Age-related changes in hematopoiesis

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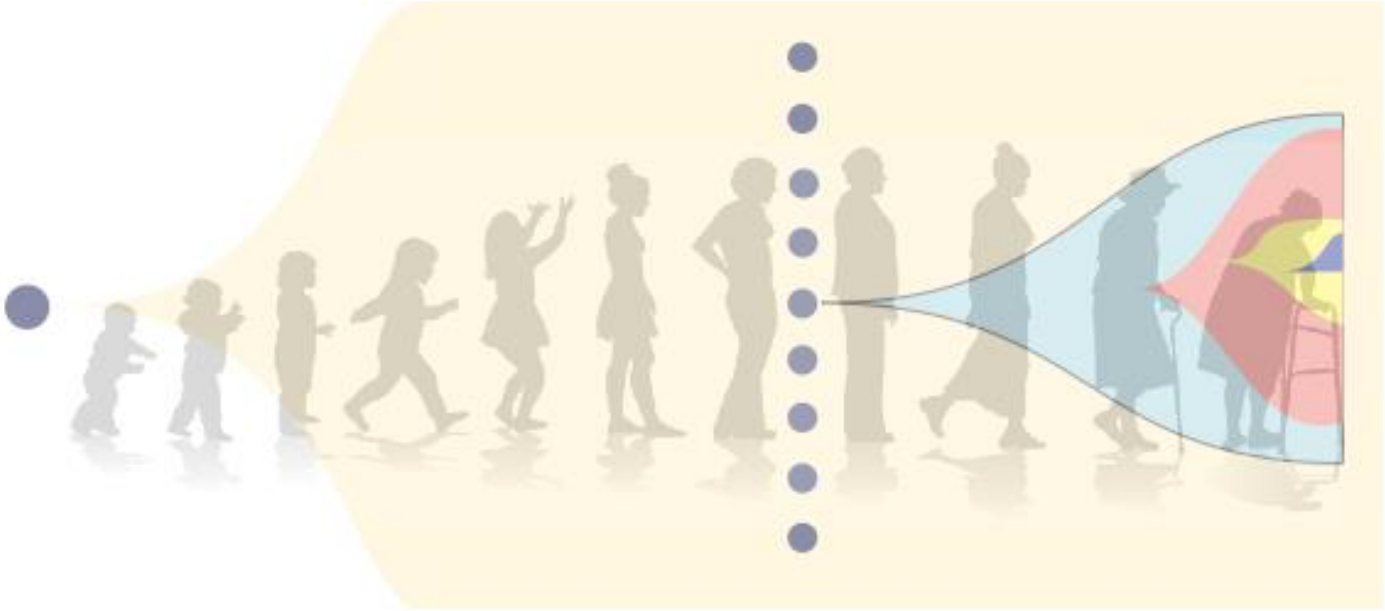
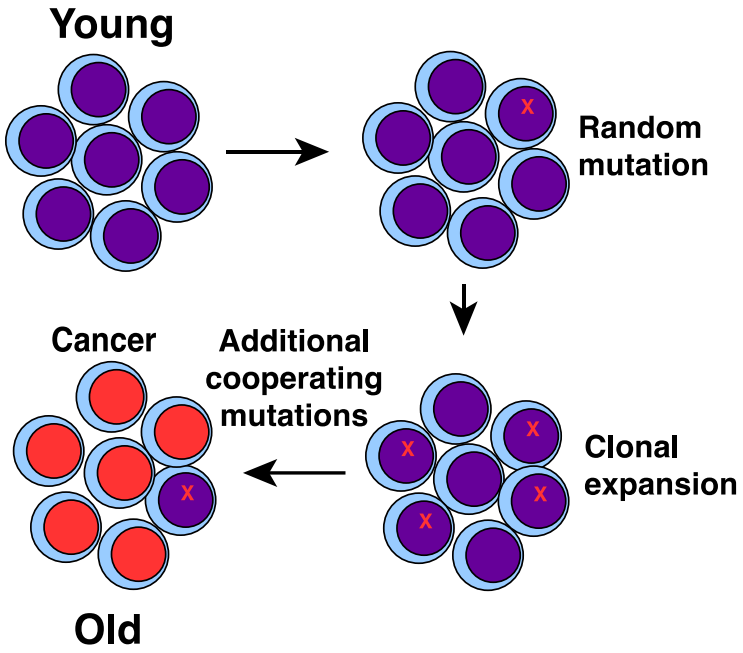
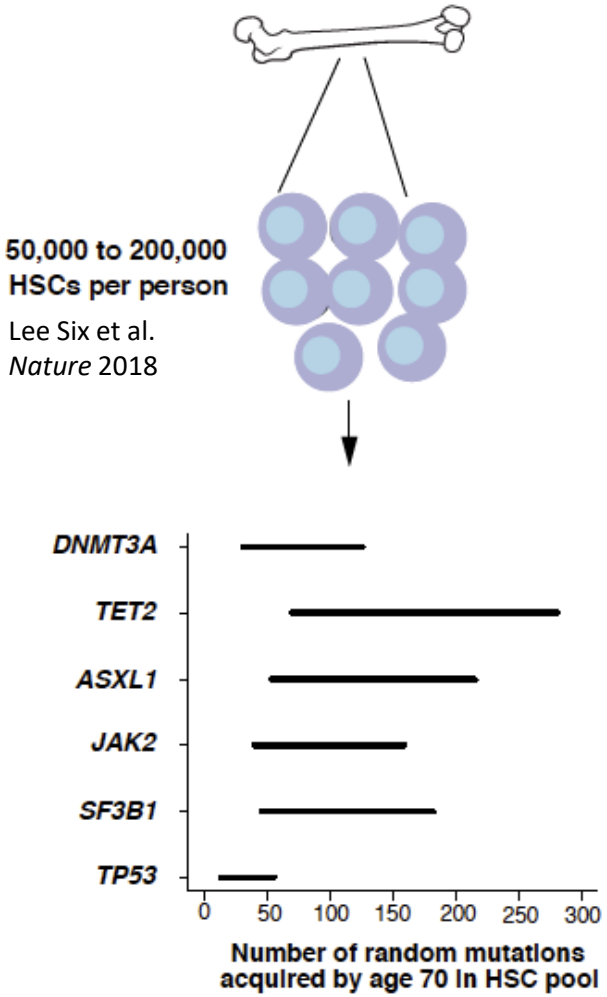


Clonal hematopoiesis



Presaged by work in skewed XCI (**Busque**, **Gilliland**, **Levine**, et al.) and pre-leukemic HSCs in AML (**Majeti**, **Slush** et al.)

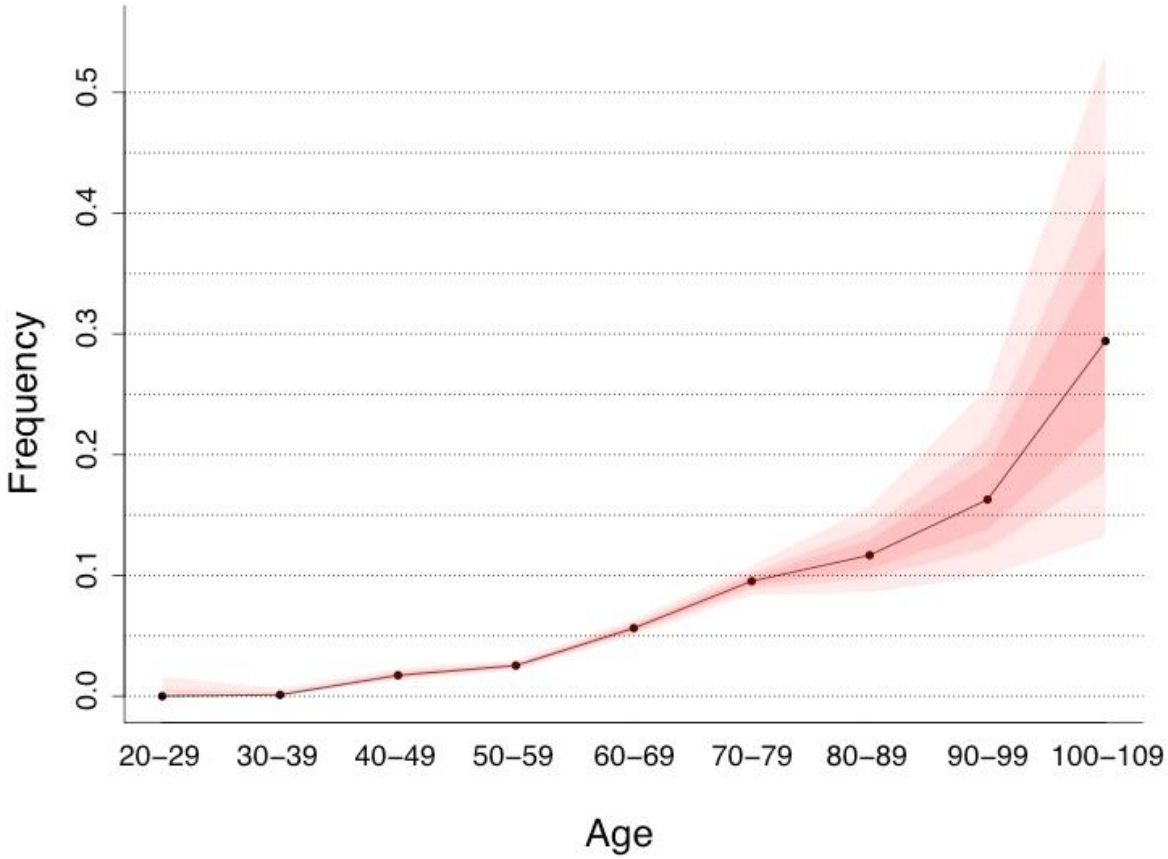


HSCs acquire 1 protein-coding mutation per decade (Welch et al. *Cell* 2012)

By age 70, 1.4 million coding mutations in HSCs

A new clinical entity: Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Defined as a cancer-associated, clonal mutation with VAF>2% in the blood of healthy persons without a known hematologic disorder
- Is **common** with aging (present in at least 10% of all persons age>70)
- Associated with increased relative risk of malignancy, risk of progression is 1% per year



Jaiswal et al., *NEJM* 2014
Genovese et al., *NEJM* 2014
Xie et al., *Nat Med* 2014
Bick et al., *Biorxiv* 2019
McKerrell et al., *Cell Reports* 2015
Coombs et al., Cell Stem Cell 2017

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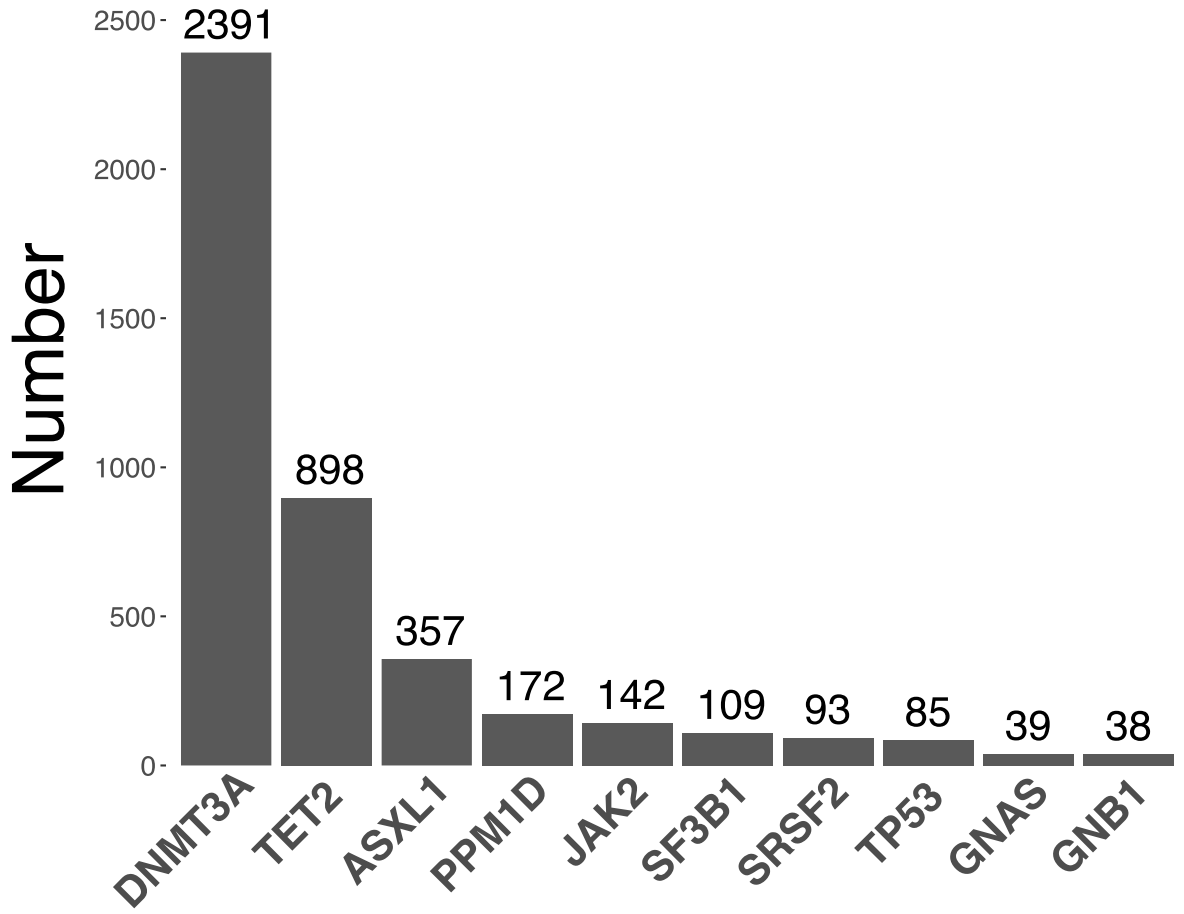
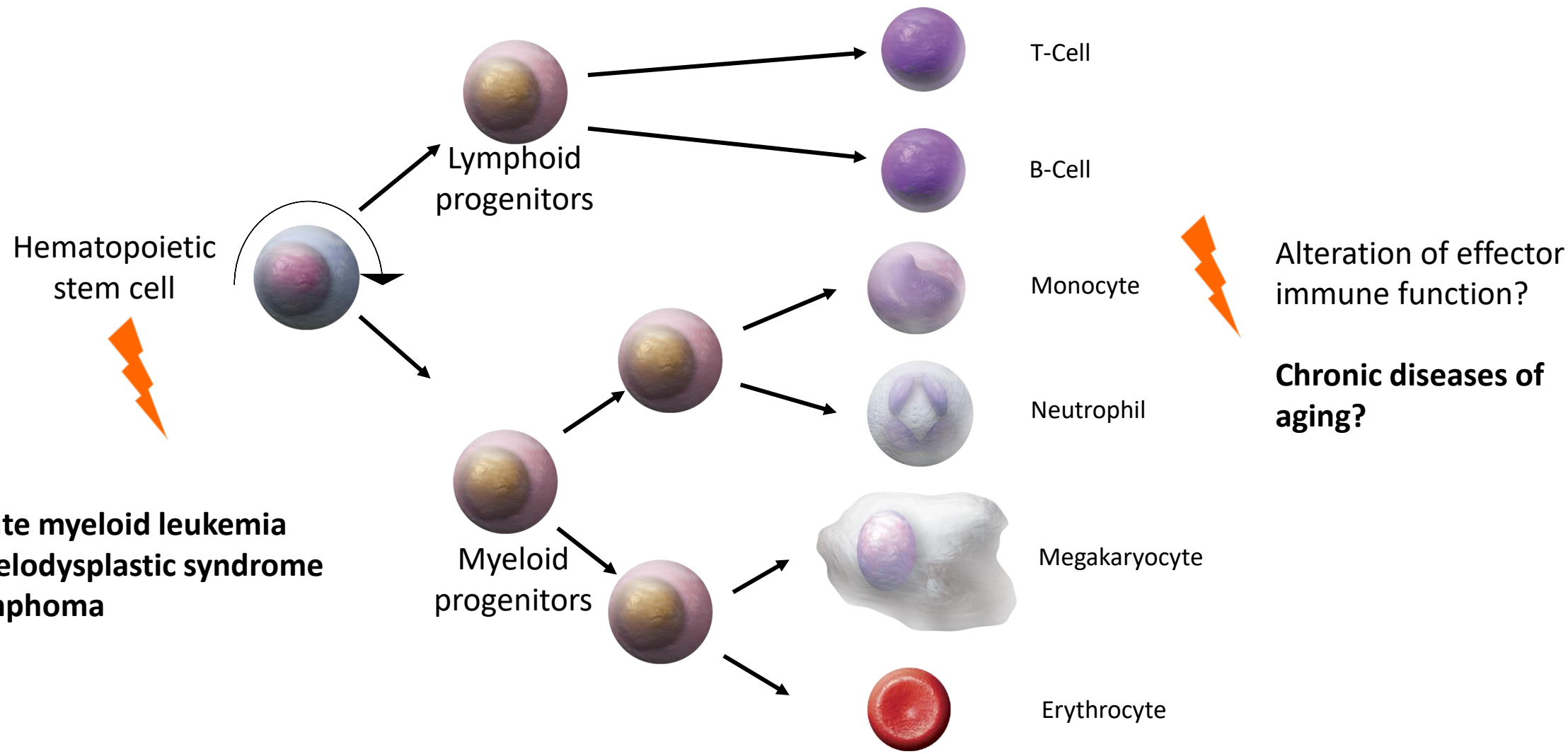
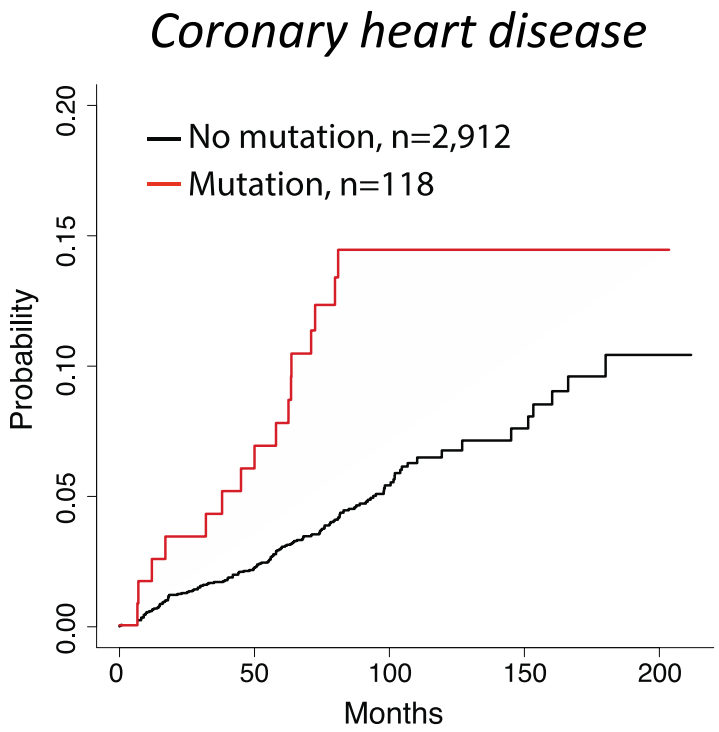


Mutations persist in mature blood lineages



CHIP is associated with higher risk of incident coronary heart disease

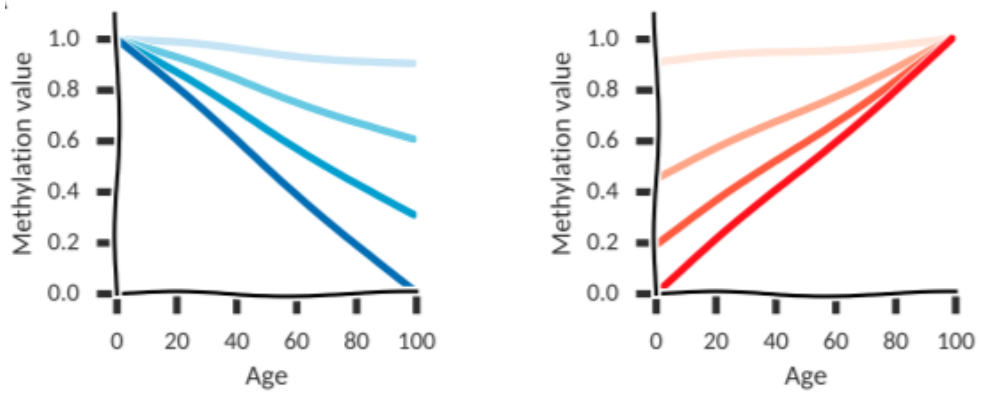


Jaiswal et al., *NEJM* 2014

Risk factor	HR (95% CI)
Age 50–59 years	2.20 (1.32–3.69)
Age 60–69 years	2.41 (1.44–4.02)
Age ≥70 years	6.27 (3.77–10.42)
Female sex	0.68 (0.50–0.93)
Type 2 diabetes mellitus	2.18 (1.62–2.94)
Former or current smoker	1.40 (1.04–1.90)
Hypertension stage II–IV	1.20 (0.89–1.62)
Total cholesterol level >200 mg/dl	1.40 (1.04–1.88)
HDL-cholesterol level <35 mg/dl	1.46 (0.98–2.18)
HDL-cholesterol level >60 mg/dl	0.77 (0.52–1.13)
Presence of CHIP	1.82 (1.15–2.89)

From Jaiswal and Libby, *Nat Rev Card* 2019

DNA methylation clocks



Field et al., *Mol Cell* 2018

Horvath/IEAA
353 CpGs
Works in most tissues

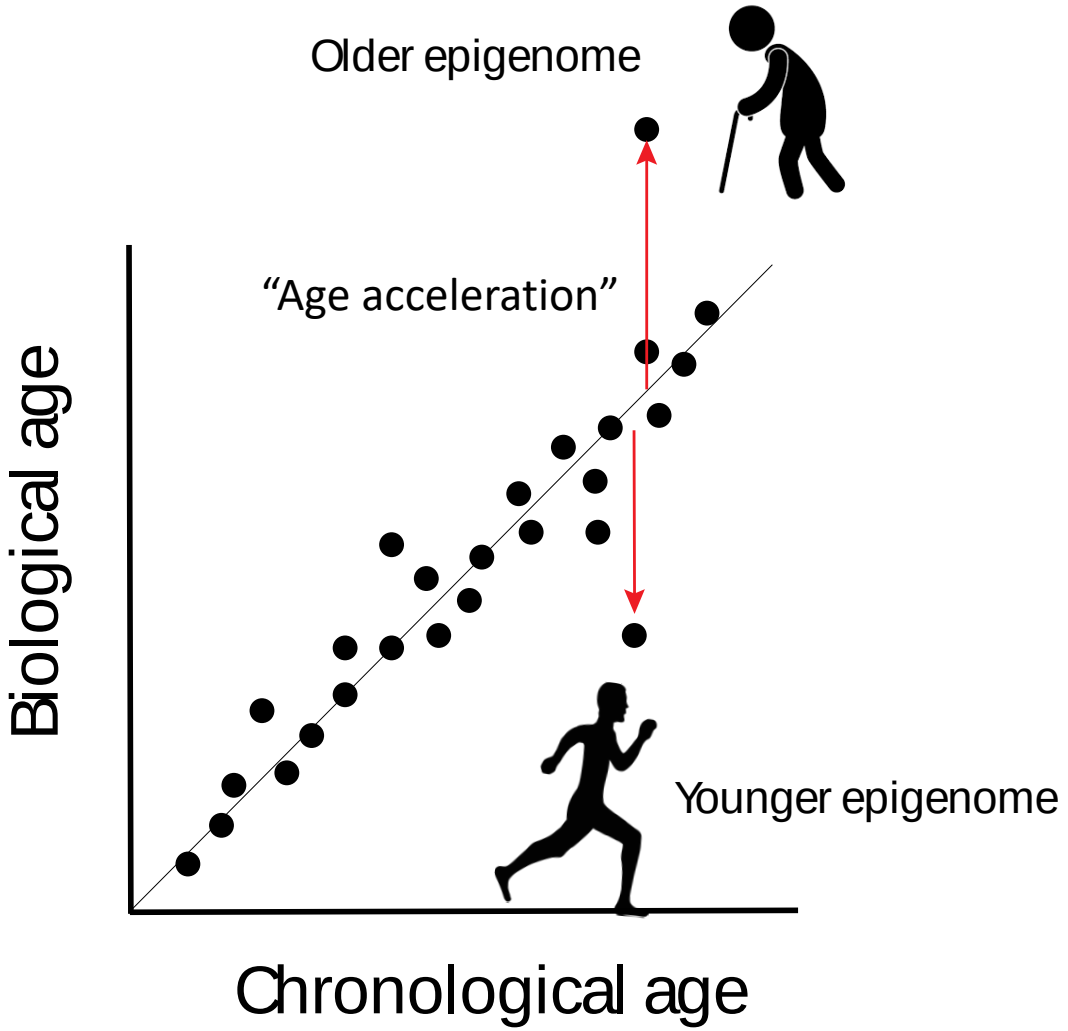
Hannum/EEAA
71 CpGs
Influenced by blood cell composition

GrimAge
1030 CpGs
Smoking
Blood biomarkers

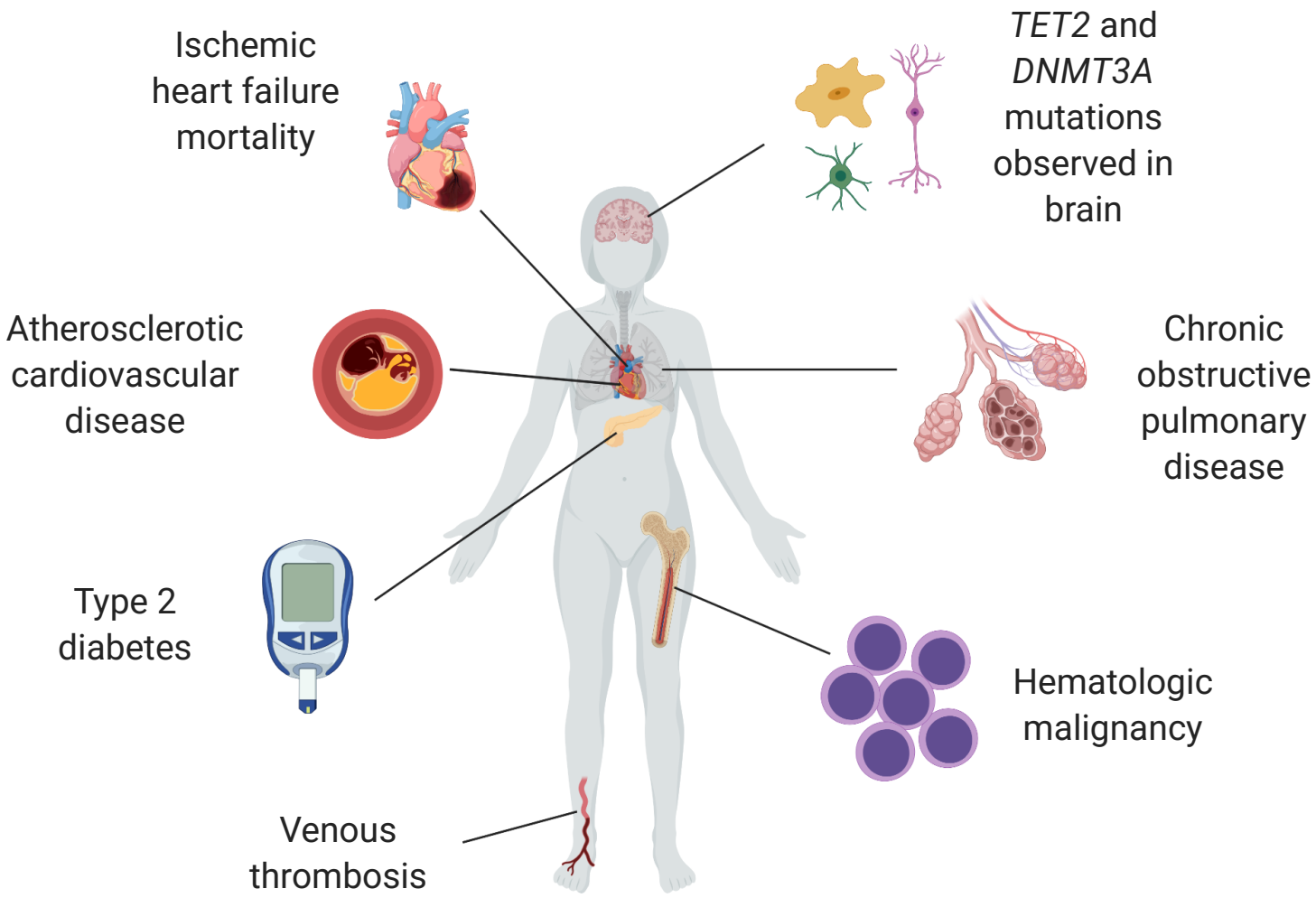
Skin and Blood
391 CpGs
Works in most tissues

PhenoAge
513 CpGs
Mortality/disease

Cell intrinsic (proliferation) ⟷ *Cell extrinsic (biomarkers)*

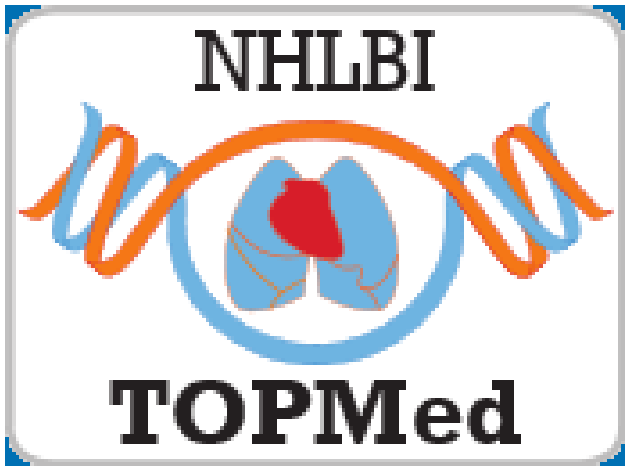


Could CHIP be a modifying factor in many non-neoplastic age-related diseases?



Does CHIP have any association with biological aging?

TOPMed CHIP-Methylation Project



Trans-Omics for Precision Medicine
(>100K participants)

Whole genome sequencing

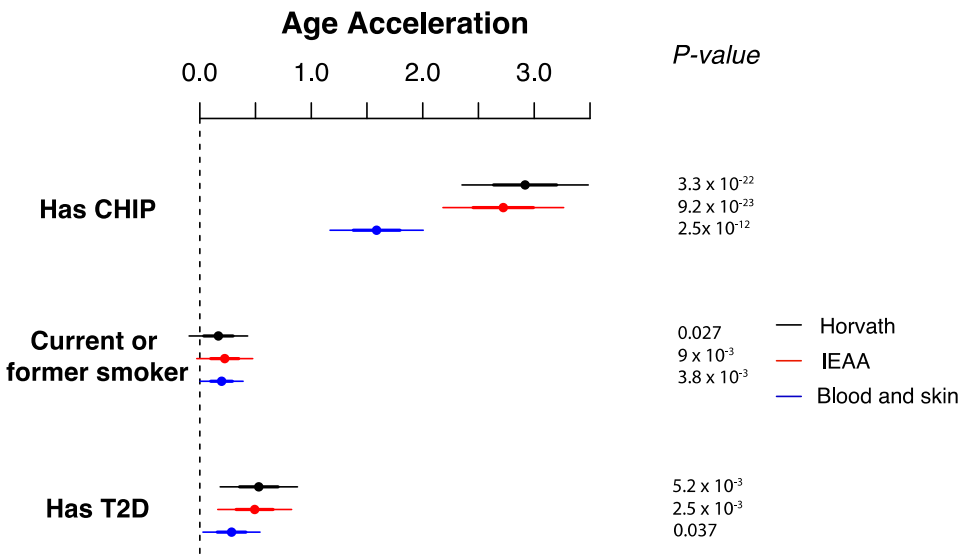
Blood DNA methylation arrays

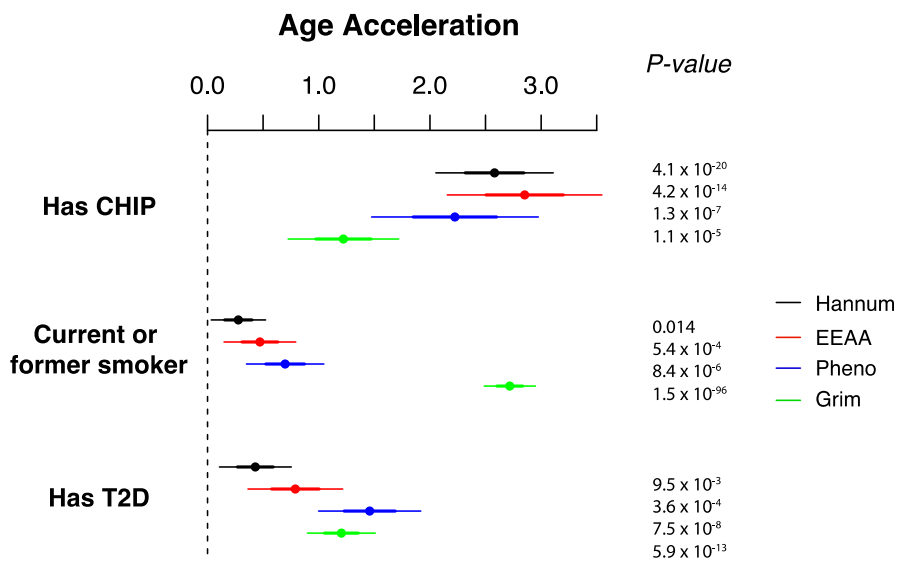
CHIP and methylation age acceleration
~5000 people

CHIP is strongly associated with epigenetic age acceleration

Daniel Nachun

Ake Lu





Adjusted for age at blood draw, sex, race, study cohort, smoking, T2D

Mendelian randomization supports a **causal** role for CHIP in epigenetic aging

Results similar to Robertson et al., *Current Biology* 2019

Nachun et al., *Aging Cell* 2021

Does the combination of CHIP plus epigenetic age predict outcomes?

Cohorts:
FHS (1374)
JHS (1725)
WHI (1235)

269 CHIP carriers

→

Defined 'AgeAccel':
>0 age acceleration in a clock

Horvath
IEAA
Skin and Blood
Hannum
EEAA
PhenoAge
GrimAge

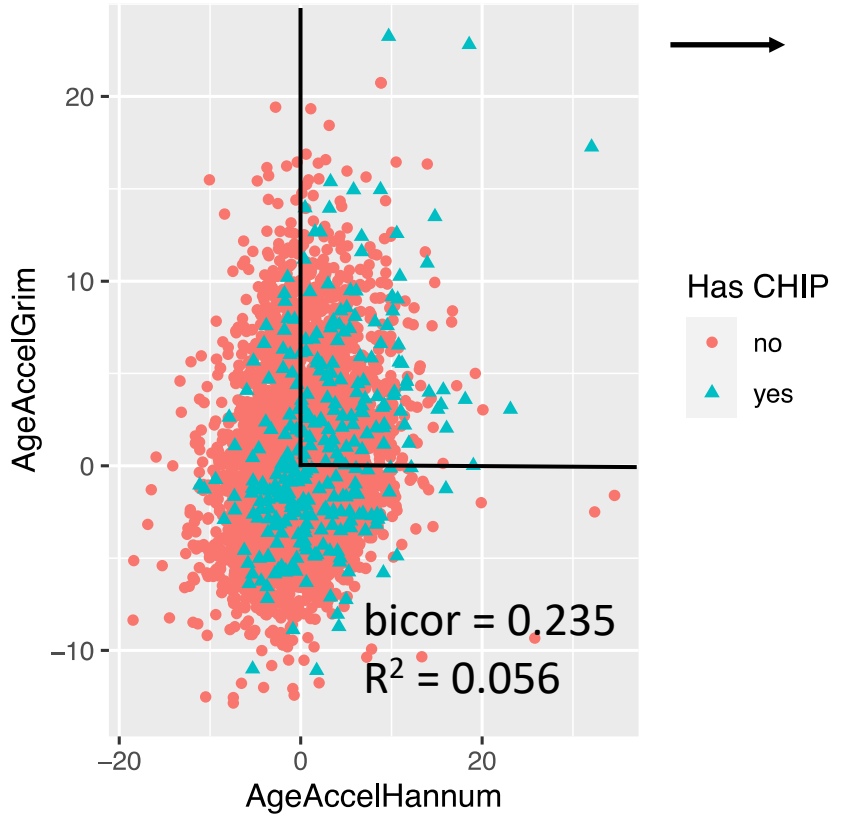
→

Analysis:
All-cause mortality
Cox proportional hazards

Looking for interaction effects in regression model (CHIP*AgeAccel) to identify the most predictive clocks

Does the combination of CHIP plus epigenetic age predict outcomes?

Clock	Interaction Coefficient	P-value
Horvath	0	1
IEAA	-0.26	0.31
Skin/Blood	-0.07	0.81
Hannum	**0.56**	**0.050**
EEAA	0.15	0.58
Pheno	-0.14	0.59
Grim	**0.48**	**0.097**



Defined 'AgeAccelComb':

AgeAccelHannum > 0

AND

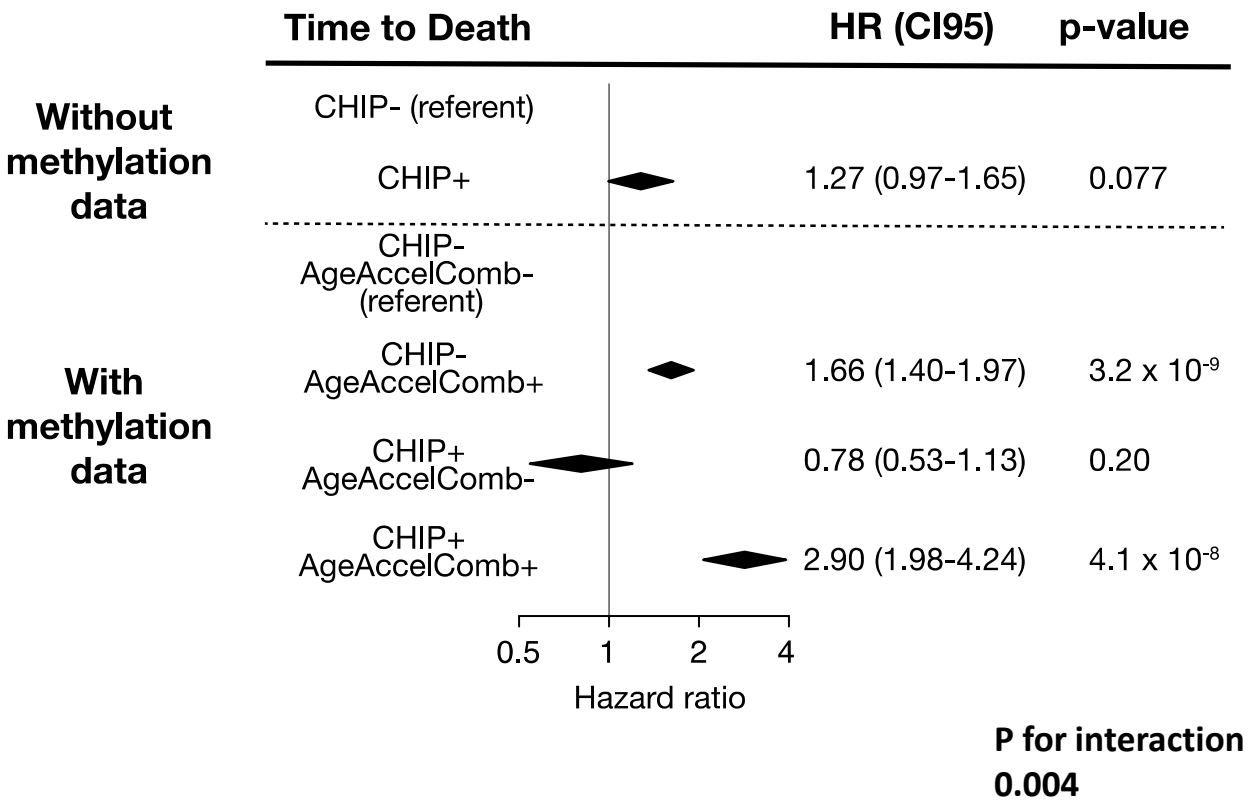
AgeAccelGrim > 0

24.3% of CHIP- (989/4065)
39.4% of CHIP+ (106/269)

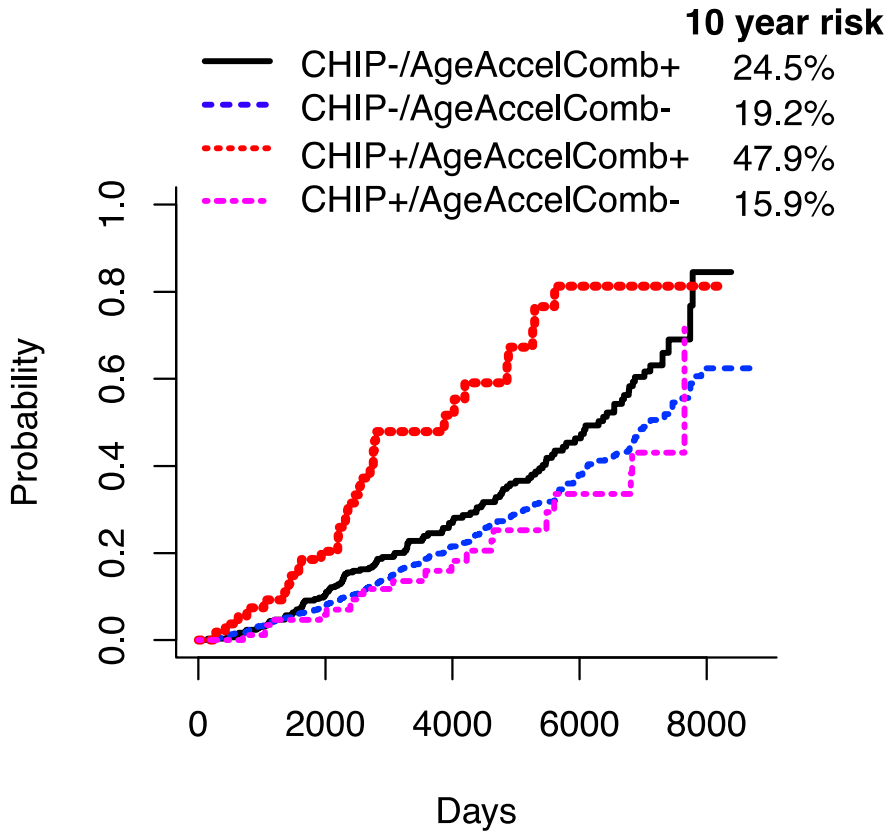
Does being AgeAccelComb+ affect outcomes differently depending on CHIP status?

Time to death~Age+Sex+Race+T2D+LDL+HDL+TG+SBP+smoking+**CHIP*AgeAccel**

Nearly all risk for adverse events resides in ~40% of CHIP carriers

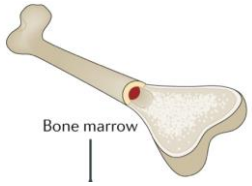


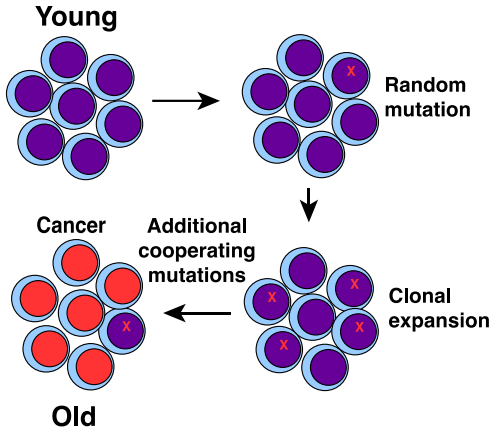
P for interaction = 0.004

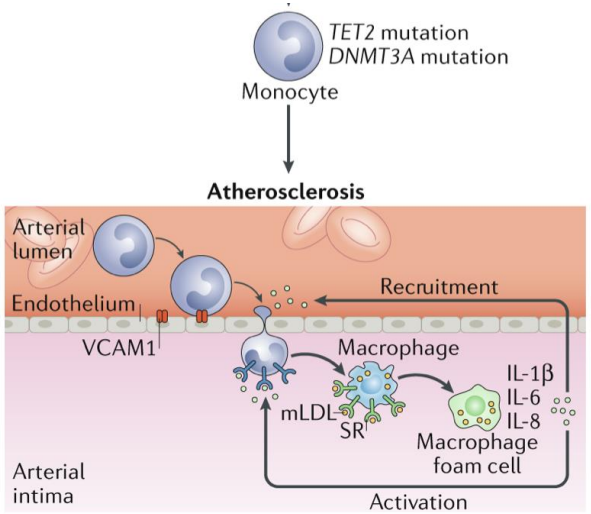


Age >65 and no CHD at baseline

Time to death~Age+Sex+Race+T2D+LDL+HDL+TG+SBP+smoking+**CHIP*AgeAccelComb**







Adapted from Jaiswal and Libby, *Nat Rev Card* 2019

Summary

- Mutations accumulate steadily over time in stem cell compartments, creating diversity and material for natural selection
- CHIP is common in aging
- CHIP is associated with increased risk of cancer and CVD
- CVD appears to be due to enhanced inflammation
- The combination of CHIP and epigenetic aging identifies a high-risk population
- CHIP carriers may preferentially respond to drugs targeting inflammatory pathways

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