CHIP, ICUS, CCUS & other 4 letter words: "The Emperor(s) of All Maladies"?

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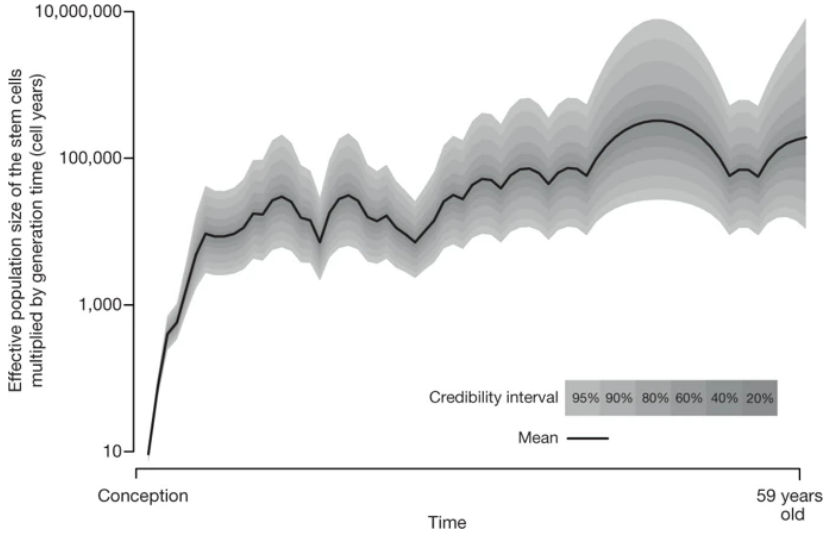
Normal Hematopoiesis



Lee-Six H. et al. Nature 2018

Clonal Hematopoiesis

- Clonal
- Acquired (not inherited) gene mutation
- Characteristic of MDS and leukemias
- May also be found in individuals with*out* a detectable hematologic malignancy
- Prevalence rises with increasing age
- Most individuals will **NOT** ultimately develop a hematologic malignancy

Classification of Clonal Hematopoiesis

1. Size of the hematopoietic clone
2. Presence or absence of cytopenias
3. Exclusion of hematologic malignancy
4. DNA sequencing identifying a mutation in blood or bone marrow cells
   - Not present in other tissues

Detection of Clonal Hematopoiesis

- Next-generation sequencing (NGS) of DNA
  - Less commonly: karyotype, FISH, PCR, or other techniques.
- Clonality is reported as VAF
  - VAF = variant allele frequency
  - % of mutated DNA sequencing reads at a given genetic locus
  - Threshold set at: 1, 2 or 5%
  - VAF parallels the size of the clone
    - % of blood/marrow cells that bear the mutation
  - VAF ~100% → result from:
    - A germline polymorphism of an X-linked gene
    - A mutation of one allele with loss of heterozygosity or deletion of the other allele

Acquired vs Germline

Patient 1

FINAL DIAGNOSIS AND ATTENDING SIGNATURE

Results:

Gene	Variant	VAF	Variant Classification
DNMT3A	c.958C>T (p.R320*)	5%	Tier I: Strong clinical significance

Patient 2

Biomarker	Result (Variant Allele Frequency)
ASXL1	L815P c.2444T>C (99.7%)
TP53	P72R c.215C>G (51.6%)

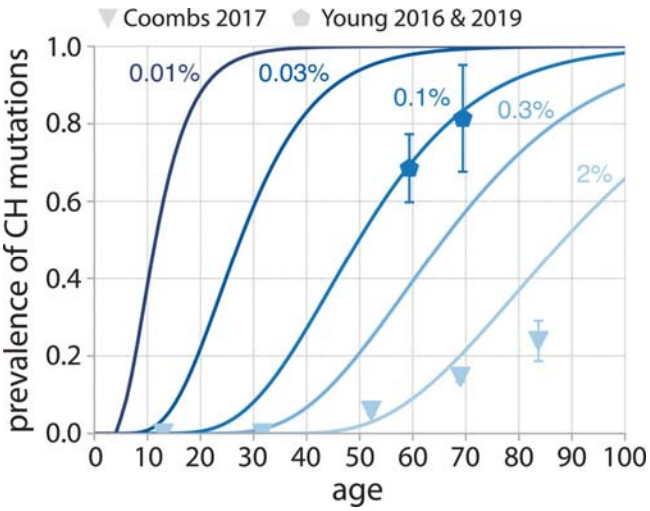
Exclude a germline mutation in the following situations:

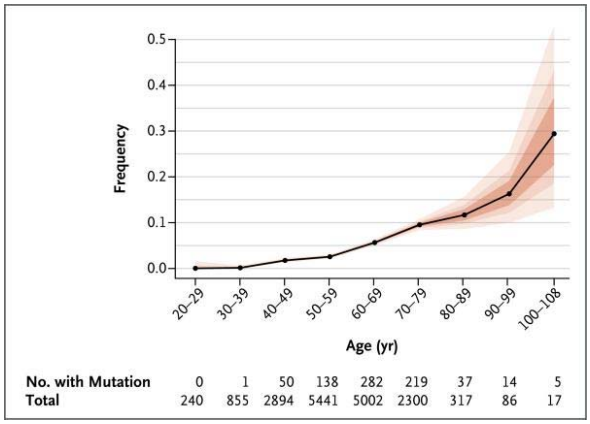
- VAF of 40-60% for mutations of *RUNX1, GATA2,* or *DDX41*
- VAF ≥20% for mutations of *TP53*

CHIP-Associated Mutations

- "Leukemia-associated genes" or "leukemia driver genes"
- One or more distinct mutations
- Reflect a broad array of cellular functions
  - Transcription factors
  - Chromatin modifiers
  - DNA repair
  - Ribonucleoprotein binding proteins
  - Spliceosome components
  - Signal transduction
  - Regulator of cellular metabolism
- These mutated genes give a proliferative or survival advantage to affected cells → enabling the expansion of the clone

When Does CHIP start?



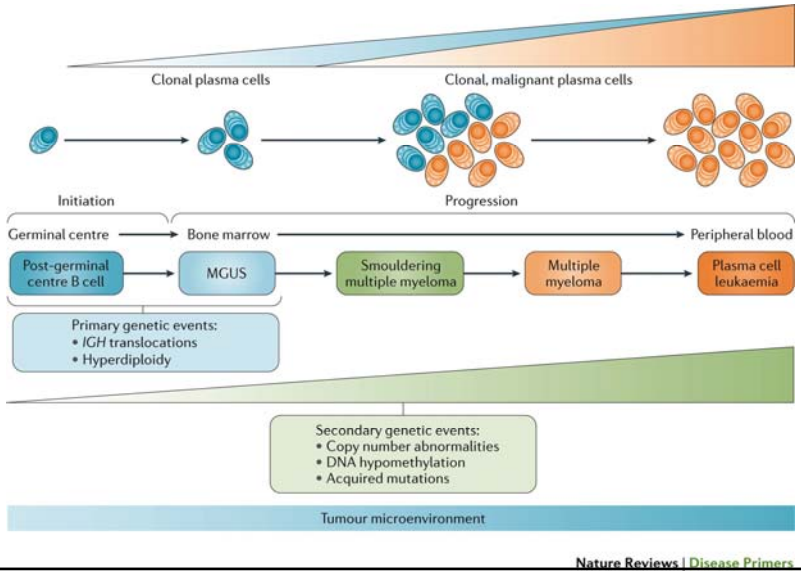


Watson CJ et al. Science 2020
Jaiswal S. et al NEJM 2014

Who Should Be Evaluated?

- There are no clear guidelines or consensus regarding who should be evaluated for CH.
- CH most commonly encountered in NSG is performed for:
  - Evaluation of cytopenias or another hematologic disorder
  - Bone marrow for MM, Lymphoma, etc
  - Evaluation for premature cardiovascular events
  - Testing for an inherited hematologic condition or genetic predisposition to cancer that was found in a relative
  - Screening evaluation of a potential donor for HCT
  - Direct-to-consumer genetic testing

The development of monoclonal gammopathies

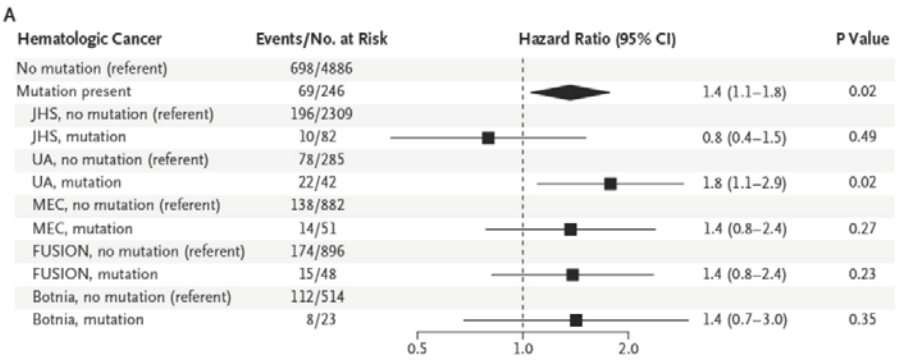


Classification of Clonal Hematopoiesis

	ARCH	CHIP	ICUS	CCUS	Lower-risk MDS	Higher-risk MDS
Clonality (VAF%)	Any, but generally <2%	≥2%	<10%	<10%	≥	Variable; usually ≥2%
Dysplasia	-	<10%	<10%	<10%	≥10% in most cases	≥10% in most cases
Cytopenias	-	-	+	+	+	+
BM blast %	<5%	<5%	<5%	<5%	<5%	<20%
Risk of progression to AML	Very low	Very low	Very low	Low	Low	High

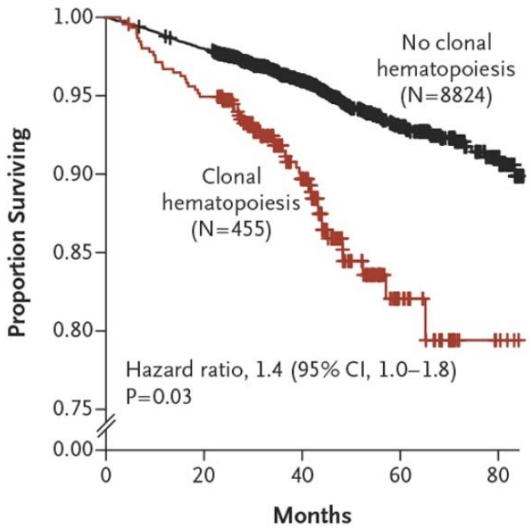
Overall Survival

- CHIP is associated with increased all-cause mortality



Jaiswal S. et al NEJM 2014

Overall Survival

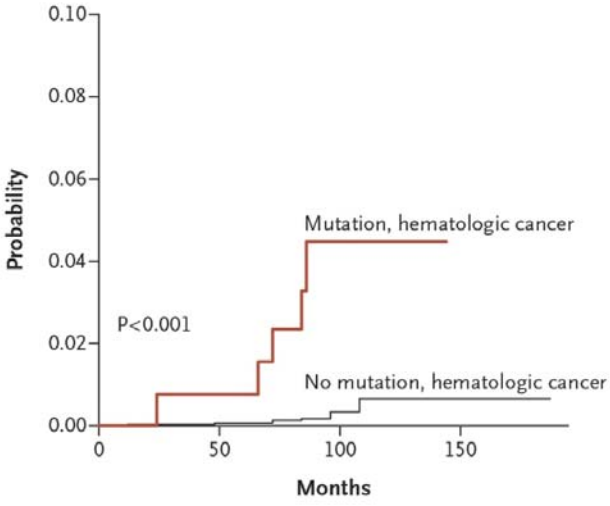


Genovese G. et al. NEJM 2014

Rate of Transformation to HM

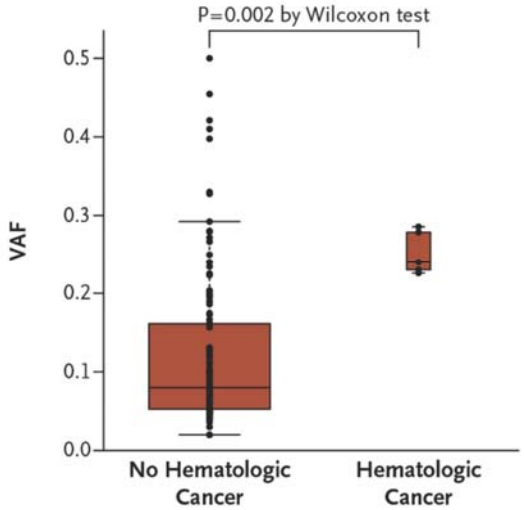
- Rates of progression vary with:
  - The specific mutations
  - The number of mutations
  - The size of the hematopoietic clone (VAF)
- For individuals who carry CHIP-associated mutations, the **transition to AML** has been estimated to be approximately **0.5-1% per year**

Rate of Transformation to HM



Jaiswal S. et al NEJM 2014

Higher VAF: More Clinical Significance



Jaiswal S. et al NEJM 2014

CHIP: a newly recognized & potent risk factor for CAD

n=2,286	Model 1		Model 2		Model 3	
Covariate	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
log(Age)	5.3(2.1-12.8)	<0.001	4.7(1.9-11)	<0.001	4.6(1.9-11)	<0.001
Has T2D	3.3(2.1-5.3)	<0.001	3.4(2.1-5.4)	<0.001	3.5(2.2-5.5)	<0.001
Female	0.7(0.5-1.1)	0.11	0.7(0.5-1.1)	0.13	0.7(0.5-1.1)	0.13
HDL<35 mg/dL	1.1(0.6-2.1)	0.77	1.1(0.6-2.1)	0.81	1.1(0.6-2.1)	0.78
HDL>60 mg/dL	0.7(0.4-1.2)	0.18	0.7(0.4-1.3)	0.25	0.7(0.4-1.3)	0.26
TC >240 mg/dL	2.1(1.3-3.2)	<0.001	2(1.3-3.1)	<0.001	2(1.3-3.1)	<0.001
Former or current smoker	1.6(1.1-2.5)	0.024	1.6(1-2.4)	0.035	1.6(1.1-2.5)	0.02
Hypertension stage II-IV	1.6(1-2.5)	0.06	1.4(0.9-2.3)	0.15	1.4(0.9-2.3)	0.15
BMI>25	1.2(0.6-2.5)	0.55	1.4(0.6-2.8)	0.43	1.3(0.6-2.8)	0.42
Mutation present			2.3(1.1-4.8)	0.026		
VAF<0.10					1.4(0.5-4)	0.55
VAF≥0.10					4.4(1.9-10.5)	<0.001
Pseudo Log-likelihood		-661		-658		-656
Pseudo likelihood ratio test		103 on 9 df		109 on 10 df		113 on 11 df

Jaiswal S. et al NEJM 2014

Increases Risk of Developing Stroke

n=2,420	Model 1		Model 2		Model 3	
Covariate	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
log(Age)	14.6(4.8-44.7)	<0.001	13.3(4.3-40)	<0.001	13.1(4.3-40)	<0.001
Has T2D	2.9(1.7-5)	<0.001	2.9(1.7-5)	<0.001	3(1.7-5.2)	<0.001
Female	0.8(0.5-1.3)	0.44	0.9(0.5-1.4)	0.53	0.9(0.5-1.4)	0.55
HDL<35 mg/dL	1.2(0.6-2.4)	0.52	1.3(0.7-2.5)	0.45	1.3(0.7-2.5)	0.45
HDL>60 mg/dL	1(0.6-1.9)	0.95	1.1(0.6-2)	0.84	1.1(0.6-2)	0.86
TC >240 mg/dL	1.3(0.8-2.1)	0.29	1.3(0.8-2.1)	0.31	1.3(0.8-2.1)	0.29
Former or current smoker	1.8(1.1-2.9)	0.014	1.8(1.1-2.9)	0.016	1.8(1.1-2.9)	0.014
Hypertension stage II-IV	1.8(1-3.1)	0.037	1.7(0.9-2.9)	0.077	1.7(1-2.9)	0.074
BMI>25	1.5(0.6-3.6)	0.35	1.6(0.7-4)	0.3	1.6(0.7-3.9)	0.3
Mutation present			2.2(1.1-4.6)	0.029		
VAF<0.10					1.8(0.7-4.6)	0.2
VAF≥0.10					3.1(1.2-8.4)	0.025
Pseudo Log-likelihood		-464		-462		-462
Pseudo likelihood ratio test		79 on 9 df		83 on 10 df		83.5 on 11 df

Jaiswal S. et al NEJM 2014

Why Cardiovascular Complications?

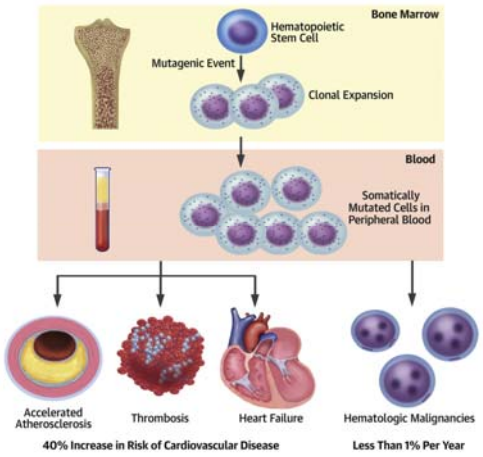
- Mechanism appears to be inflammation in the endothelium driven by clonally-derived monocytes/macrophages.
- The granulocytes bearing this mutation show heightened sensitivity to the formation of neutrophil extracellular traps.
- These structures, which consist of extruded nuclear DNA decorated with proteins implicated in inflammation and coagulation, participate in thrombosis.
- Granulocytes that bear Jak2V617F exhibit activation of the b1 and b2 integrins that mediate binding to endothelial leukocyte adhesion molecules also link CHIP with vascular inflammation

Libby P et al. J Am Coll Cardiol 2019

Why Cardiovascular Complications?

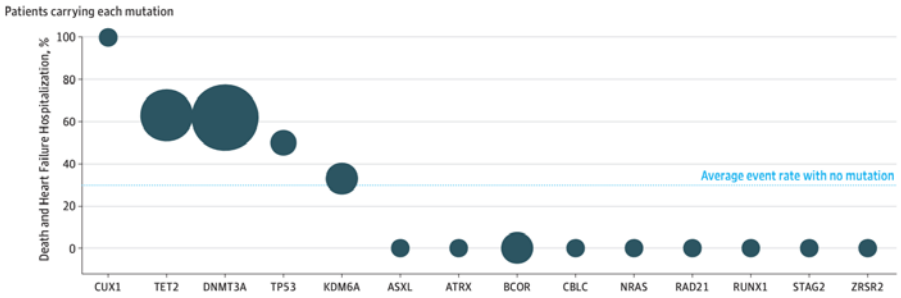
- Furthermore, introduction of Jak2V617F leukocytes into the bone marrow of atherosclerosisprone mice enhances the formation of the plaque's lipid-rich necrotic core due to a defect in clearance of dead leukocytes (a process termed efferocytosis)

- Jak2V617F macrophages also engulf red cells more voraciously compared with wild-type phagocytes. These observations indicate that CHIP due to mutant JAK2 promotes cardiovascular events, at least to some degree, through mechanisms distinct from TET2 mutations that associate with enhanced expression of pro-inflammatory mediators.



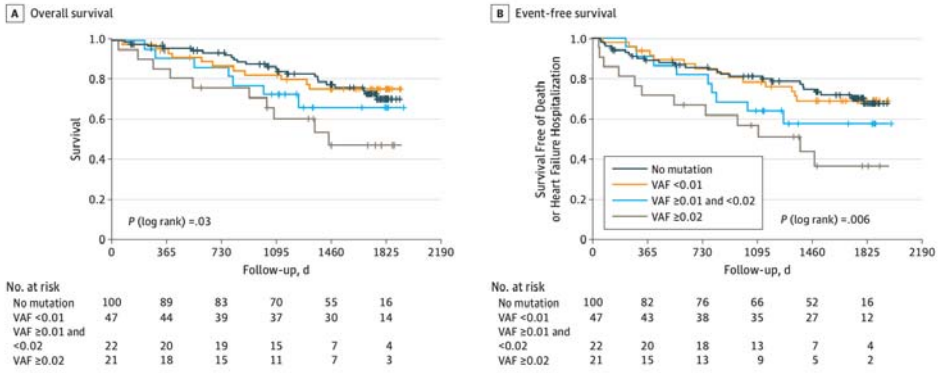
What About Survivors of MI?

- Survivors of myocardial infarction with CHIP have increased mortality and worsened heart failure outcomes.



Libby P et al. J Am Coll Cardiol 2019
Dorsheimer L et al. JAMA 2019

Non-CHIP vs CHIP & VAF fractions



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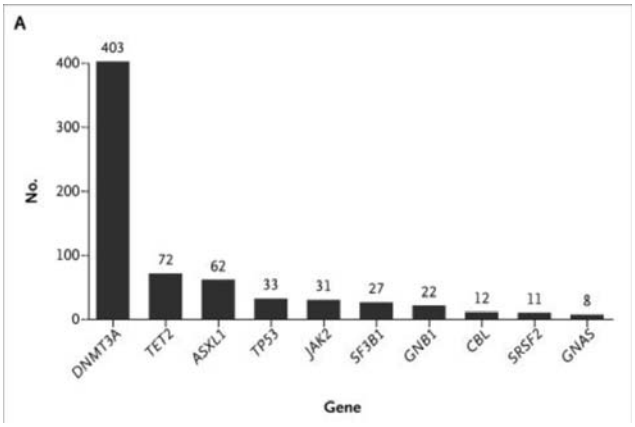

Jaiswal S. et al NEJM 2014

Monitoring

- Evaluate q3-6months
  - Interval history
  - Physical exam
  - CBC w/ differential
  - NO need to repeat NGS
  - NO need to repeat BMBx (in the absence of another indication)
- Modify frequency of visits and/or CBCs
  - High-risk mutation (eg, TP53 mut)
  - VAF ≥20%
  - ≥2 distinct mutations
  - Cytopenias (if associated w/ clinical findings and/or other CAD risk factors)

CHIP in potential transplant donors

- Presence of CHIP in donors of HCT may affect the outcome in the transplant recipient.
- If a potential transplant donor is found to have CHIP, when possible, we seek a suitable alternative donor to avoid possible progression of donor-derived CHIP or development of an overt hematologic malignancy in the recipient.
- Some institutions screen older potential donors for CHIP