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Clonal Hematopoiesis of Indeterminate Potential CHIP

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Outline

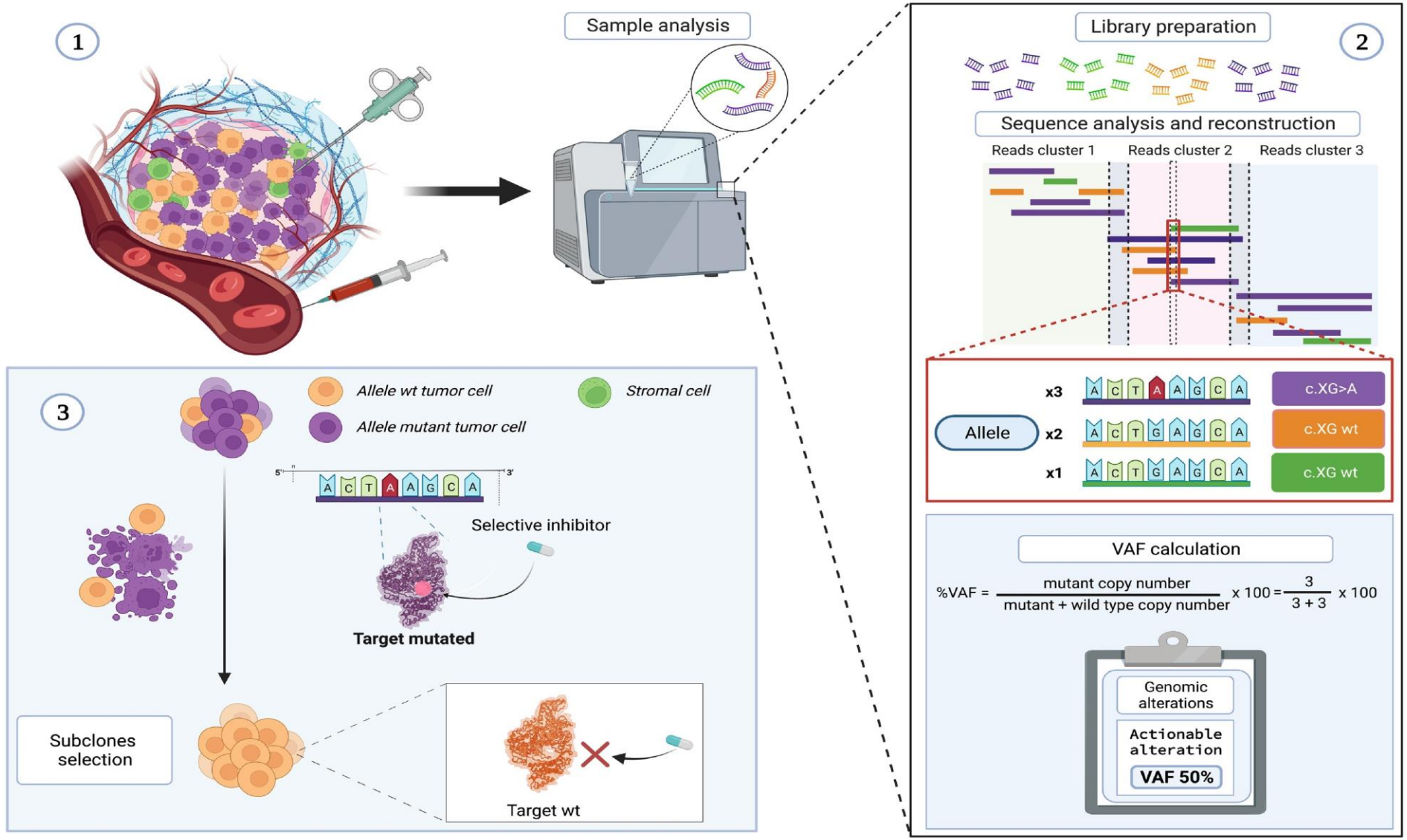
- Definition of CHIP
- Pathophysiologic mechanisms involved in CHIP
- Clinical consequences of CHIP
- Incorporation into diagnostic algorithms
- A representative case: new considerations in the clinic

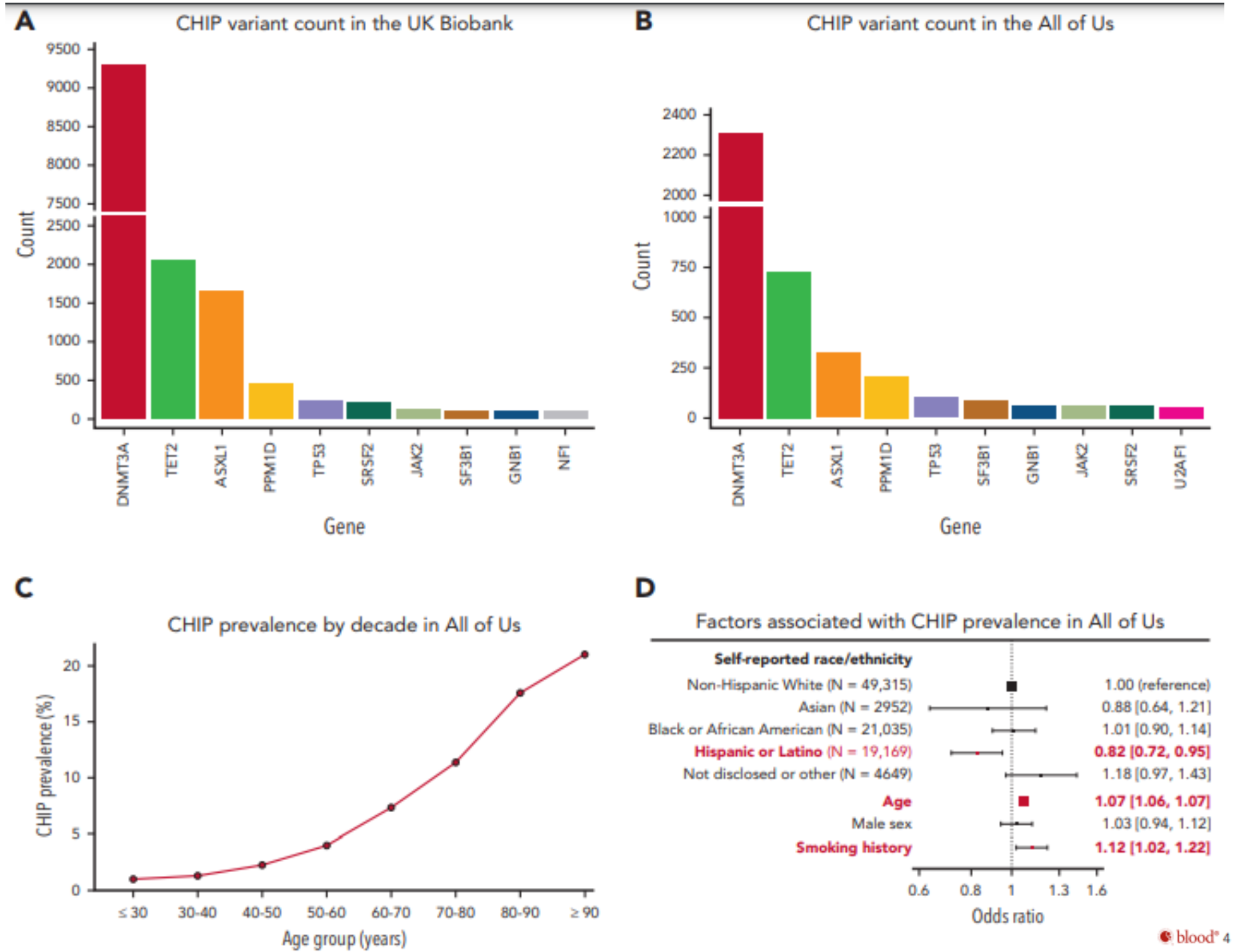
Definition

- Clonal production of blood cells
- World Health Organization (WHO) and International Consensus Classification (ICC) guidelines
  - Somatic mutation in a myeloid neoplasm gene (eg, *DNMT3A, TET2, ASXL1, JAK2, TP53*)
  - Variant allele fraction (VAF) of ≥2%
  - No diagnosed hematologic disorder

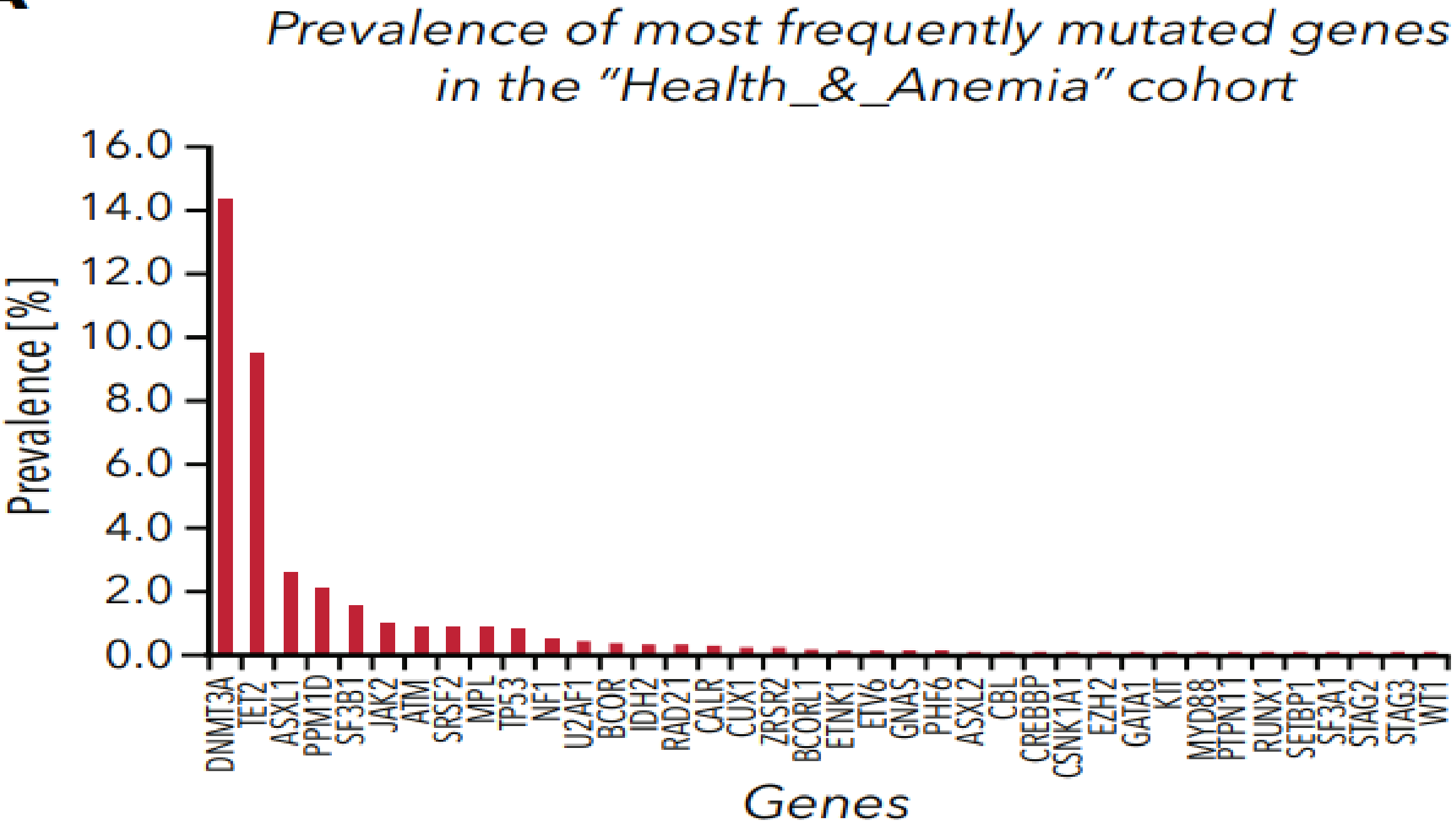
What is VAF??

It is the fraction of variant sequencing reads within a genetic locus




A
CHIP variant count in the UK Biobank
Count
9500
9000
8500
8000
7500
2500
2000
1500
1000
500
0
DNMT3A
TET2
ASXL1
PPM1D
TP53
SRSF2
JAK2
SF3B1
GNB1
NF1
Gene
B
CHIP variant count in the All of Us
Count
2400
2200
2000
1000
750
500
250
0
DNMT3A
TET2
ASXL1
PPM1D
TP53
SF3B1
GNB1
JAK2
SRSF2
U2AF1
Gene
C
CHIP prevalence by decade in All of Us
CHIP prevalence (%)
20
15
10
5
0
≤ 30
30-40
40-50
50-60
60-70
70-80
80-90
≥ 90
Age group (years)
D
Factors associated with CHIP prevalence in All of Us
Self-reported race/ethnicity
Non-Hispanic White (N = 49,315)
1.00 (reference)
Asian (N = 2952)
0.88 [0.64, 1.21]
Black or African American (N = 21,035)
1.01 [0.90, 1.14]
Hispanic or Latino (N = 19,169)
0.82 [0.72, 0.95]
Not disclosed or other (N = 4649)
1.18 [0.97, 1.43]
Age
1.07 [1.06, 1.07]
Male sex
1.03 [0.94, 1.12]
Smoking history
1.12 [1.02, 1.22]
0.6
0.8
1
1.3
1.6
Odds ratio

A


Prevalence of most frequently mutated genes
in the "Health_&_Anemia" cohort
Prevalence [%]
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
DNMT3A
TET2
ASXL1
PPM1D
SF3B1
JAK2
ATM
SRSF2
MPL
TP53
NF1
U2AF1
BCOR
IDH2
RAD21
CALR
CUX1
ZRSR2
BCORL1
ETNK1
ETV6
GNAS
PHF6
ASXL2
CBL
CREBBP
CSNK1A1
EZH2
GATA1
KIT
MYD88
PTPN11
RUNX1
SETBP1
SF3A1
STAG2
STAG3
WT1
Genes

Leukemia (2017) **31,** 1869–1871

www.nature.com/leu

CONCISE REVIEW

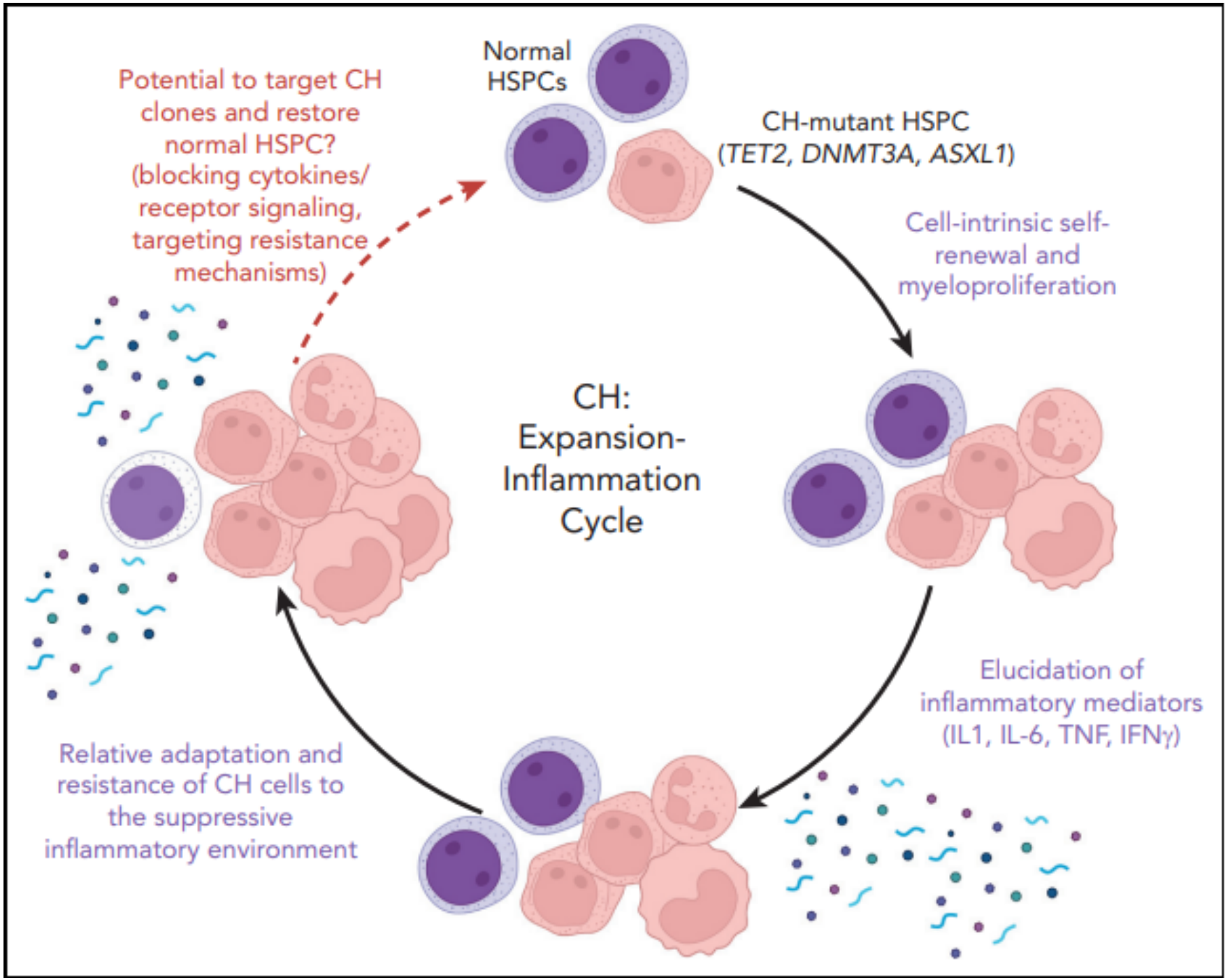
CHIP, ICUS, CCUS and other four-letter words

R Bejar

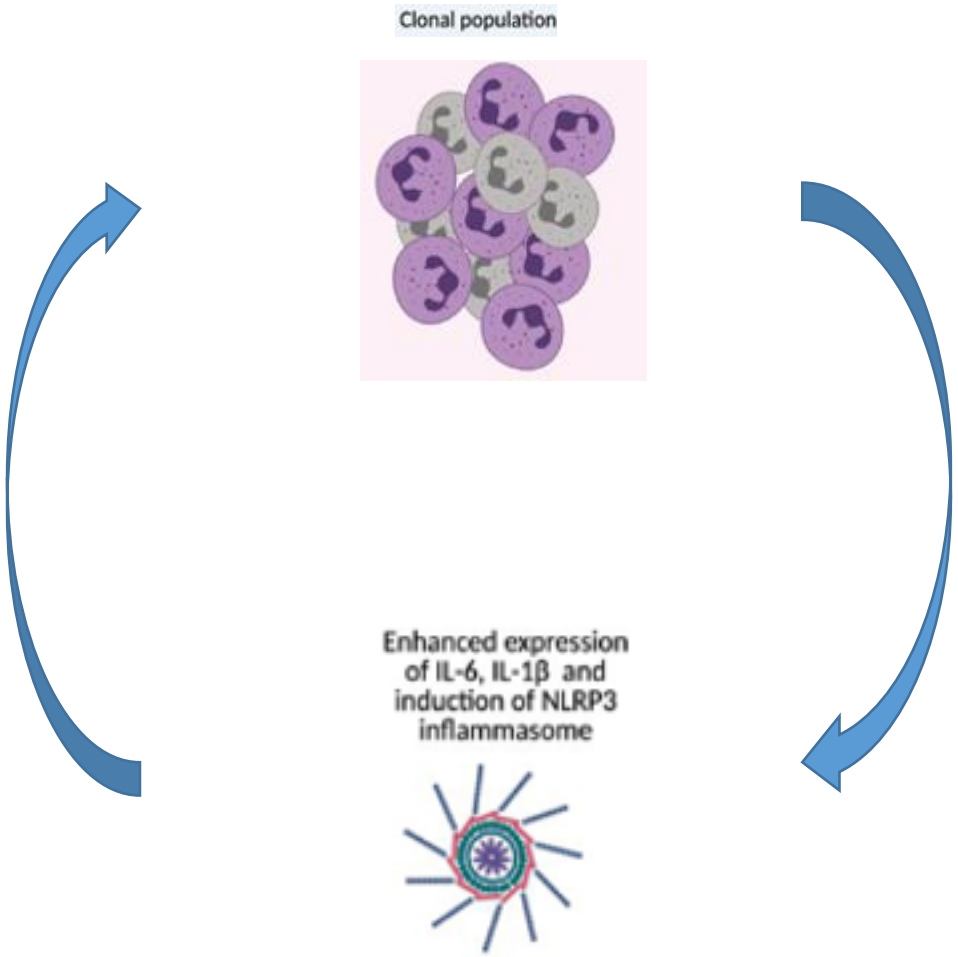
Table 1. Acronyms describing clonal hematopoiesis and related conditions

Acronym	*Condition*	*Description/Definition*
ARCH	Aging related clonal hematopoiesis	Describes the presence of detectable, benign clonal hematopoiesis (defined by the presence of somatic mutations in the blood or bone marrow) whose incidence increases with age. No formal definition involving clonal abundance or types of mutations. No clinical significance is implied.
CHIP	Clonal hematopoiesis of indeterminate potential	Defined by somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geqslant$ 2% variant allele frequency in individuals without a diagnosed hematologic disorder.
CHOP	Clonal hematopoiesis of oncogenic potential	Describes clonal hematopoiesis in a clinical context where it is associated with a significant likelihood of progressing to a frank malignancy.
IDUS	Idiopathic dysplasia of undetermined significance	Individuals with unexplained morphologic dysplasia of blood cells who are not cytopenic. Can occur with or without clonal hematopoiesis.
ICUS	Idiopathic cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder. Can occur with or without clonal hematopoiesis although often used to refer to cytopenias without evidence of clonal hematopoiesis.
CCUS	Clonal cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder, but who have somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geqslant$ 2% variant allele frequency. Can be considered as the intersection between CHIP and ICUS.

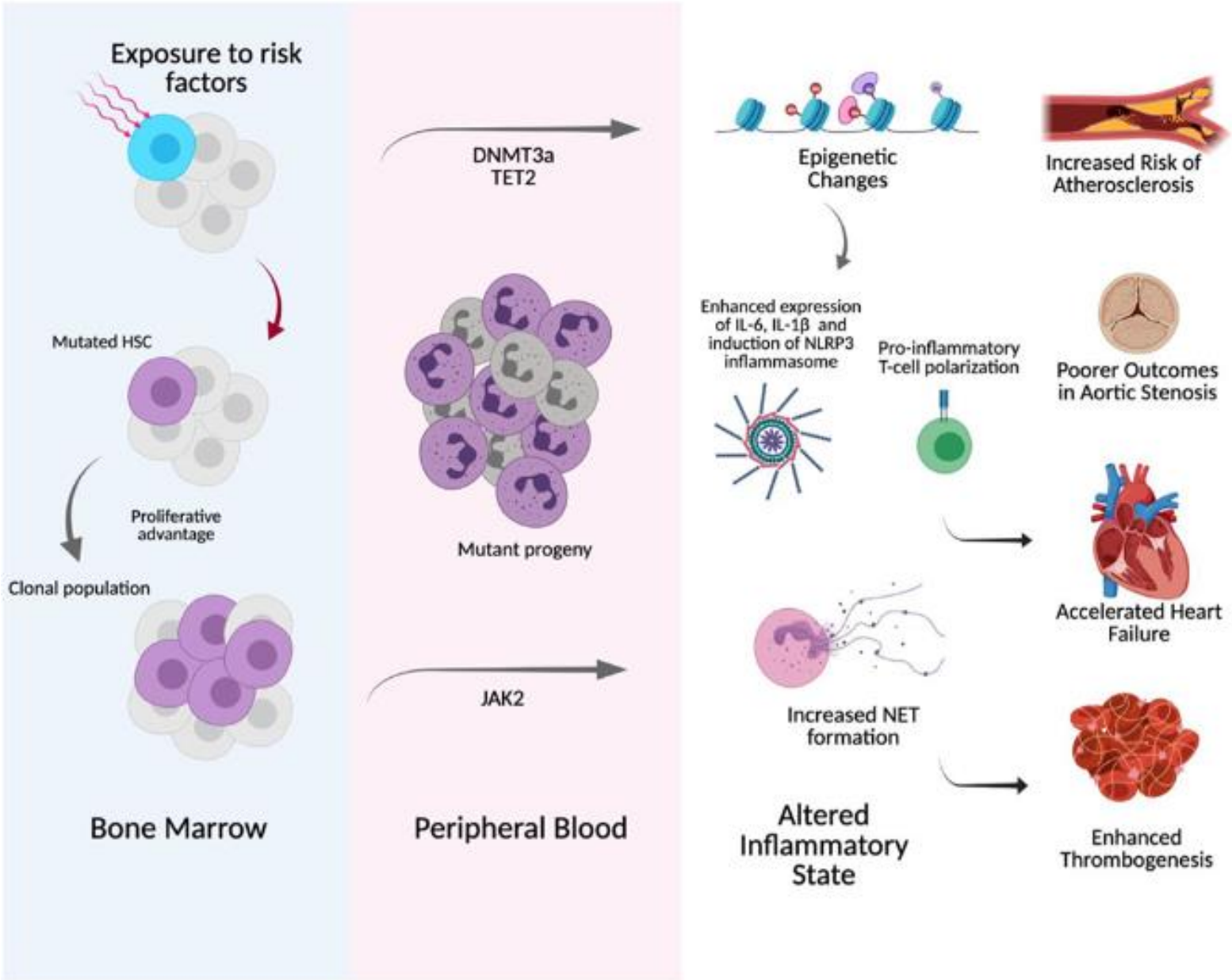
Pathophysiology



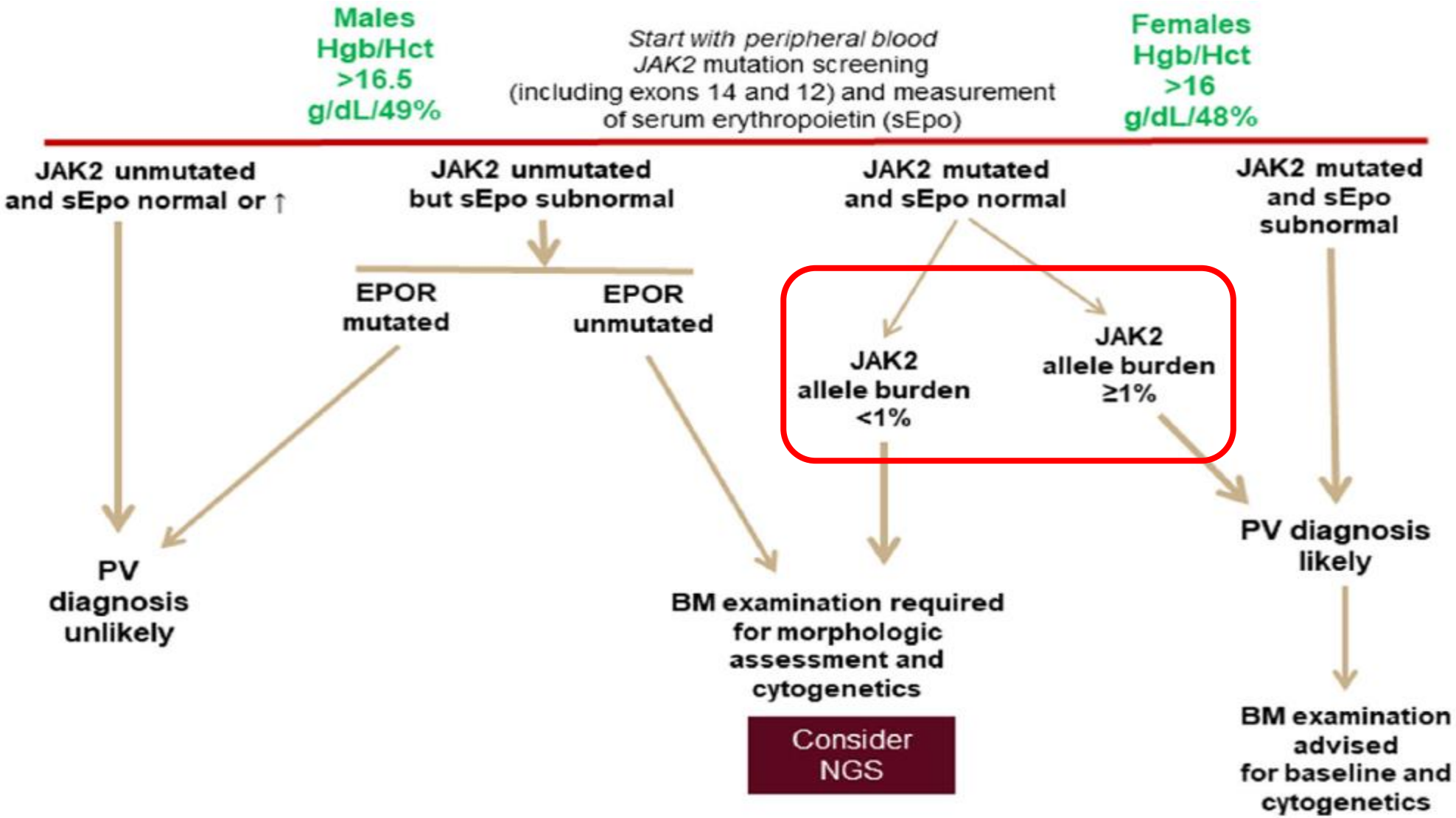
Relationship between inflammation and CHIP



Clinical consequences



Incorporation into diagnostic algorithms: P vera



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A clinical case to consider

- 24 year-old woman
- Referred for assessment with hematocrit=45%, iron deficiency and mild splenomegaly
- Initial assessment: JAK2 V627F mutation detected, serum EPO normal
- Bone marrow biopsy: overall cellularity = 65%, possible megakaryocyte abnormalities – morphology and localization
- JAK2 variant allele frequency of 1.5%
- Dilemmas:
  - Is this CHIP with another etiology for clinical/laboratory findings?
  - Is this early P vera?
  - Is this another MPN?