POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

DICHIARAZIONE

NOME COGNOME

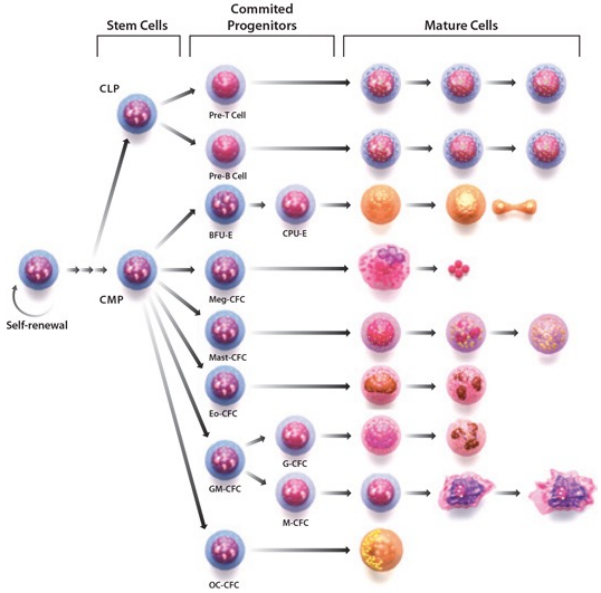
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

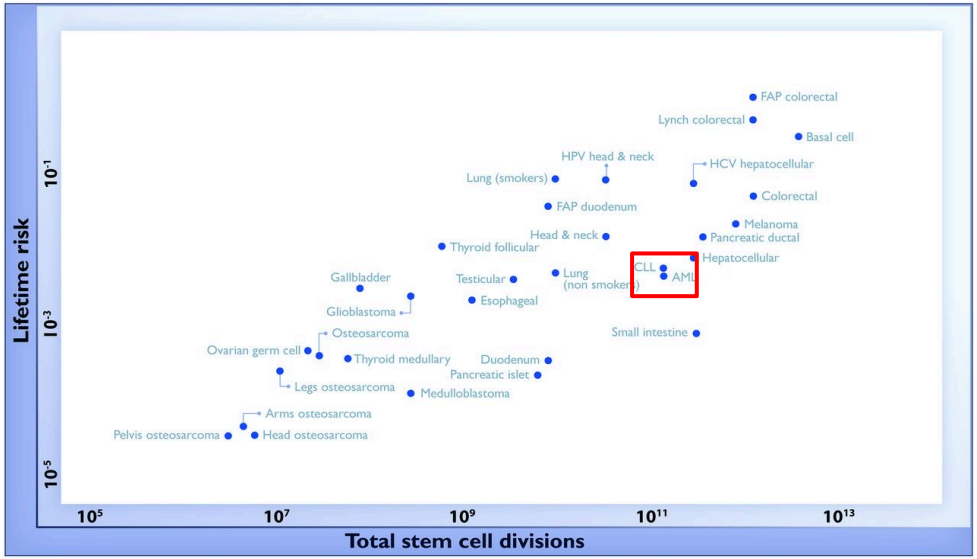
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Bristol Myers Squibb, Bluebird Bio)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE))**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Educational Objectives:

- Etiology of clonal hematopoiesis
- Clinical implications of clonal hematopoiesis
  - Hematologic malignancies
  - Non-hematologic outcomes

Somatic mutations in hematopoietic tissue

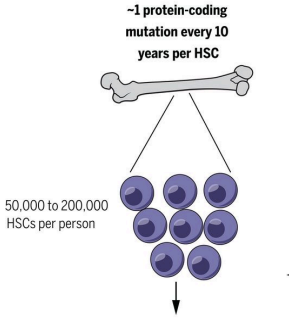


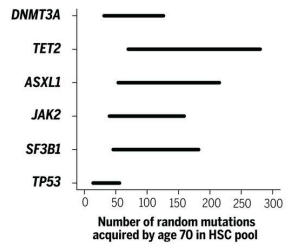


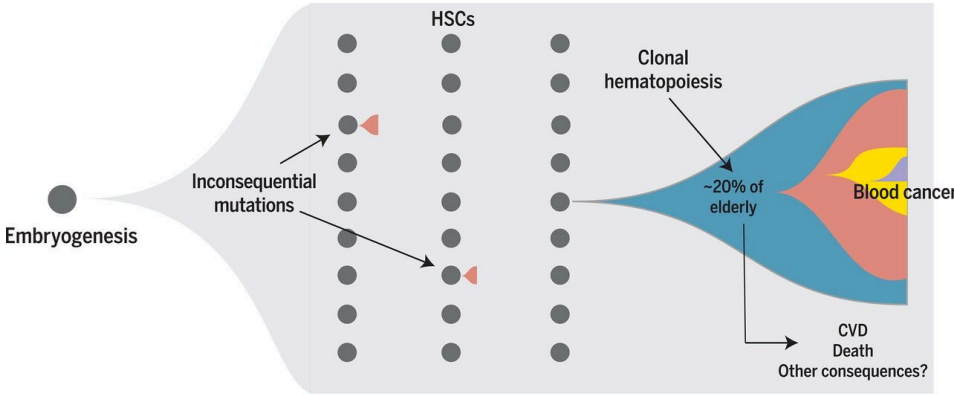
FAP = Familial Adenomatous Polyposis ◆ HCV = Hepatitis C virus ◆ HPV = Human papillomavirus ◆ CLL = Chronic lymphocytic leukemia ◆ AML = Acute myeloid leukemia

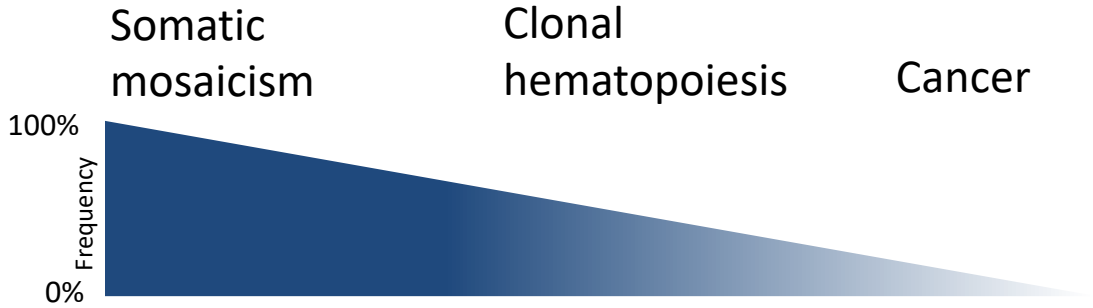
Tomasetti et al. Science 2015

Somatic mutations in hematopoietic tissue



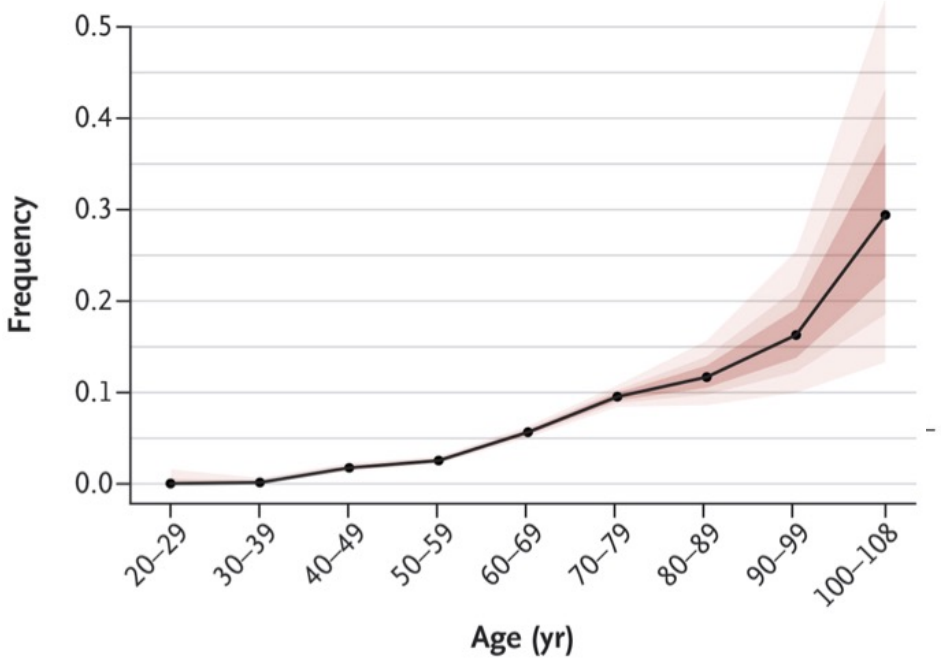






Jaiswal, Ebert Science 2019;366:eaan4673

Age-related Clonal Hematopoiesis or Clonal Hematopoiesis of Indeterminate Potential (CHIP)



Defined as cancer-associated clonal mutation with VAF > 2% in blood of “healthy” individuals

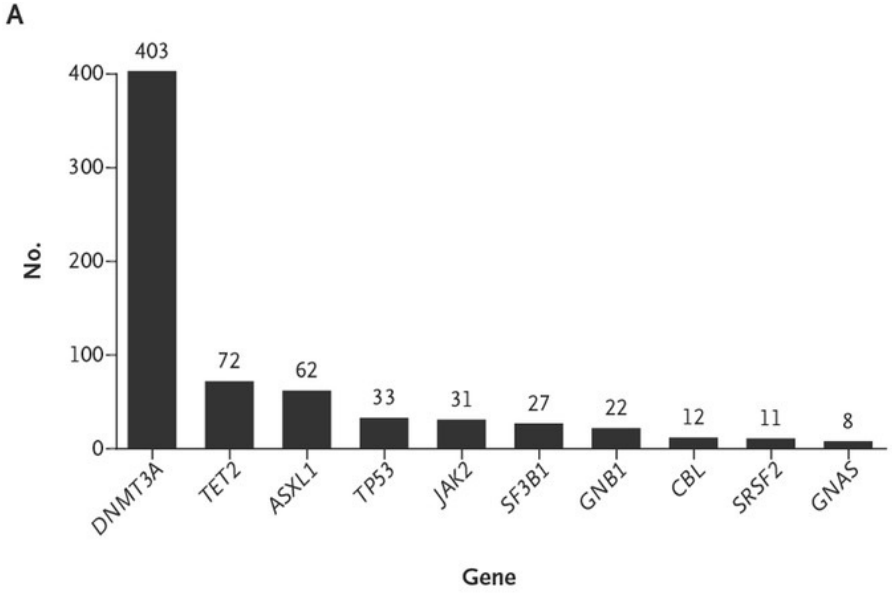
Common with aging, particularly age > 40

Direct connection between clonal hematopoiesis and myeloid malignancies

Associated with adverse outcome

Jaiswal S et al. N Engl J Med 2014
Genovese et al. N Engl J Med 2014
Xie et al. Nat Med 2014

Age-related Clonal Hematopoiesis or Clonal Hematopoiesis of Indeterminate Potential (CHIP)



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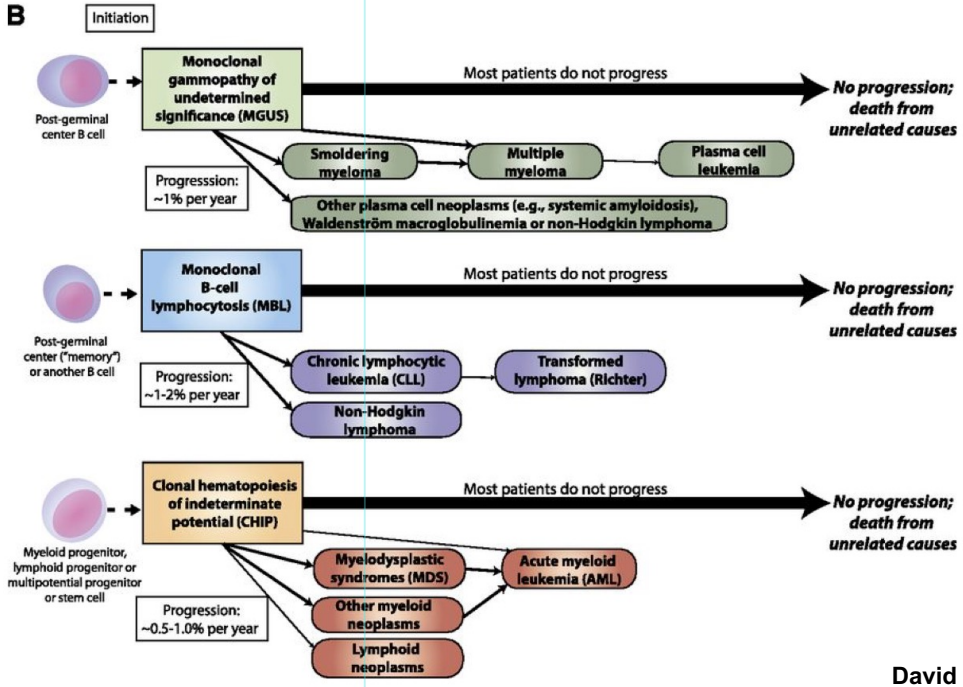
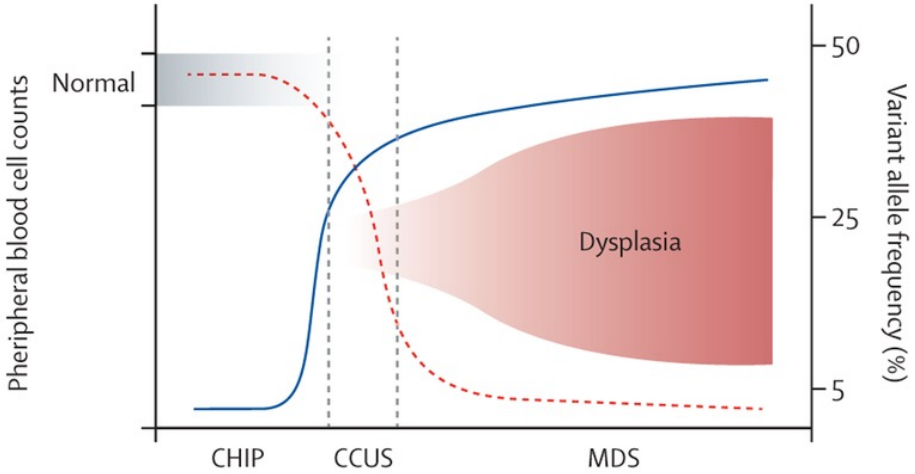
Jaiswal S et al. N Engl J Med 2014
Genovese et al. N Engl J Med 2014
Xie et al. Nat Med 2014

CHIP as a precursor for hematologic malignancies

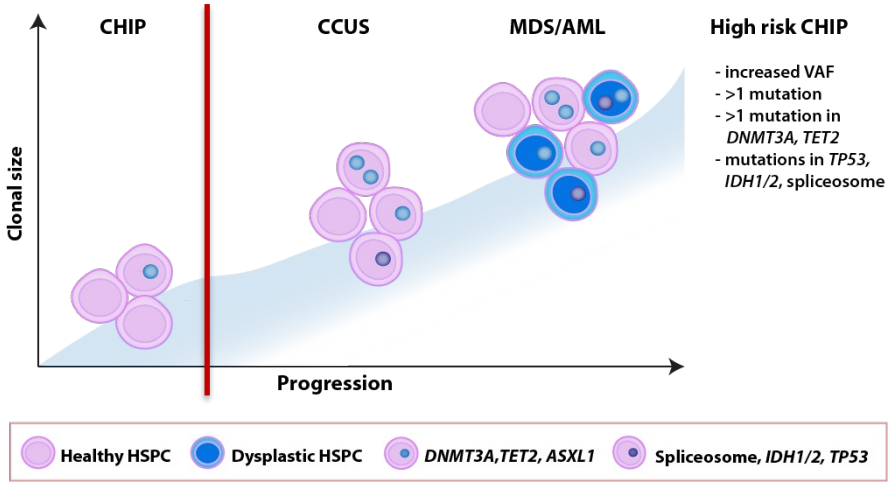


David P. Steensma et al. Blood 2015;126:9-16

CHIP and progression to myeloid malignancy



95%



Rate of progression 0,5-1%

Gondek L, Lancet Haematology 2020

Abstract # 926

Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis

Lachelle D. Weeks, Abhishek Niroula, Donna S. Neuberg, Waihay J. Wong, R. Coleman Lindsley, Marlise R. Luskin, Nancy Berliner, Richard M. Stone, MD, Daniel J DeAngelo, Robert J Soiffer, Md Mesbah Uddin, Christopher J. Gibson, Alexander G. Bick, Gabriel K. Griffin, Siddhartha Jaiswal, Luca Malcovati, Pradeep Natarajan and Benjamin L. Ebert

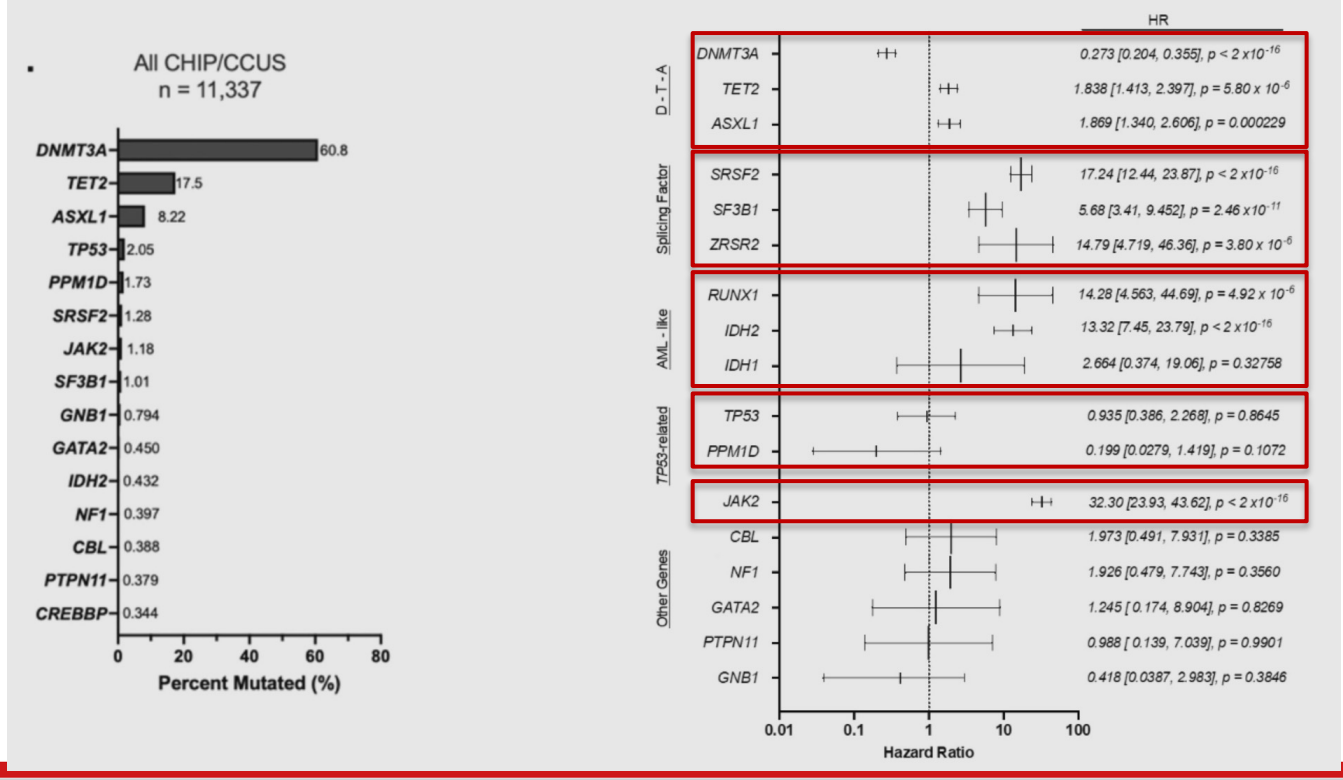
Study objectives and cohort

1. Identify features that predict risk of incidence of myeloid neoplasm in people with CHIP/CCUS
2. Derived a clinically useful risk model that distinguishes high risk from low risk CHIP/CCUS

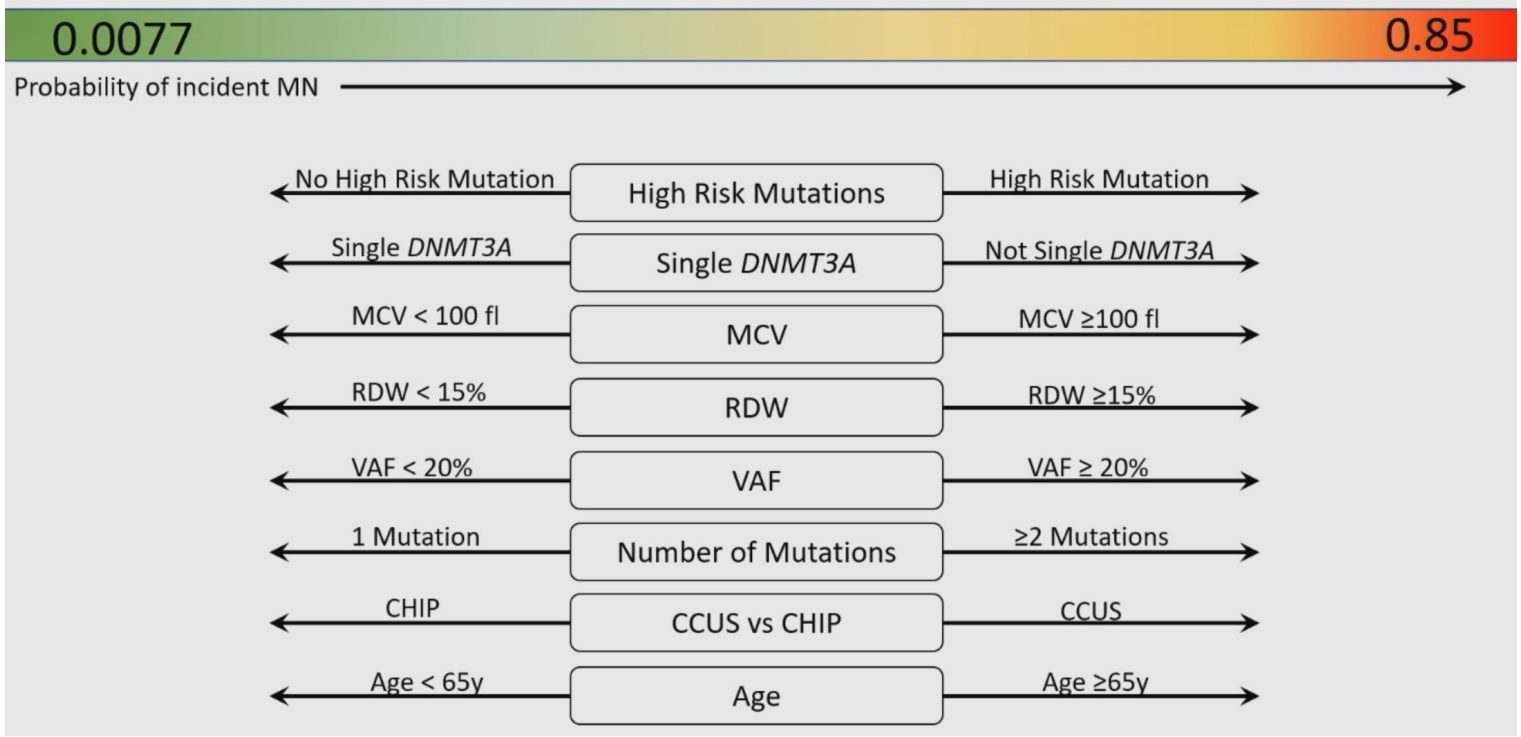
UK Biobank (>500,000)
Independent validation cohort from DFCI and University of Pavia

Genotypes associated with MN incidence

Myeloid neoplasm (MN) incidence: **2.37%**



Features prognostic of incidence of MN

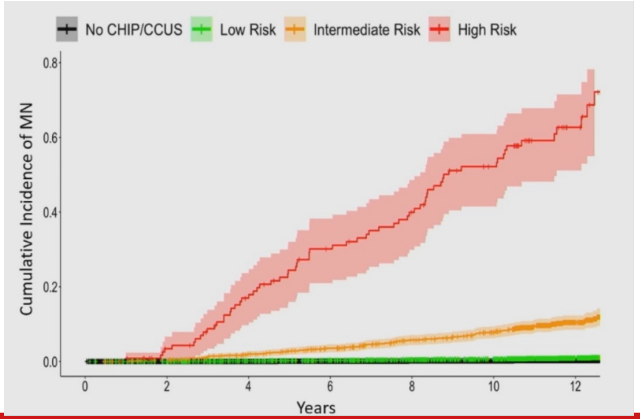


Clonal Hematopoiesis Risk Score (CHRS)

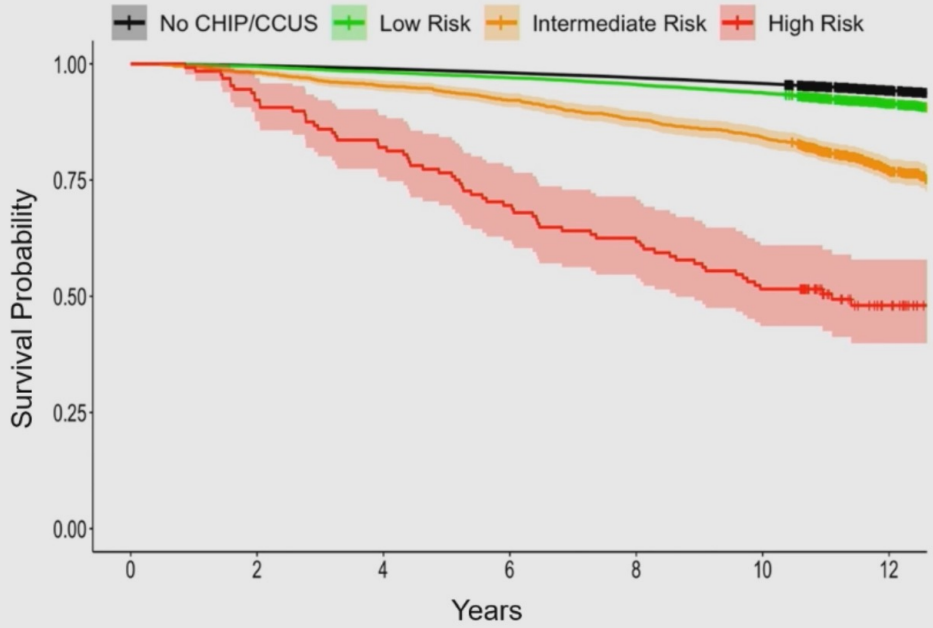
Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–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

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%



CHRS and survival in 2 independent cohort



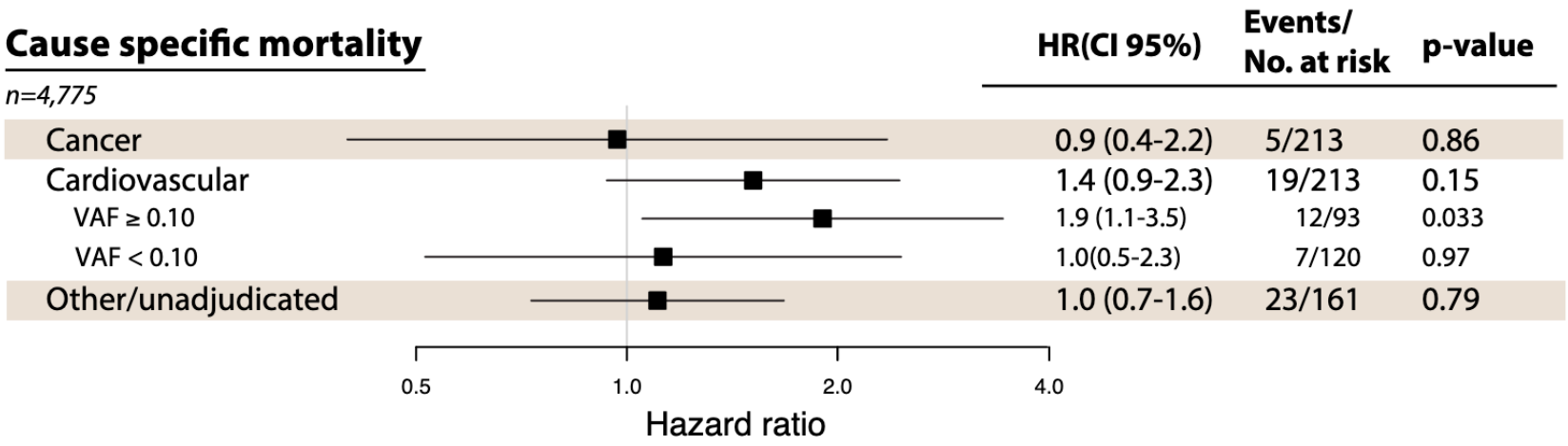
No CHIP/CCUS: 10-yr survival = 95.8 ± 0.0471%

Low Risk: 10-yr survival = 93.7 ± 0.243%

Intermediate Risk: 10-yr survival = 84.0 ± 1.06%

High Risk 10-yr survival = 51.2 ± 4.51%

CHIP and cardiovascular disease

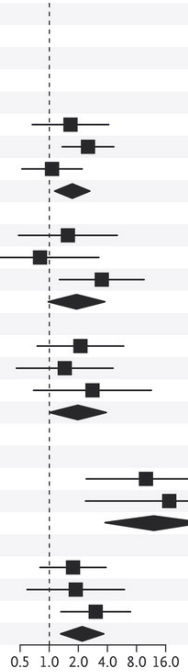


Jaiswal S et al. N Engl J Med 2014

CHIP and cardiovascular risk factors

A CHIP and Coronary Heart Disease, According to Mutated Gene

Subgroup	No. of Participants with Myocardial Infarction/ No. at Risk	Hazard Ratio (95% CI)	P Value
No mutation			
BioImage	94/326		
MDC	299/607		
JHS/FUSION/FHS	169/3505		
DNMT3A			
BioImage	5/14	1.7 (0.7–4.1)	0.27
MDC	11/15	2.5 (1.4–4.7)	0.003
JHS/FUSION/FHS	8/99	1.1 (0.5–2.2)	0.90
Fixed-effects meta-analysis		**1.7 (1.1–2.6)**	**0.01**
TET2			
BioImage	3/7	1.6 (0.5–5.0)	0.46
MDC	2/6	0.8 (0.2–3.3)	0.76
JHS/FUSION/FHS	4/16	3.5 (1.3–9.6)	0.01
Fixed-effects meta-analysis		**1.9 (1.0–3.7)**	**0.06**
ASXL1			
BioImage	4/6	2.1 (0.7–5.8)	0.16
MDC	3/6	1.4 (0.5–4.6)	0.53
JHS/FUSION/FHS	2/10	2.8 (0.7–11.4)	0.15
Fixed-effects meta-analysis		**2.0 (1.0–3.9)**	**0.05**
JAK2			
BioImage	0/0		
MDC	2/2	10.0 (2.4–41.5)	0.001
JHS/FUSION/FHS	1/3	17.4 (2.4–127.6)	0.005
Fixed-effects meta-analysis		**12.0 (3.8–38.4)**	**<0.001**
Other			
BioImage	7/17	1.8 (0.8–3.9)	0.16
MDC	3/4	1.9 (0.6–6.0)	0.28
JHS/FUSION/FHS	6/35	3.0 (1.3–6.9)	0.009
Fixed-effects meta-analysis		**2.2 (1.3–3.7)**	**0.002**

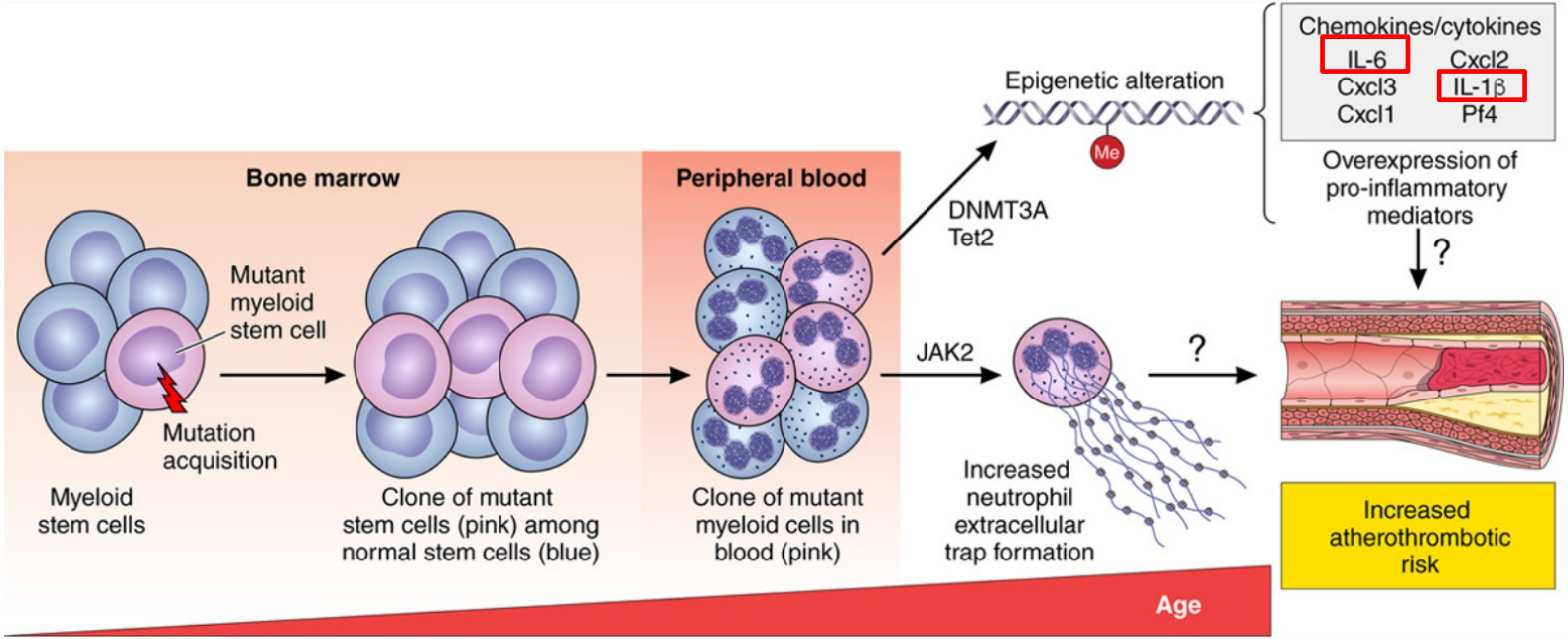


B

	HR (95% CI)
Age 50-59	**2.2** (1.3-3.7)
Age 60-69	**2.4** (1.4-4.0)
Age ≥70	**6.3** (3.8-10.4)
Female	**0.7** (0.5-0.9)
Has T2D	**2.2** (1.6-3.0)
Former or current smoker	**1.4** (1.0-1.9)
Hypertension stage II-IV	**1.4** (1.0-1.9)
TC >200 mg/dL	**1.4** (1.0-1.9)
HDL<35 mg/dL	**1.4** (1.0-2.2)
HDL>60 mg/dL	**0.8** (0.5-1.1)
CHIP present	**1.8** (1.1-2.9)

Jaiswal S et al. N Engl J Med 2017
Jaiswal, Ebert Science 2019

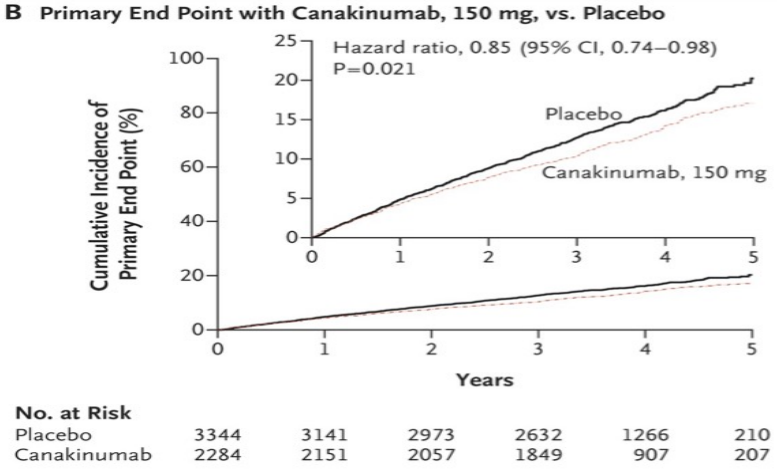
CHIP-mediated inflammation and cardiovascular disease



Libby et al. Circulation 2018
Jaiswal et al. NEJM 2017
Fuster et al. Science 2017

CANTOS trial – anti IL-1β in CVD prevention

- Canakinumab Anti-Inflammatory Thrombosis Outcome Study (N= 10,061)
- Secondary prevention of MACE in patients with elevated hsCRP
- MACE defined as nonfatal MI, stroke or cardiovascular death



CAI

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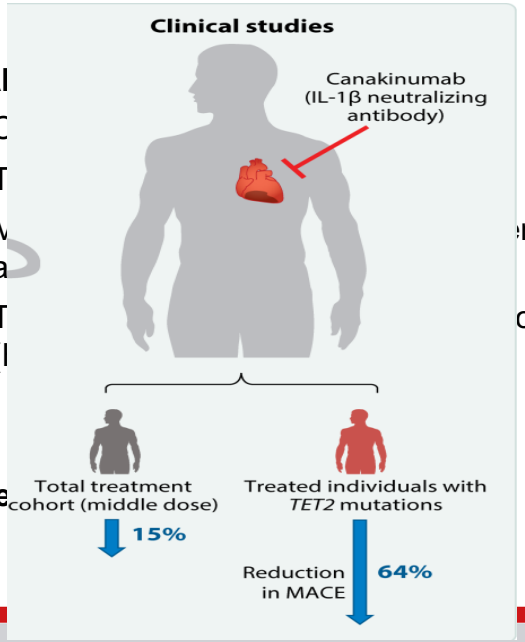
- M … nts then in placebo a
- T … canakinumab (I

Sve



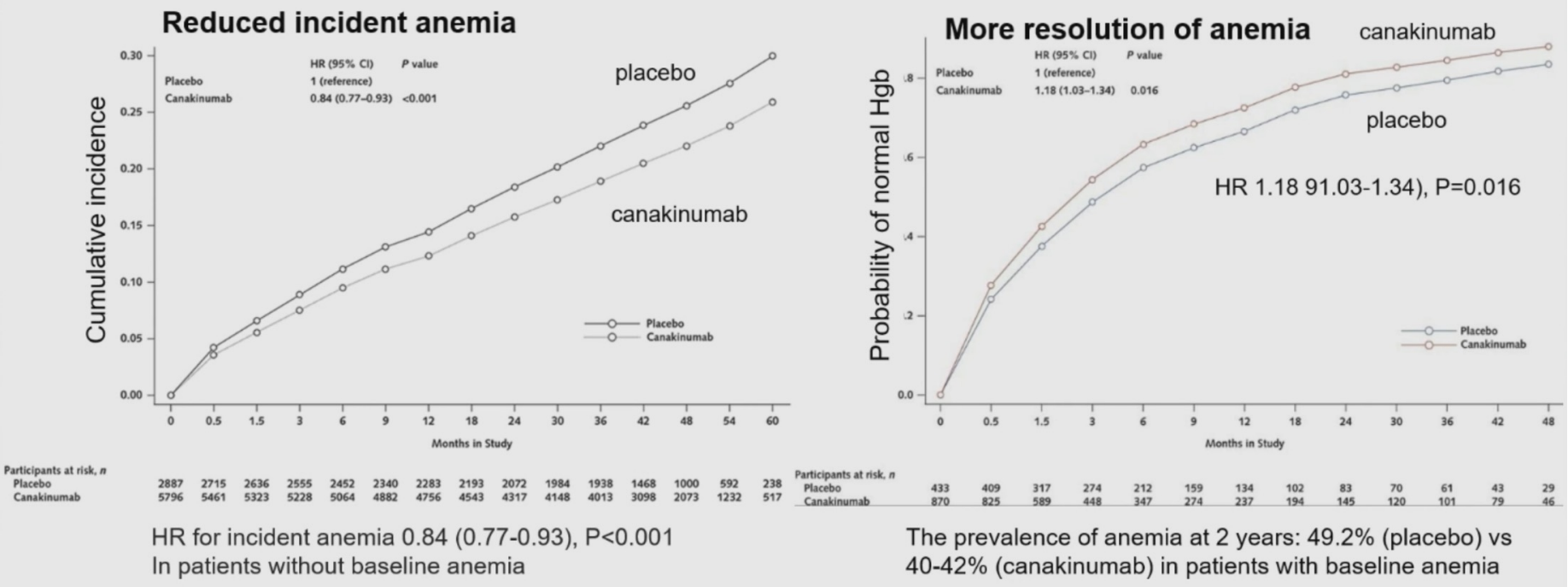
Ridker, NEJM 2017

Abstract # 929

Canakinumab Effects on Erythropoiesis, Cardiovascular Risk, and Clonal Hematopoiesis: Proteogenomic Analysis of the Cantos Randomized Clinical Trial

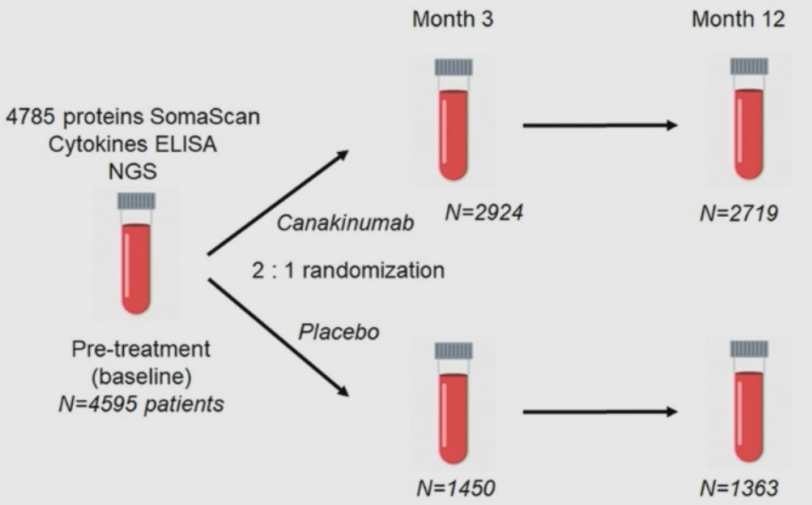
Janghee Woo, Darlene Lu, Andrew Lewandowski, Paul M. Ridker, Benjamin L. Ebert and David Steensma

Canakinumab reduces the incidence of anemia



Vallurupalli, Ann Intern Med, 2020

Study design and aims



N represents the number of patients with ≥1 observed expression result

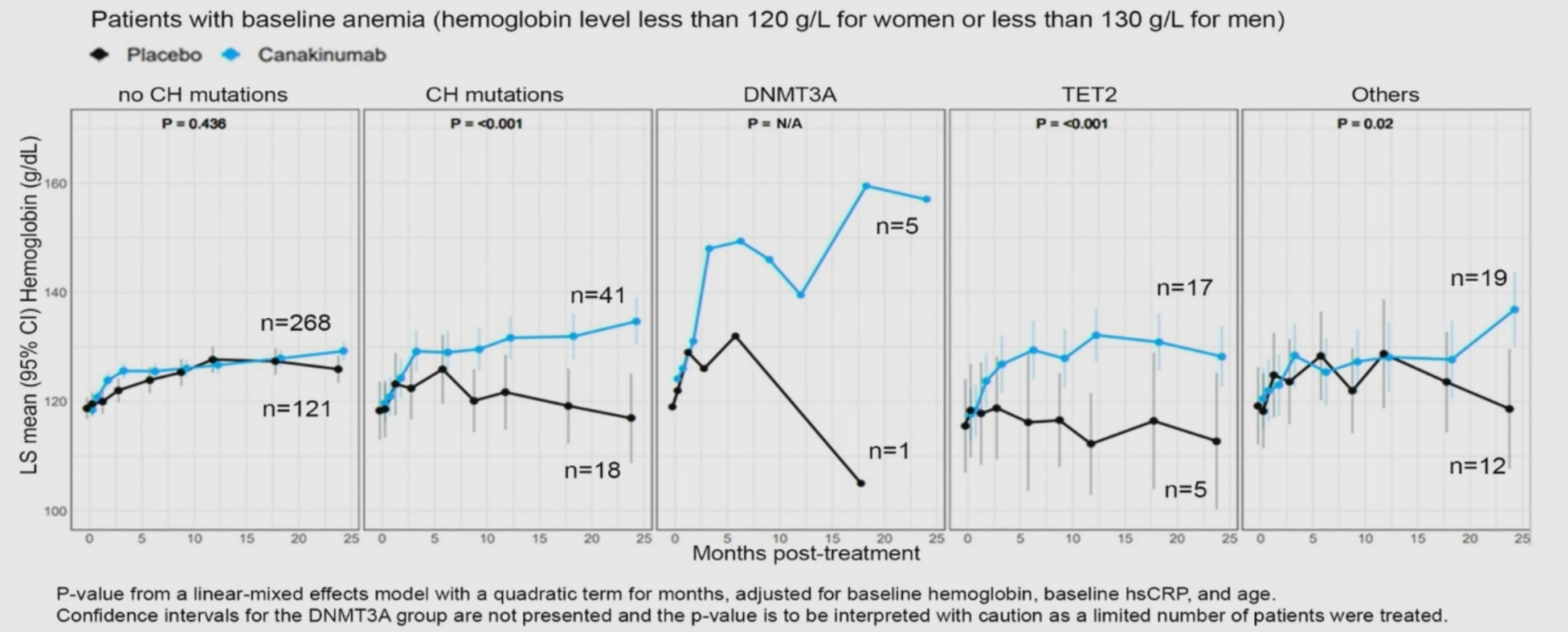
Aims

To determine the association between CH mutations and anemia response to canakinumab

To determine the underlying molecular mechanisms of canakinumab that enhances erythropoiesis and prevent anemia

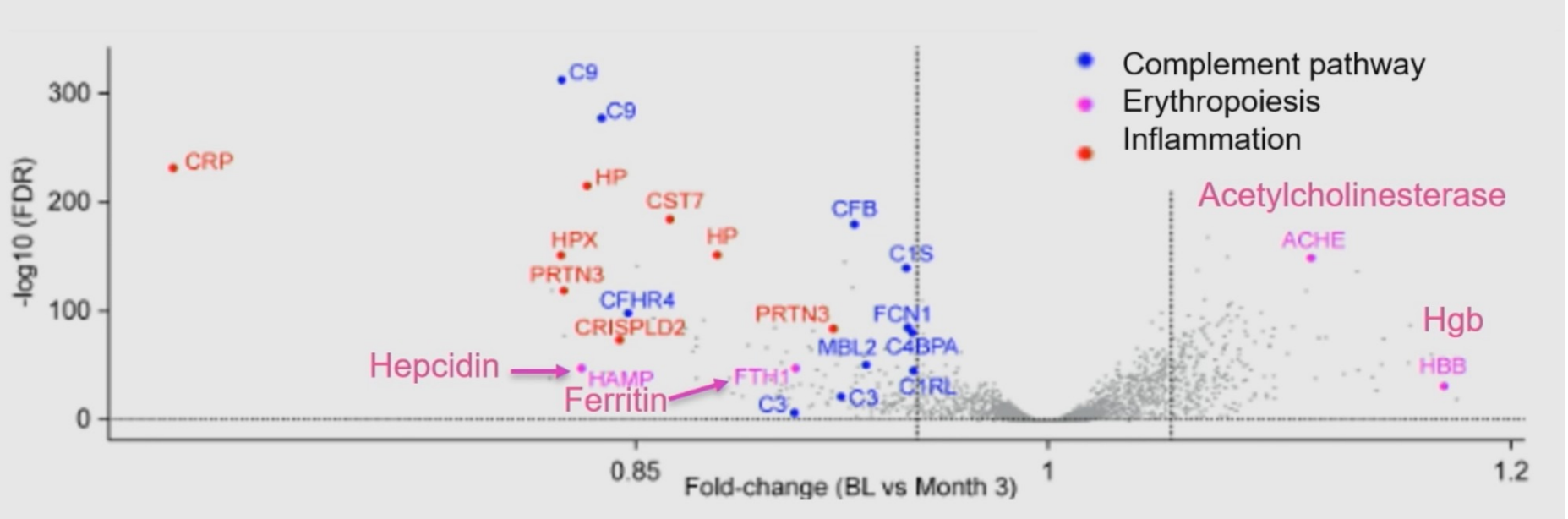
To identify biomarkers associated with robust response to canakinumab

Canakinumab improved Hgb levels in patients with CHIP and anemia

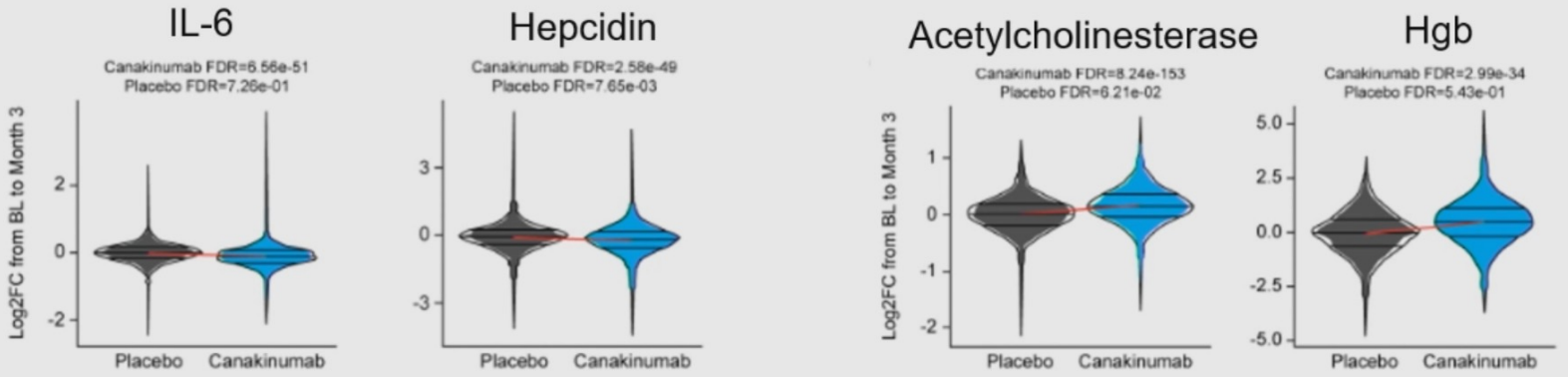


P-value from a linear-mixed effects model with a quadratic term for months, adjusted for baseline hemoglobin, baseline hsCRP, and age.
Confidence intervals for the DNMT3A group are not presented and the p-value is to be interpreted with caution as a limited number of patients were treated.

Canakinumab altered key factors of inflammation and RBC clearance.



Canakinumab lowers IL6 and hepcidin levels and increases erythroid response

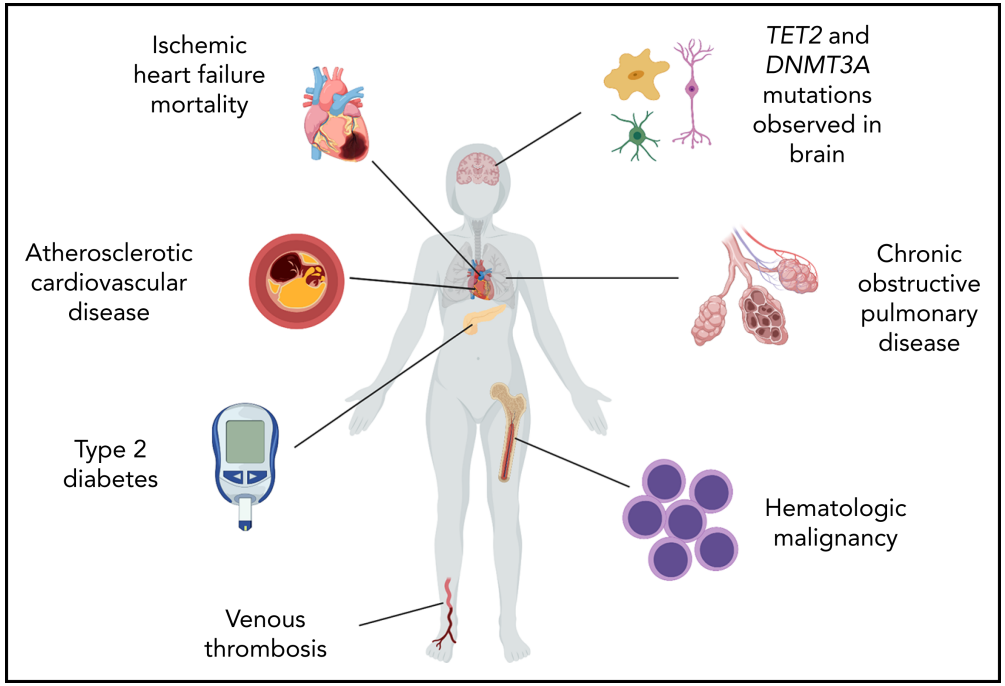


Higher odds of both a decrease in IL-6 and an increase in hemoglobin (OR=3.46; 95%CI=3.00 - 4.00; *P*<0.001) were observed with canakinumab treatment compared to placebo

Summary

- CHIP may evolve to hematologic malignancies (0.5-1% per year)
- CHIP is an independent cardiovascular risk factor (HR~2)
- Therapeutic interventions may reduce the risk of CVD and anemia in older patients with CHIP/CCUS
  - anti-inflammatory therapies directed against IL-1 and IL6

Summary



Jaiswal, Blood 2020

Grazie!

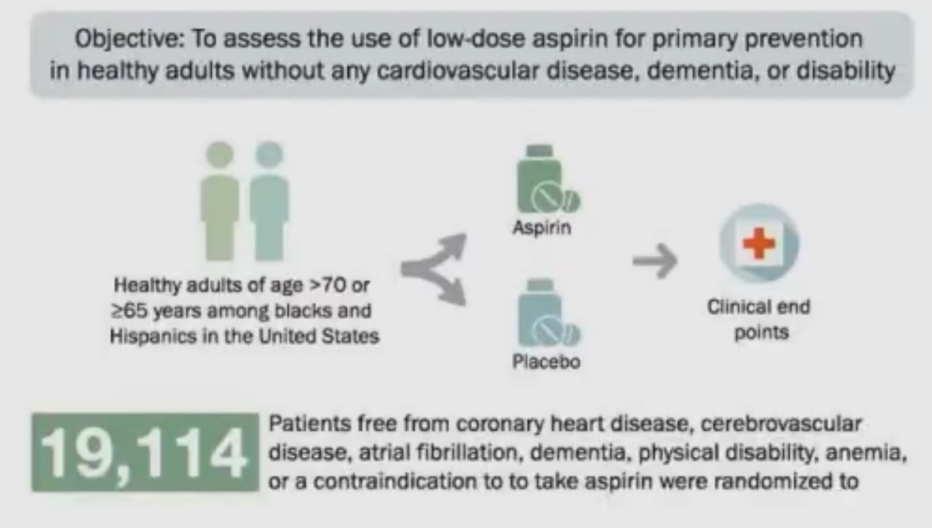
lgondek1@jhmi.edu

Abstract # 930

The Effect of Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Aspirin on Clinical Outcomes in the Healthy Elderly: A Sub-Study of the Aspirin in Reducing Events in the Elderly (ASPREE) Randomized Controlled Trial

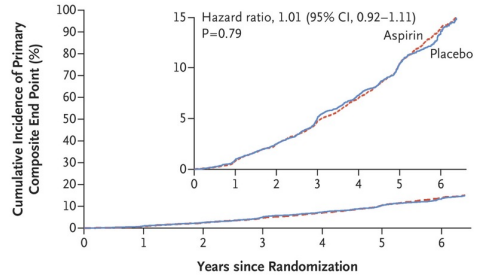
Zoe McQuilten, Nicholas C. Wong, Anna Leichter, Le T.P. Thao, James Phung, Andrew J Murphy, Moeen Riaz, Robert Sebra, Alexander G. Bick, John J. McNeil, Rory Wolfe, Robyn L. Woods, Paul Lacaze, Erica M. Wood and David J. Curtis

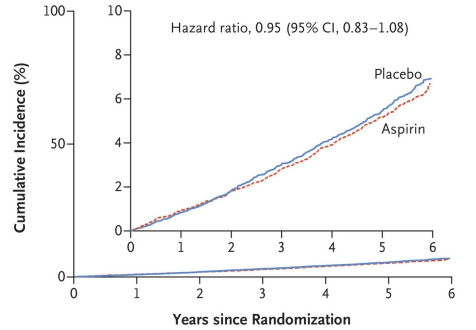
ASPREE study design and outcome risk factors



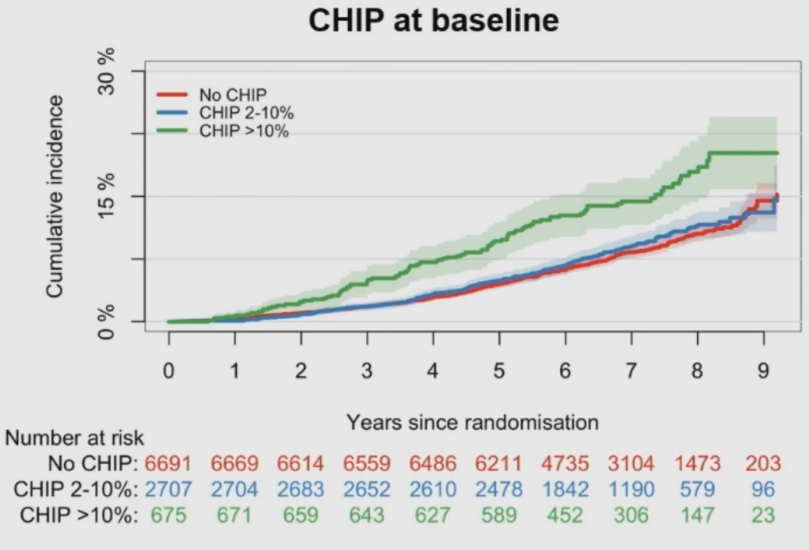
Over 12,000 samples (baseline and 3 months)

McNeil JJ et al. NEJM 2018

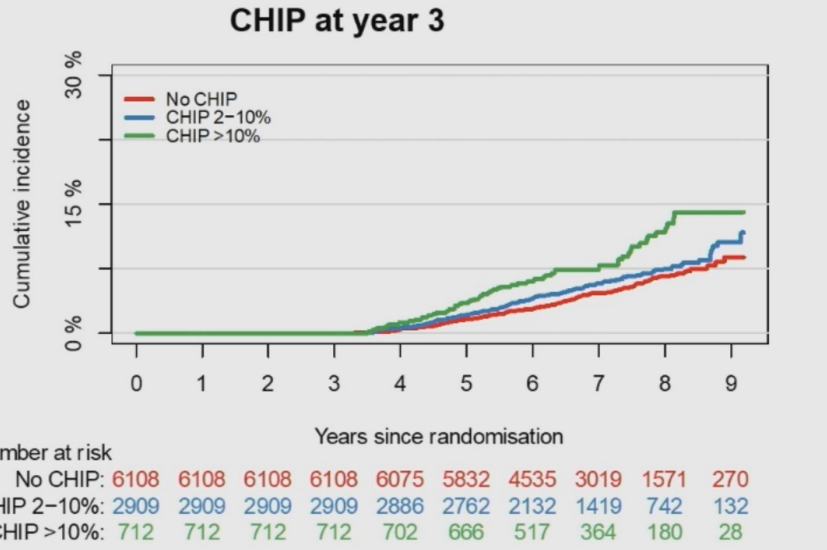




CHIP with VAF >10% was associated with mortality

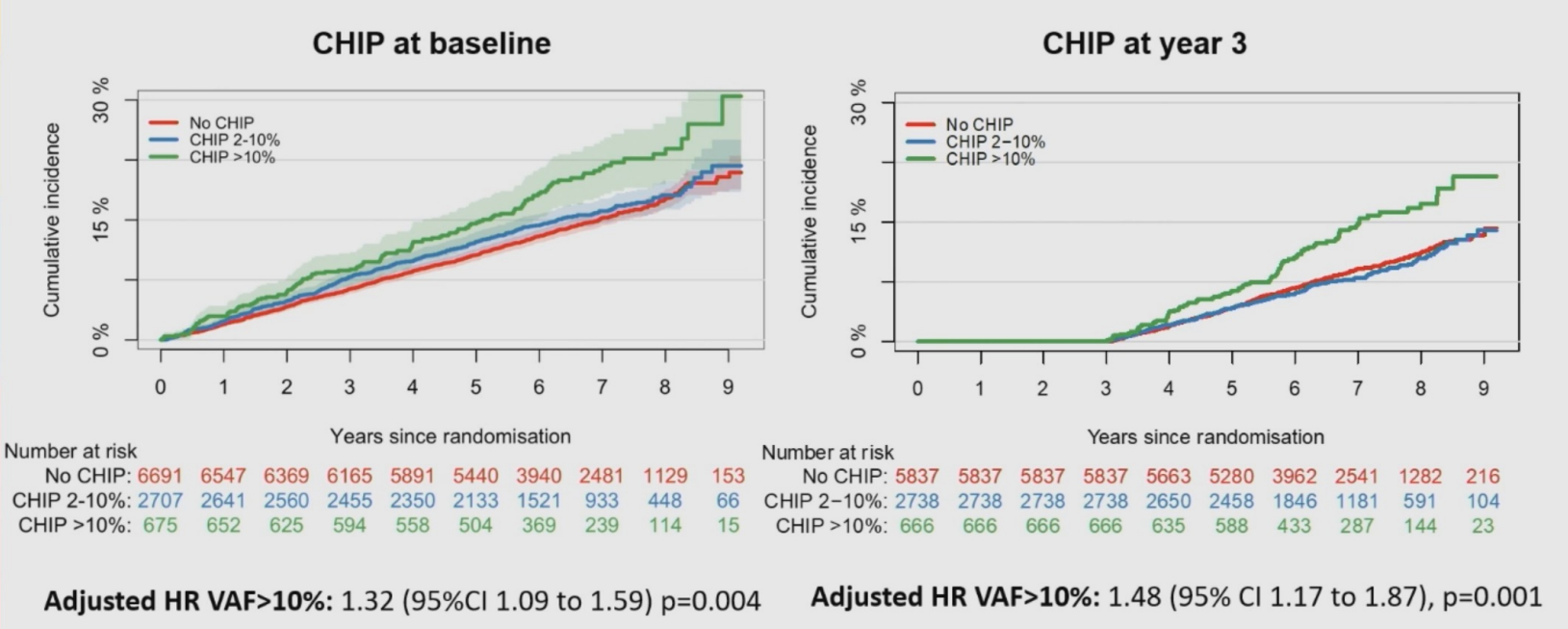


Adjusted HR VAF >10%: 1.57 (95% CI 1.26 to 1.95), p<0.001



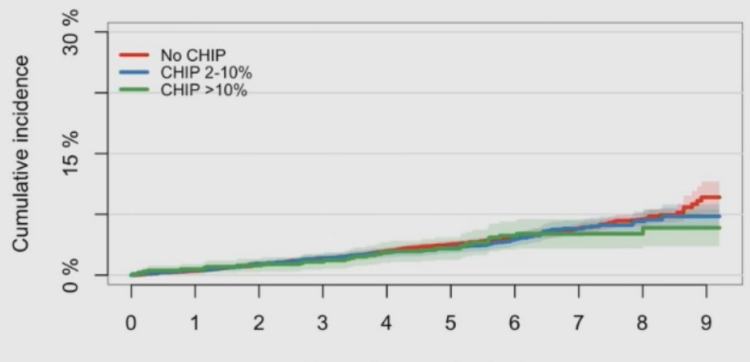
Adjusted HR VAF>10%: 1.61 (95% CI 1.22 to 2.14), p<0.001

CHIP with VAF >10% was associated with cancer both hematologic and non-hematologic



CHIP was not associated with cardiovascular events

CHIP at baseline

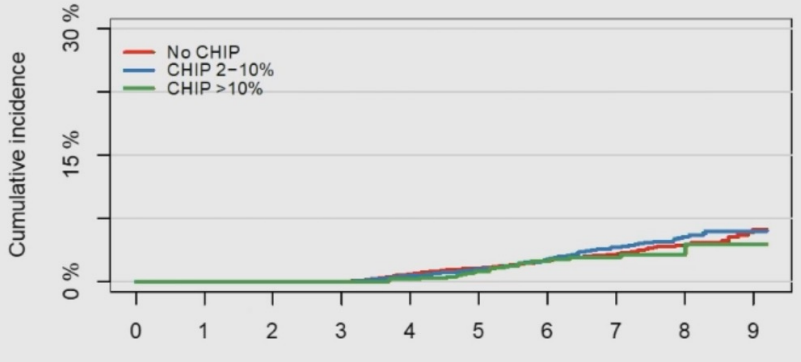


Number at risk

No CHIP:	6691	6632	6528	6399	6189	5764	4237	2695	1250	171
CHIP 2-10%:	2707	2687	2641	2582	2494	2289	1650	1010	488	76
CHIP >10%:	675	665	649	627	599	552	415	274	130	21

Adjusted HR VAF >10%: 0.73 (95% CI 0.50 to 1.07) p=0.11

CHIP at year 3



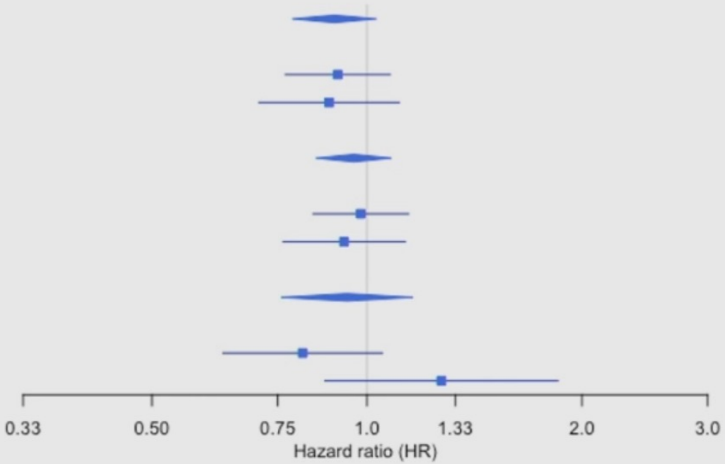
Number at risk

No CHIP:	6008	6008	6008	6008	5895	5576	4230	2753	1410	241
CHIP 2−10%:	2874	2874	2874	2874	2810	2635	1986	1278	657	113
CHIP >10%:	702	702	702	702	687	640	484	331	159	25

Adjusted HR VAF >10%: 0.75 (95% CI 0.46 to 1.20), p=0.23

Effect of Aspirin vs. placebo by subgroup

Subgroup	N	Placebo events(rate)	Aspirin events(rate)	Comparison HR(95% CI)	Test for heterogeneity p-value
Disability-free survival					
Overall	**10073**	**442(19.8)**	**399(17.8)**	**0.90(0.79-1.03)**	
CHIP					**0.84**
- No CHIP	6691	281(19.0)	258(17.2)	0.91(0.77-1.08)	
- CHIP 2%	3382	161(21.3)	141(19.1)	0.88(0.71-1.11)	
Cancer					
Overall	**10073**	**532(24.8)**	**510(23.8)**	**0.96(0.85-1.08)**	
CHIP					**0.67**
- No CHIP	6691	325(22.8)	322(22.3)	0.98(0.84-1.14)	
- CHIP 2%	3382	207(28.8)	188(26.8)	0.93(0.76-1.13)	
MACE					
Overall	**10073**	**178(8.0)**	**167(7.5)**	**0.94(0.76-1.16)**	
CHIP					**0.05**
- No CHIP	6691	129(8.8)	106(7.1)	0.81(0.63-1.05)	
- CHIP 2%	3382	49(6.6)	61(8.4)	1.27(0.87-1.85)	



Asa better

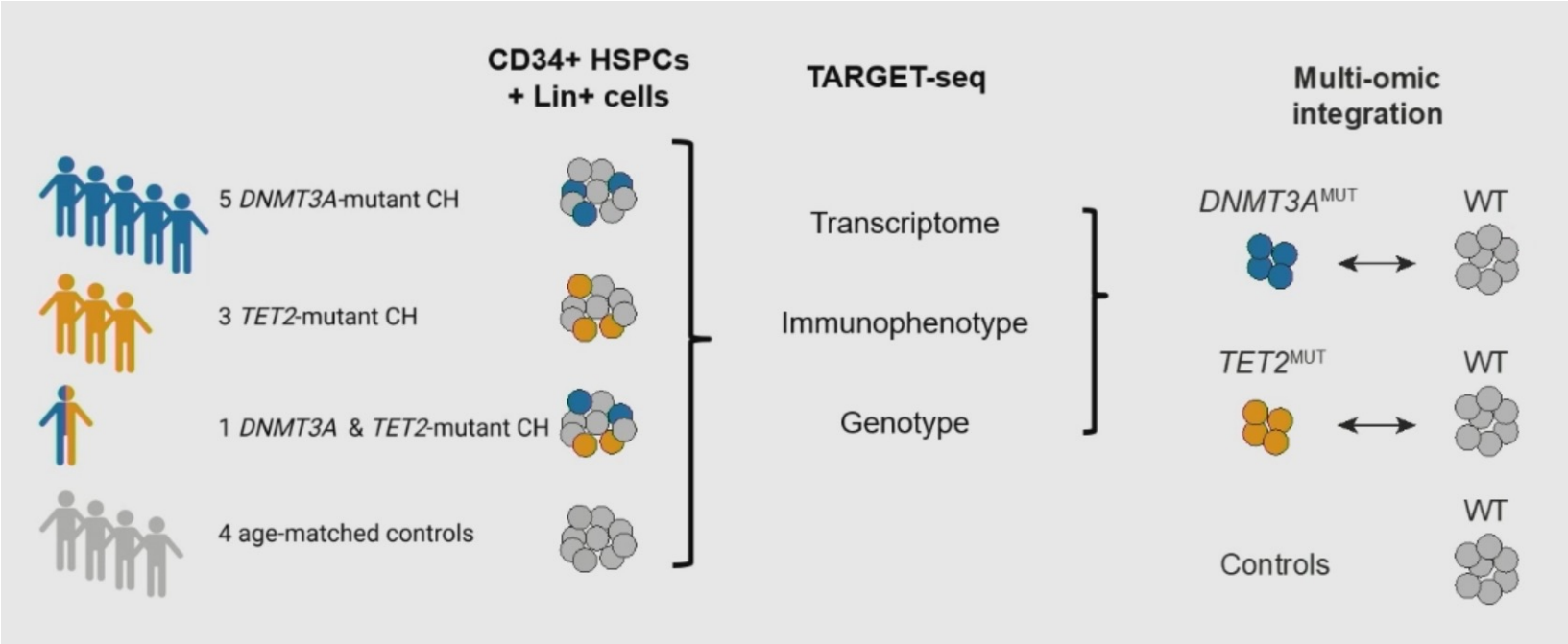
Placebo better

Abstract # 925

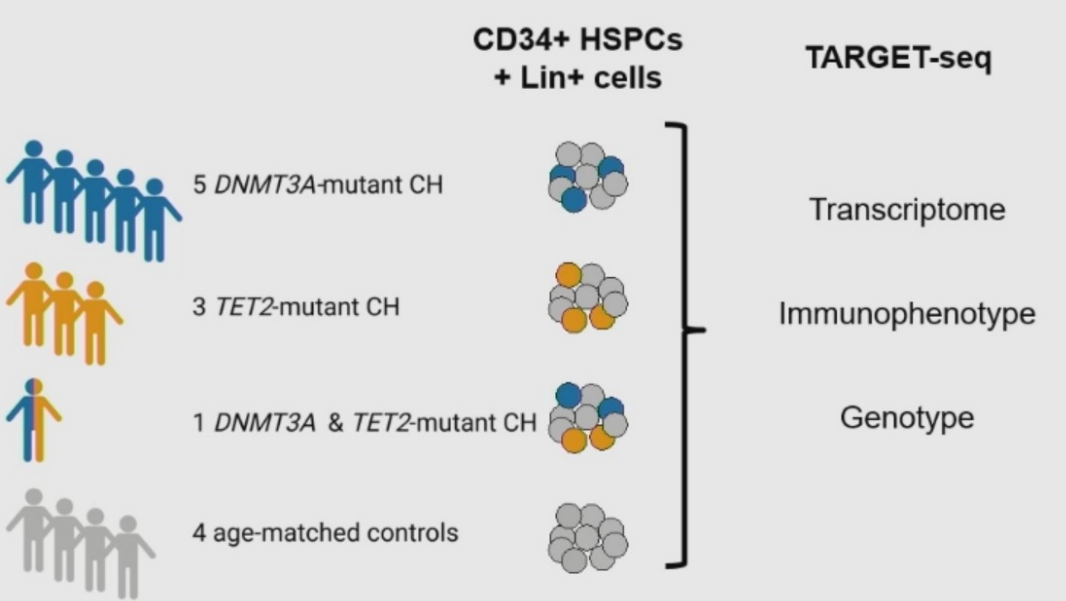
Single-Cell Analysis of Human Clonal Hematopoiesis Identifies Distinct Impact of DNMT3A and TET2 mutations on Hematopoietic Differentiation

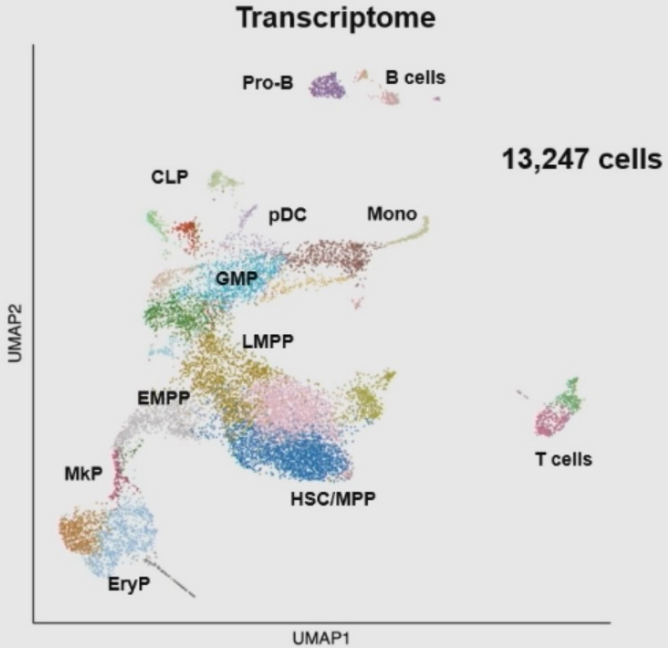
Niels Asger Jakobsen, Sven Turkalj, Bilyana Stoilova, Marlen Metzner, Rachel Moore, Batchimeg Usukhbayar, Mirian Angulo Salazar, Alison Kennedy, Simon Newman, Benjamin Kendrick, Adrian Taylor, Rasheed Afinowi-Luitz, Roger Gundle, Bridget Watkins, Kim Wheway, Debra Beazley, Andrew Carr and Paresh Vyas

Single cell multiome in primary human HSPC

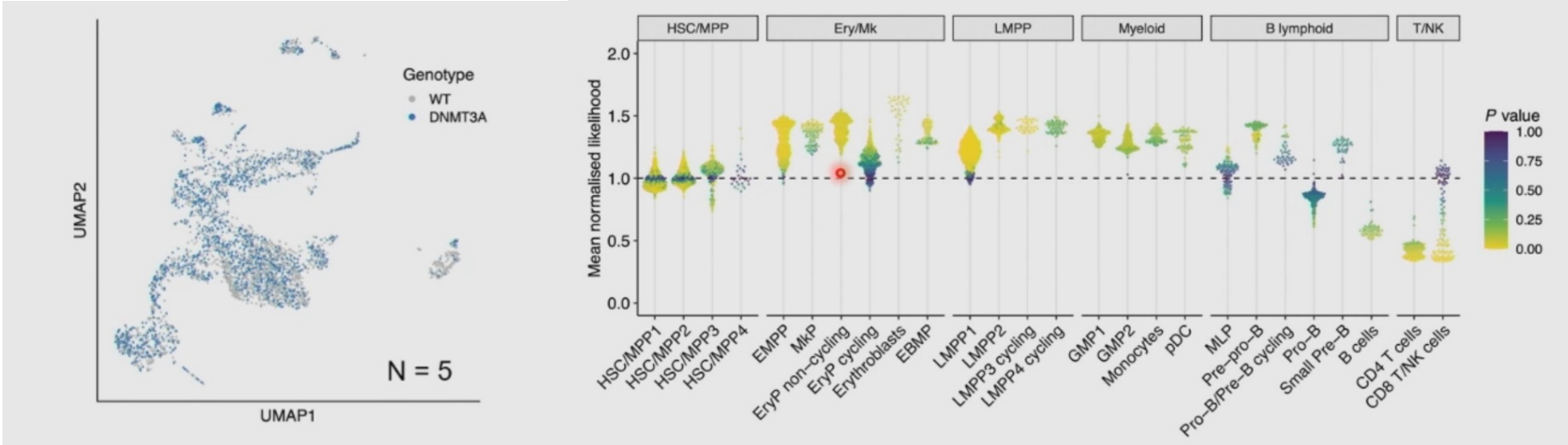


Single cell multiome in primary human HSPC

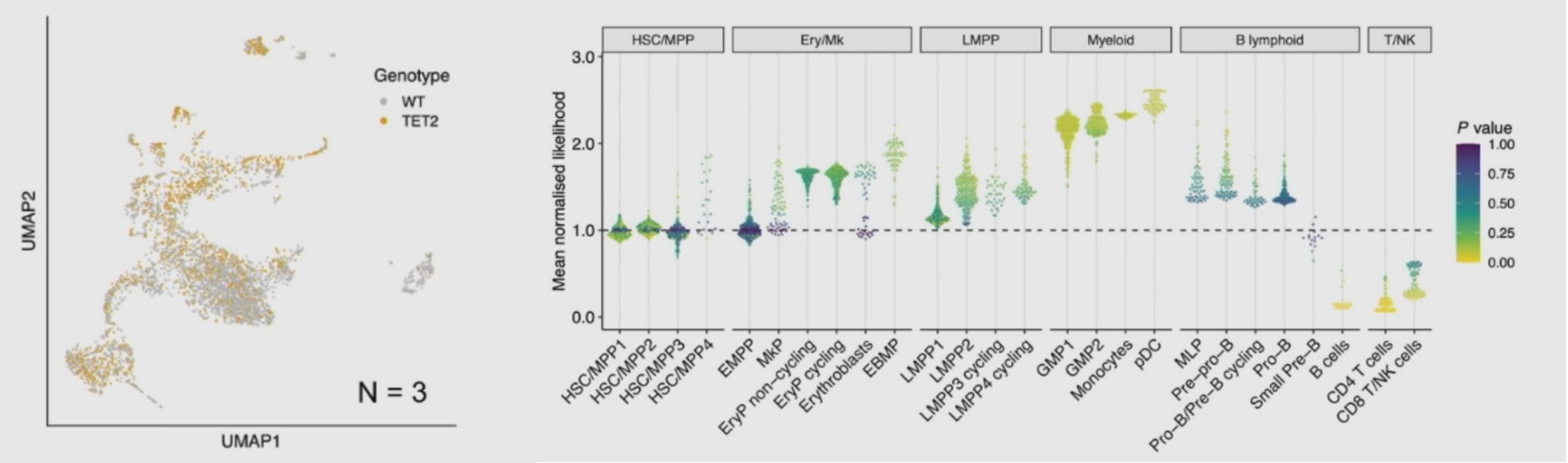




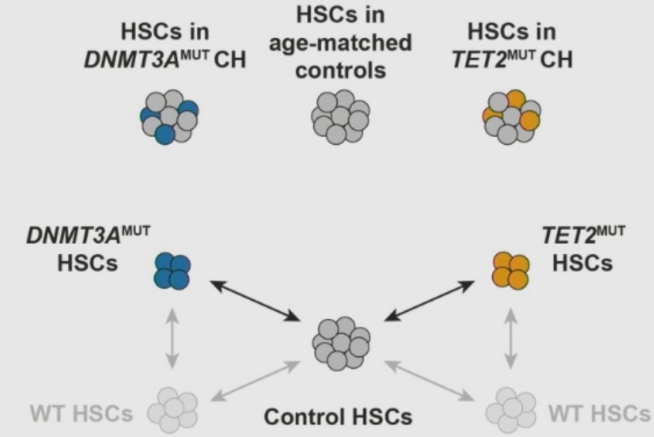
DNMT3A mutation leads to expansion of early progenitors

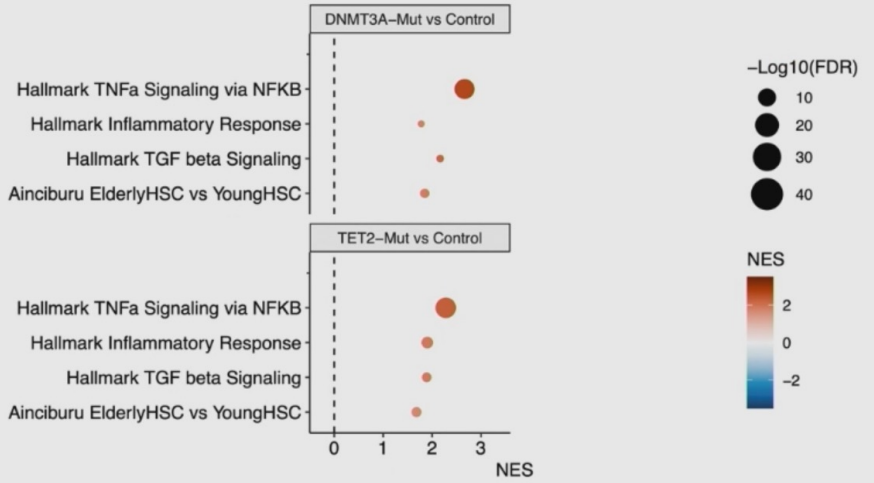


TET2 mutation leads to expansion of late progenitors

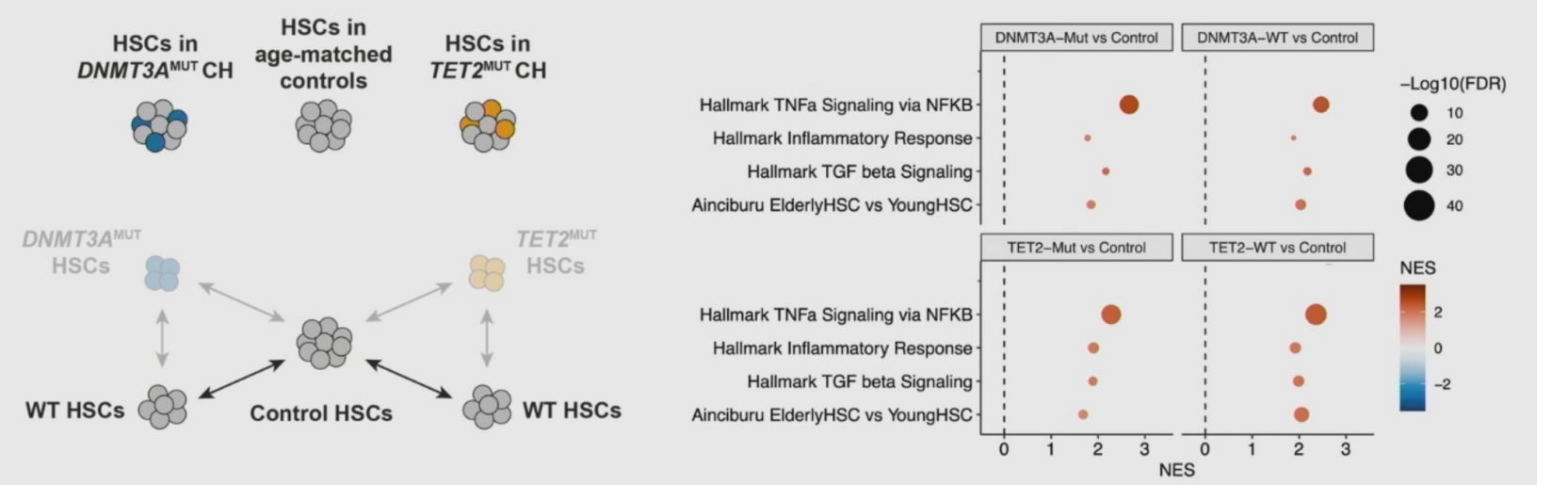


Non-cell-autonomous effect on HSPC in CHIP

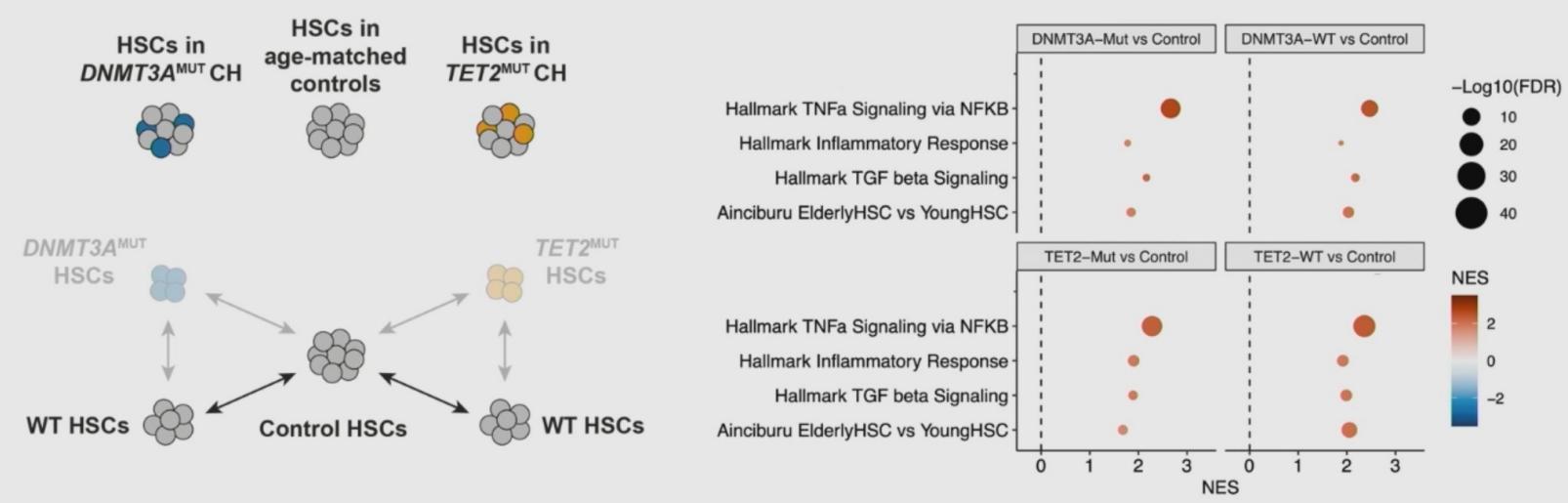




Non-cell-autonomous effect on HSPC in CHIP



Non-cell-autonomous effect on HSPC in CHIP



Non-cell-autonomous effect on HSPC in CHIP