ 100 femtoliters, red cell distribution width is ≥
- After entering patient information, click 'Calculate CHRS'.

www.chrsapp.com



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

Weeks, NEJM Evidence 2023

Ongoing Clonal Hematopoiesis Clinical Trials

There are no FDA approved therapies for CHIP

Targeting Specific Driver Mutations

- Ivosidenib for Patients With Clonal Cytopenia of Undetermined Significance and Mutations in IDH1 [NCT05030441]
- A Study of Enasidenib in People With Clonal Cytopenia of Undetermined Significance [NCT05102370]

Targeting bone marrow environment

- Canakinumab for the Prevention of Progression to Cancer in Patients With Clonal Cytopenias of Unknown Significance, IMPACT Study [NCT05641831]

The under-appreciation of CHIP

It's time to drop the "indeterminate" and get serious about this biomarker

ERIC TOPOL

MAY 21, 2023

Each day the 50,000 to 200,000 blood stem cells in our bone marrow, known as hematopoietic (HSC), produce billions of specialized blood cells—red blood cells, platelets, B and T lymphocytes, and various myeloid cells (white blood cells, such as neutrophils and monocytes). As we age, the repeated cell divisions of the HSCs lead to acquired ("somatic") mutations. When such a mutation of an HSC leads to a clone that expands—which denotes some fitness advantage— it is known as clonal hematopoiesis. CHIP, which stands for clonal hematopoiesis of indeterminate potential, refers to presence of myeloid blood cells with a driver gene mutation (with a frequency of ≥ 2%) without any clinical criteria of a blood cancer. It turns out CHIP is a major biomarker, not just for blood cancer (an 11-fold risk of a blood malignancy, or absolute 0.5% risk per year), but also for heart disease, blood clot events such as stroke and pulmonary embolism, and many other chronic illnesses (simplified Figure below).

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