Clonal Precursors with Clinical Consequences: MGUS, MBL, CHIP & TCUS in Perspective

Molecular Biology and Cytometry Course
UCLL, Campus Gasthuisberg, Leuven

06/02/2026

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"CHiPs"

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Seek and you shall find

Agarose gel electrophoresis

Detection of Major bcr-abl Gene Expression at a Very Low Level in Blood Cells of Some Healthy Individuals

By C. Biernaux, M. Loos, A. Sels, G. Huez, and P. Stryckmans

The major bcr-abl fusion gene is presently seen as the hallmark of chronic myeloid leukemia (CML) and presumably as the cause of its development. Accordingly, long-term disappearance of bcr-abl after intensive therapy is considered to be a probable cure of CML. The nested reverse transcriptase-polymerase chain reaction (RT-PCR) provides a powerful tool for minimal residual CML detection. The RT-PCR was optimized by (1) increasing the amount of total RNA involved in the reverse transcription reaction to correspond to total RNA extracted from 10^8 cells, (2) using a specific abl primer in this reverse reaction, and (3) reamplifying 10% of the RT-PCR product in nested amplification. This optimized RT-PCR permitted us to detect up to 1 copy of RNA bcr-abl synthezised in vitro, mixed with yeast RNA in an equivalent quantity to 10^8 white blood cells (WBCs). Using this highly sensitive RT-PCR during the follow-up of CML patients, a signal was unexpectedly found in healthy controls. Therefore, a systematic study of the possible expression of bcr-abl RNA in the WBCs of healthy adults and children and in umbilical cord blood was undertaken. It showed the presence of bcr-abl transcript in the blood of 22 of 73 healthy adults and in the blood of 1 of 22 children but not in 22 samples of umbilical cord blood.

From the Laboratory of Biological Chemistry (Rhode-St-Genèse) and the J. Bordet Institute, Université Libre de Bruxelles, Bruxelles, Belgium.

Blood, Vol 86, No 8 (October 15), 1995: pp 3118-3122

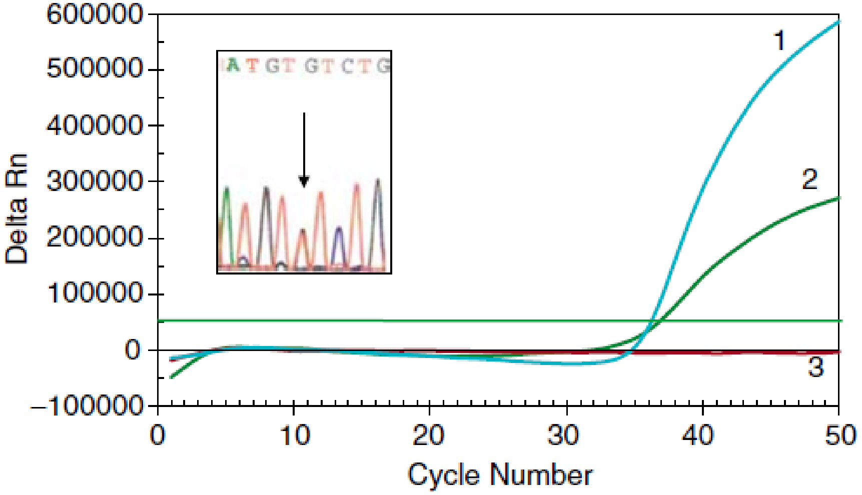
Seek harder and you shall find more

qPCR

The *JAK2*V617F mutation is detectable at very low level in peripheral blood of healthy donors

Leukemia (2006) **20,** 1622. doi:10.1038/sj.leu.2404292;
published online 15 June 2006

The *JAK2*V617F mutation has been recently described in several subsets of Philadelphia-negative myeloproliferative diseases (MPD) (for a review see McClure *et al.*[1]). However, its precise role and position in the multistep genetic events leading to such MPD is still unknown. It may be that this mutation represents an early molecular onset causing the MPD phenotype or occurs as a mutation associated with disease progression.[2] Its identification in normal patients would favour the first hypothesis, and could thus help in understanding the function of the *JAK2*V617F



Found in ~10% of healthy volunteers

P Sidon, H El Housni, B Dessars and P Heimann
Department of Medical Genetics, Faculty of Medicine, Erasme Hospital, Free University of Brussels, Brussels, Belgium
E-mail: pheimann@ulb.ac.be

Seek harder and you shall find more

NGS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

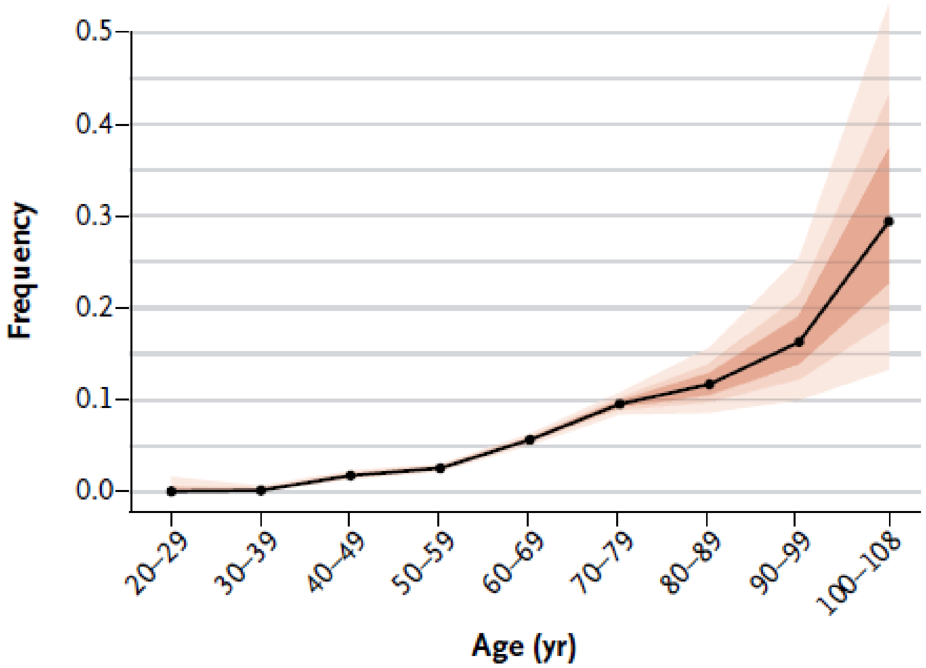
Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D., Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D., R. Coleman Lindsley, M.D., Ph.D., Craig H. Mermel, M.D., Ph.D., Noel Burtt, B.S., Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Moltchanov, Ph.D., Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D., Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Claes Ladenvall, Ph.D., Gad Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin F. Banahan, Ph.D., Stacey Gabriel, Ph.D., Sekar Kathiresan, M.D., Heather M. Stringham, Ph.D., Mark I. McCarthy, M.D.,* Michael Boehnke, Ph.D.,* Jaakko Tuomilehto, M.D., Ph.D., Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., Gil Atzmon, Ph.D., James G. Wilson, M.D., Donna Neuberg, Sc.D., David Altshuler, M.D., Ph.D.,* and Benjamin L. Ebert, M.D., Ph.D.†

This article was published on November 26, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1408617

- Large gene panels to screen patients
  - 17 182 healthy patients – 160 genes
  - LOD: 3,5% (SNVs) 7,0% (indels)

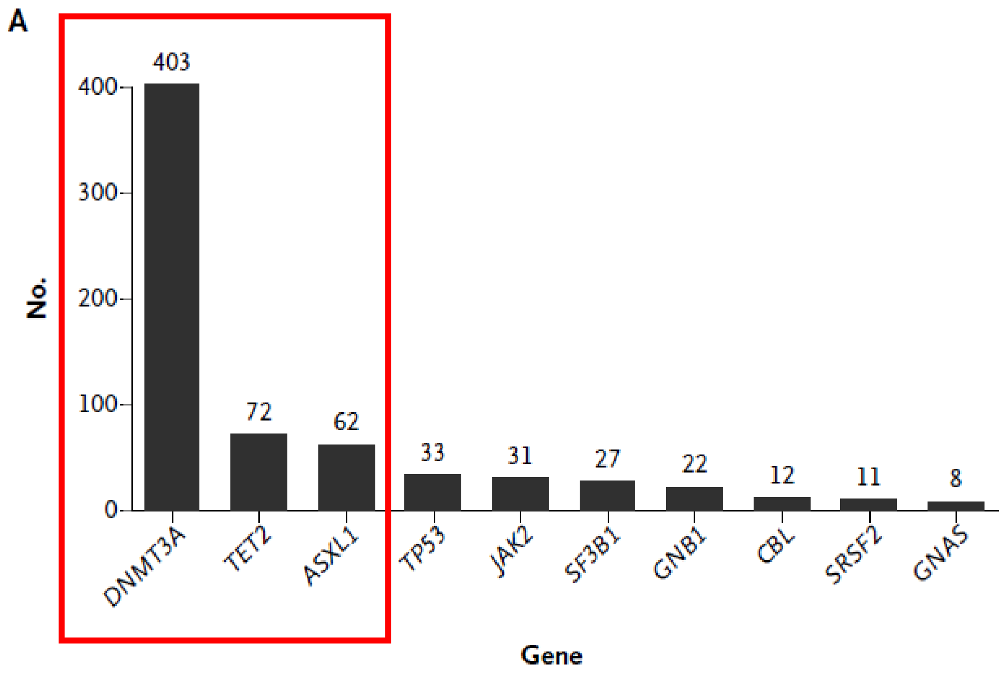


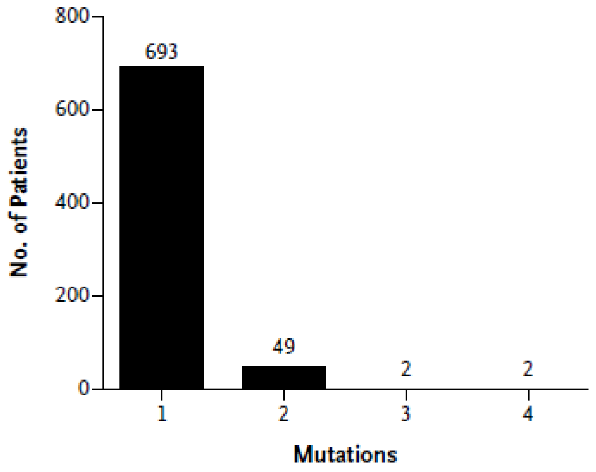
Jaiswal et al., NEJM 2014

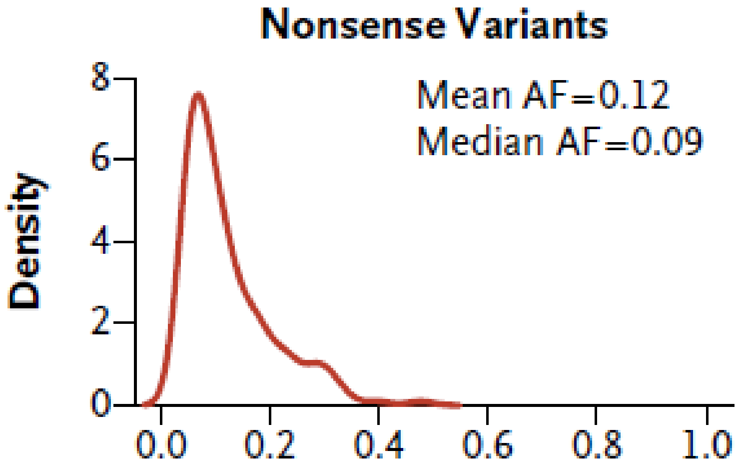
Seek harder and you shall find more

Not alle genes are created equal

- ‘DTA genes’ most prevalent: DNMT3A / TET2 / ASXL1
- Mean / median frequency ~10%
- Most patients only have one mutation

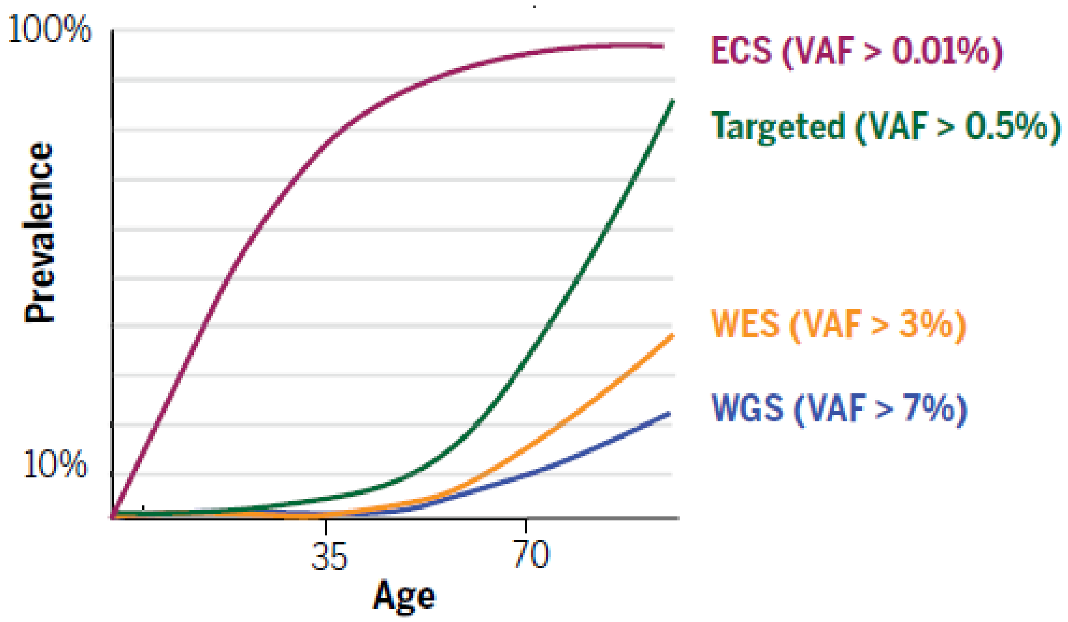






NGS – Deep sequencing

To infinity and beyond

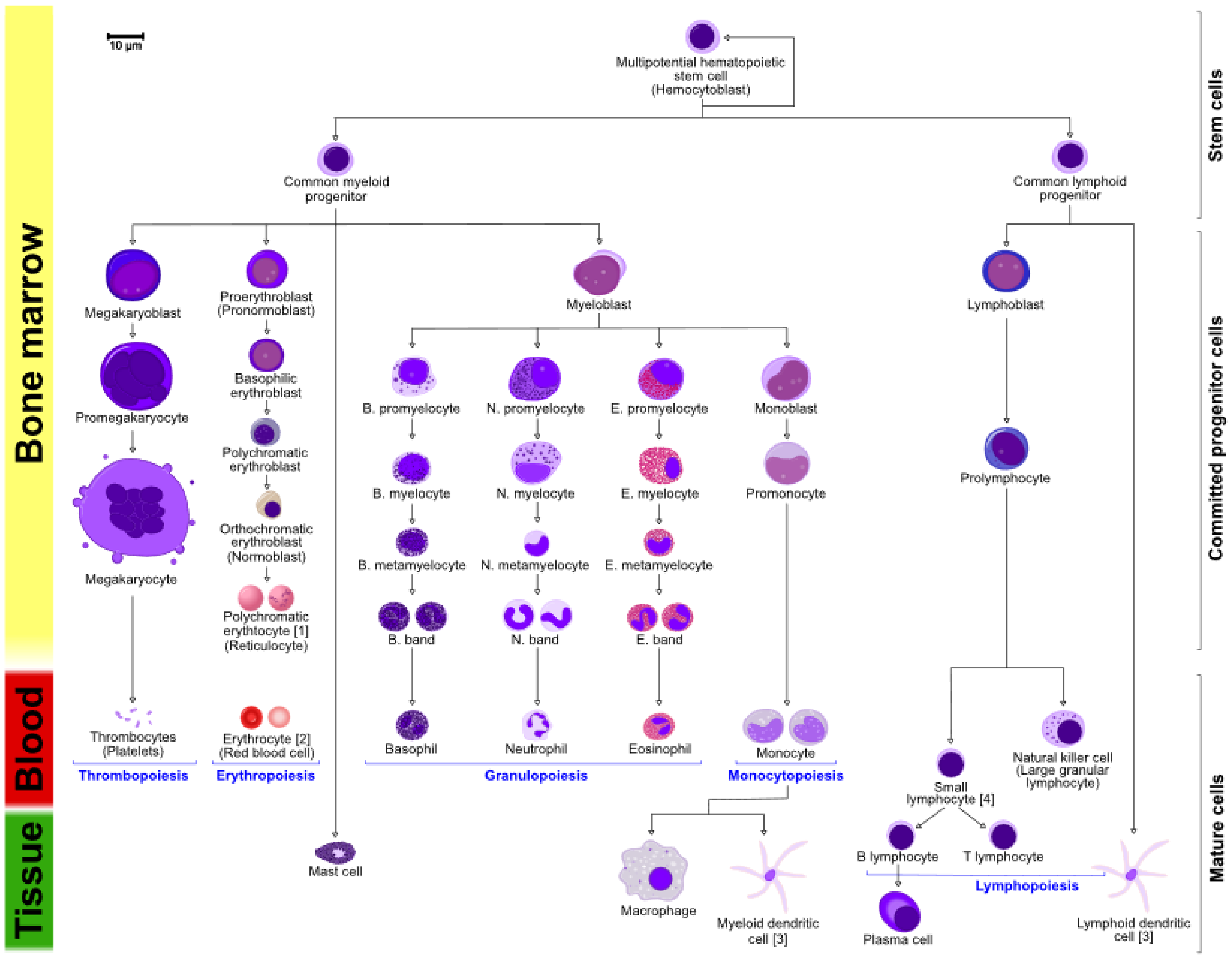


Jaiswal and Ebert, Science 2019

ECS: error-corrected sequencing
WES: whole exome sequencing
WGS: whole genome sequencing

Hematopoietic stem cells

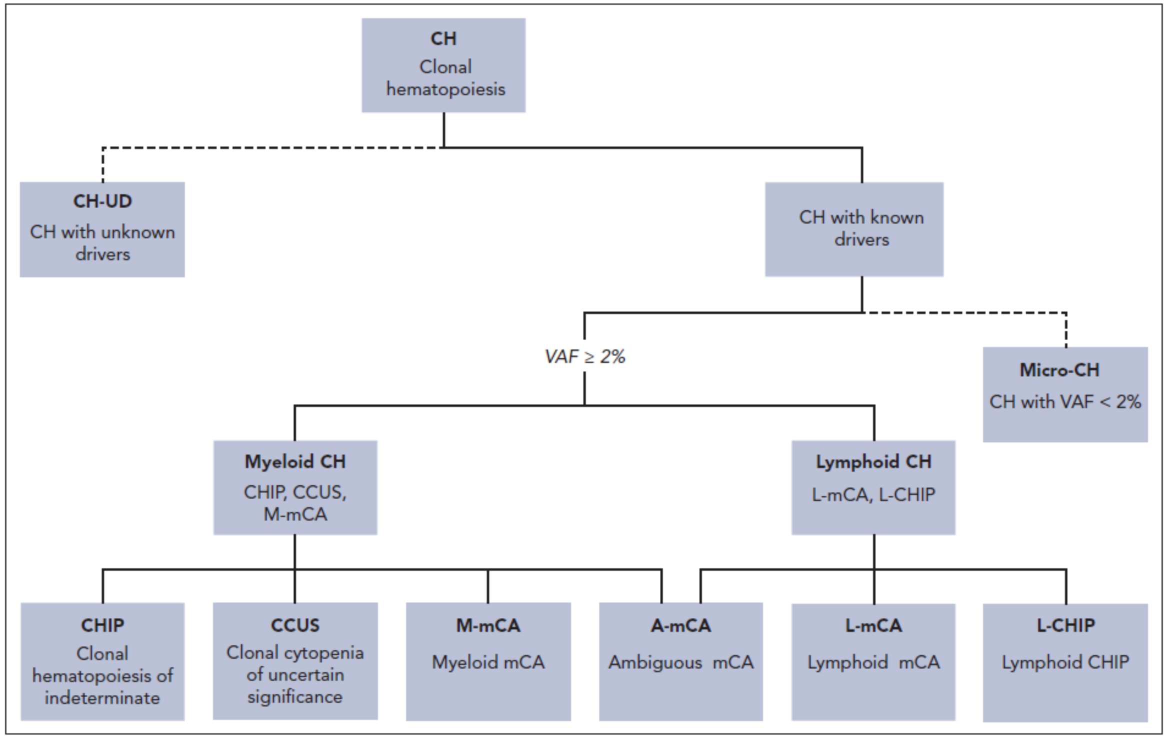
- 50 000 – 200 000 hematopoietic stem cells
- 10 000 000 000 to 500 000 000 000 new blood cells every day
  - 2-3 million RBC / second
- Low frequency variation:
  - Expected just by chance
- Higher frequency variation:
  - growth advantage => clonal population



How do you define normal?

From ARCH to CHIP and further

- CHIP: Clonal Hematopoiesis of Indeterminate Potential (definition according to NIH)
  - The presence of somatic mutations in hematopoietic stem cells in an individual **without a detectable hematologic cancer**. The definition of CHIP requires that mutations are present with a **variant allele frequency of 2% or higher** and they are located **in genes described to be affected in hematologic cancers**.
  - Cut-off chosen due to technical reasons (< 2% more difficult to distinguish from sequencing artefact)

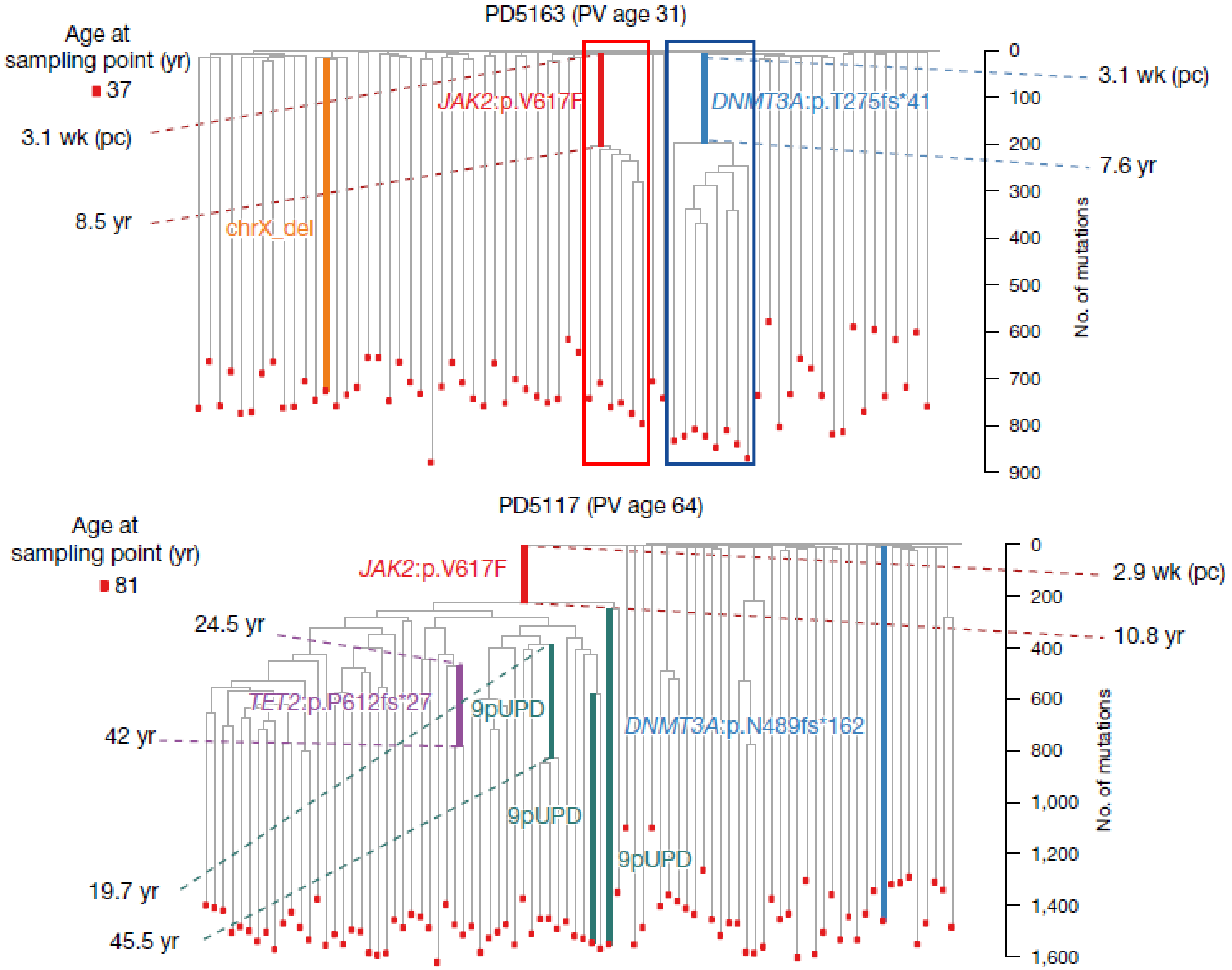


Weeks and Ebert, Blood 2023

NGS – Single cell sequencing

When does it begin?

- Single cell sequencing and phylogenetic clustering on shared passenger mutations
- Origins of CHIP mutations can be traced back to very early age
- Initial mutations are predicted to have occurred even before birth!



Williams et al., Nature 2022
pc: post conception

Are we doomed?

- Genome wide association study (GWAS) in 43 619 CHIP carriers and 598 761 controls
- Genetic variant in MSI2 (Musashi RNA-binding protein 2) controlling its expression
- 1 or 2 copies of this variant confer a ~20-30% reduced risk of CHIP, most prominent for JAK2
- (overall 20% reduced risk for myeloid malignancy)

Some of us (~5-6%) are protected …

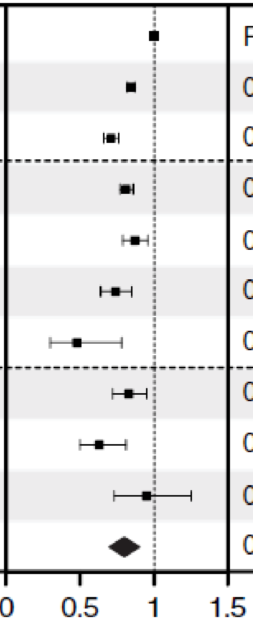
RESEARCH ARTICLES
Science 1 JANUARY 2026

HEMATOLOGY

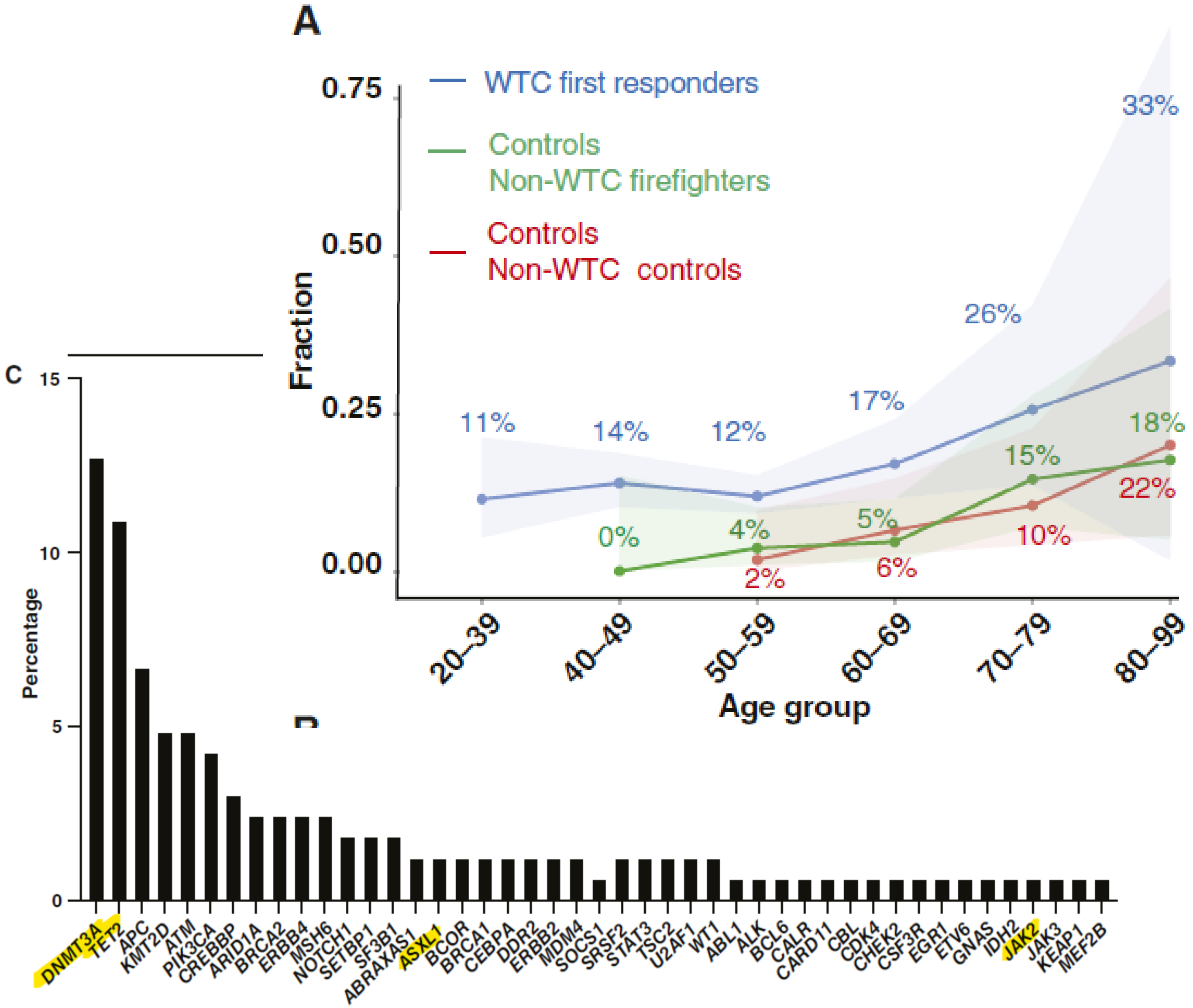
Inherited resilience to clonal hematopoiesis by modifying stem cell RNA regulation

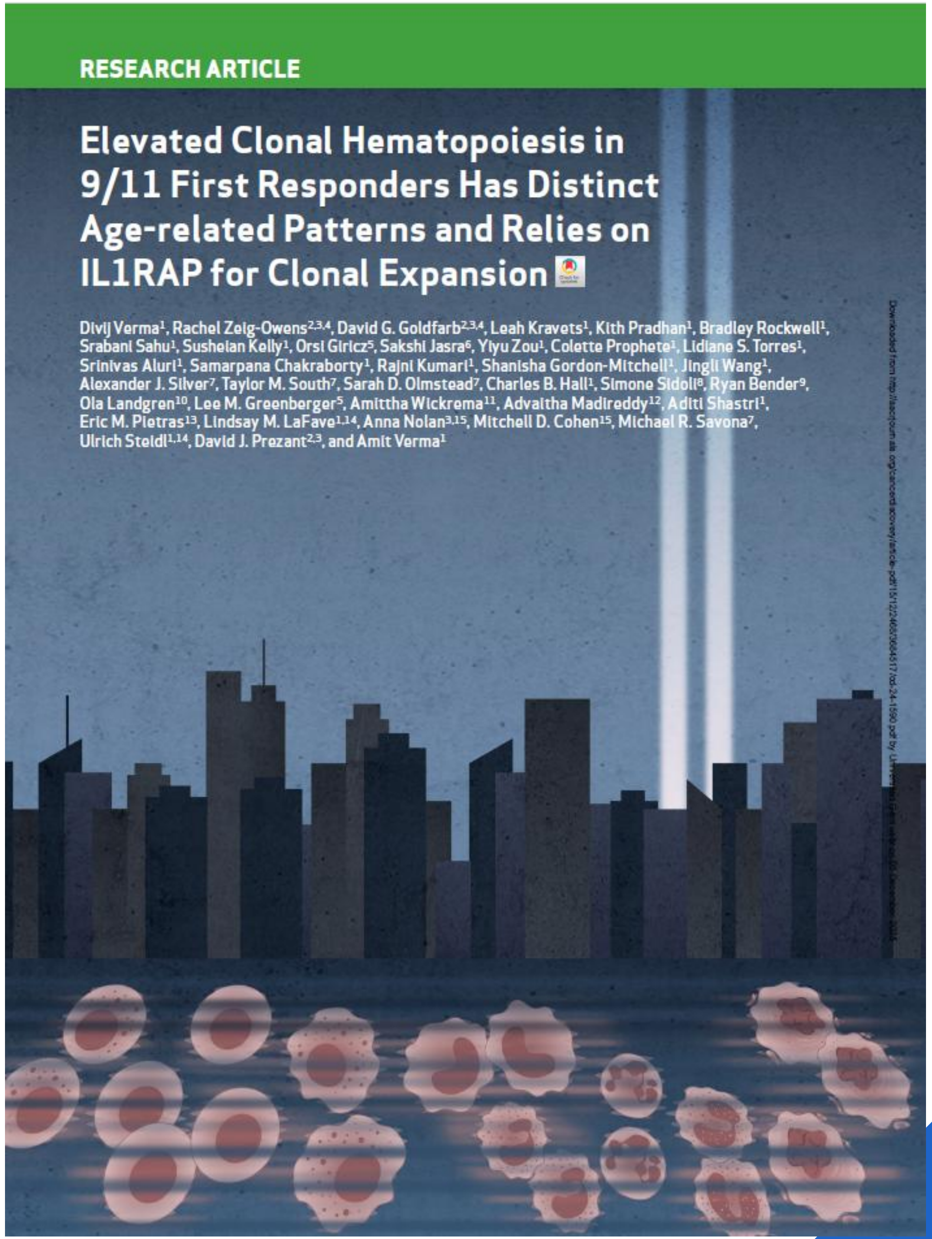
Gaurav Agarwal[1,2,3,4], Mateusz Antoszewski[1,2,3,4], Xueqin Xie[5], Yash Pershad[6], Uma P. Arora[1,2,3,4], Chi-Lam Poon[7], Peng Lyu[1,2,3,4], Andrew J. Lee[1,2,3,4], Chun-Jie Guo[1,2,3,4], Tianyi Ye[1,2,3,4], Laila Barakat Norford[1,2,3,4,8], Anna-Lena Neehus[1,2,3,4], Lucrezia della Volpe[1,2,3,4], Lara Wahlster[1,2,3,4], Diyanath Ranasinghe[9], Tzu-Chieh Ho[5]†, Trevor S. Barlowe[5], Arthur Chow[5], Alexandra Schurer[5]‡, James Taggart[5]§, Benjamin H. Durham[5]¶, Omar Abdel-Wahab[5], Kathy L. McGraw[10,11,12], James M. Allan[9], Ruslan Soldatov[7], Alexander G. Bick[6], Michael G. Kharas[5]*, Vijay G. Sankaran[1,2,3,4,13]*

Genotype	Absent	587,026	Reference	
	1 allele	59,198	0.84 [0.82, 0.87]	9.6E-22
	2 alleles	1,489	0.71 [0.66, 0.76]	
CHIP Driver	DNMT3A	21,467	0.81 [0.77, 0.86]	4.5E-15
	TET2	6,325	0.87 [0.79, 0.96]	0.0052
	ASXL1	2,906	0.74 [0.64, 0.85]	3.4E-5
	JAK2	918	0.48 [0.30, 0.78]	0.0030
Blood cancer	AML	4,012	0.83 [0.72, 0.95]	0.0081
	MPN	1,086	0.63 [0.50, 0.81]	0.0002
	MDS	907	0.95 [0.73, 1.25]	0.7249
	All MyM	6,005	0.80 [0.70, 0.90]	8.7E-5



But be careful what job you choose





RESEARCH ARTICLE

Elevated Clonal Hematopoiesis in 9/11 First Responders Has Distinct Age-related Patterns and Relies on IL1RAP for Clonal Expansion

Divij Verma[1], Rachel Zeig-Owens[2,3,4], David G. Goldfarb[2,3,4], Leah Kravets[1], Kith Pradhan[1], Bradley Rockwell[1], Srabani Sahu[1], Susheian Kelly[1], Orsi Giricz[5], Sakshi Jasra[6], Yiyu Zou[1], Colette Prophete[1], Lidiane S. Torres[1], Srinivas Aluri[1], Samarpana Chakraborty[1], Rajni Kumari[1], Shanisha Gordon-Mitchell[1], Jingli Wang[1], Alexander J. Silver[7], Taylor M. South[7], Sarah D. Olmstead[7], Charles B. Hall[1], Simone Sidoli[8], Ryan Bender[9], Ola Landgren[10], Lee M. Greenberger[5], Amittha Wickrema[11], Advaitha Madireddy[12], Aditi Shastri[1], Eric M. Pietras[13], Lindsay M. LaFave[1,14], Anna Nolan[3,15], Mitchell D. Cohen[15], Michael R. Savona[7], Ulrich Steidl[1,14], David J. Prezant[2,3], and Amit Verma[1]

DECEMBER 2025 CANCER DISCOVERY | 2469

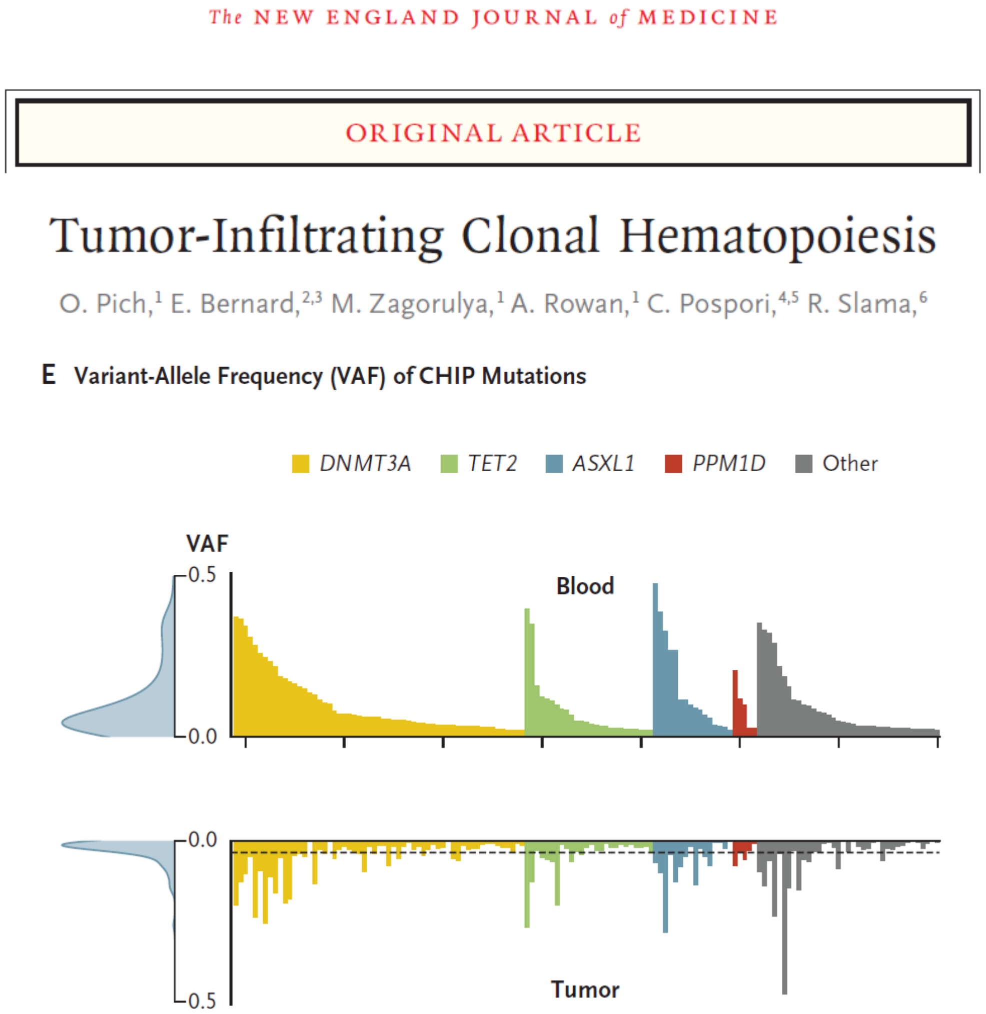
Impact in other tumors

Complications

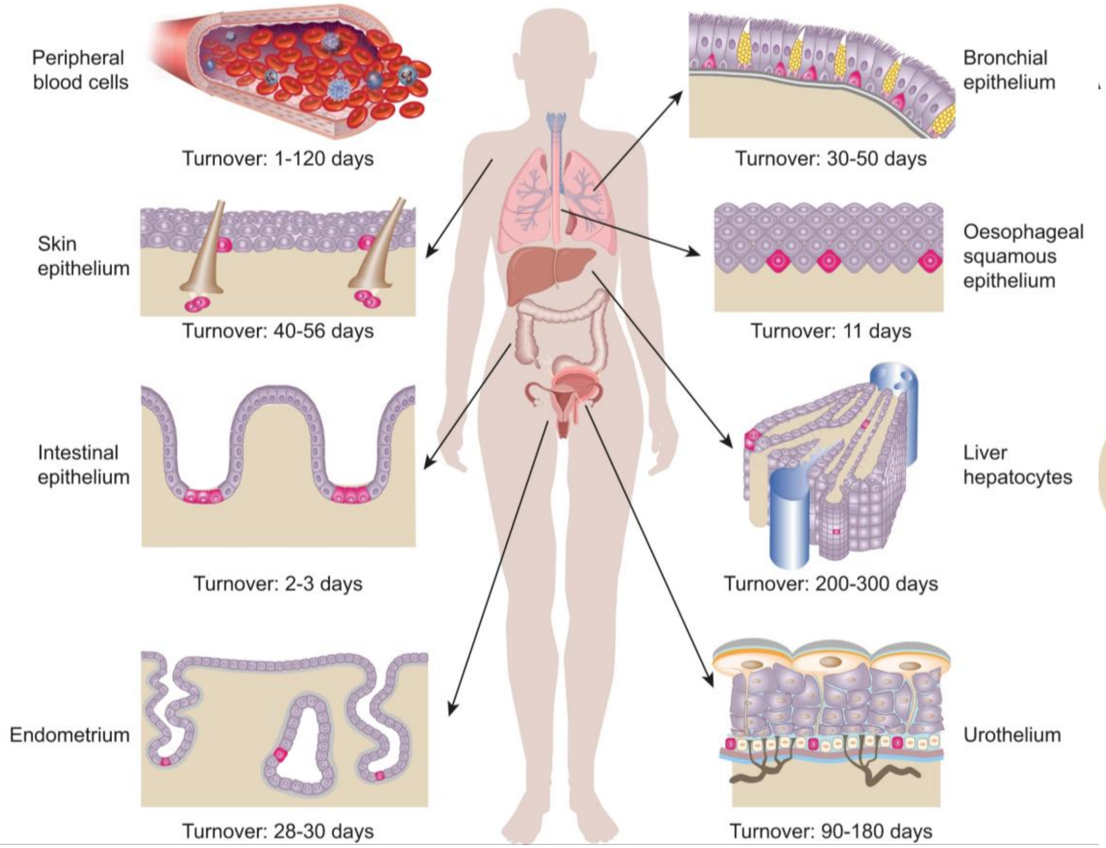
- Mutation analysis of lung tumors shows the presence of clonal hematopoietic cells in the solid tumor
  - 26% of patients with CHIP have TI-CHIP
- Where is the mutation?
  - DNMT3A / TET2 / ASXL1 / PPM1D: not typically found in solid tumors
  - TP53?

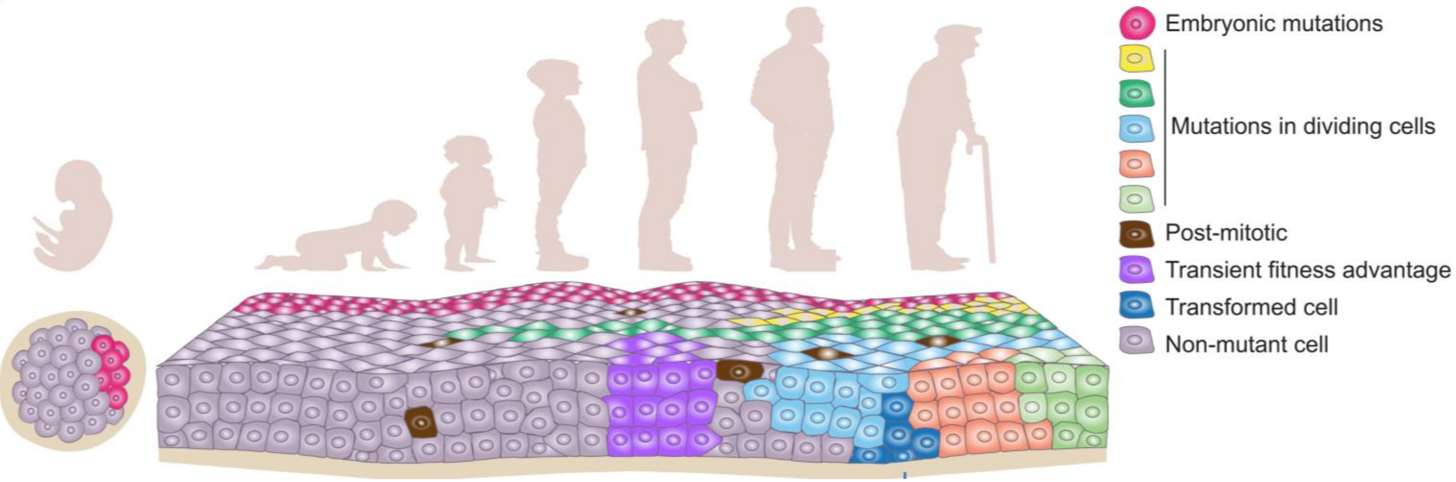
Coombs et al., Clin Canc Res 2018

- 65% of solid cancer patients have mutations in CHIP genes (of which half is in TP53)
- 8% of detected mutations are clonal hematopoiesis events



Clonal outgrowth is not restricted to blood





By the time we're old, our cells are less identical twins and more distant cousins.

Acha-Sagredo et al., Ann Oncol 2022

Does CHIP hurt? Is CHIP bad? Is it cancer?

Clonal Precursors with Clinical Consequences: MGUS, MBL, ~~CHIP~~ & TCUS in Perspective

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Acronyms

Clonal populations

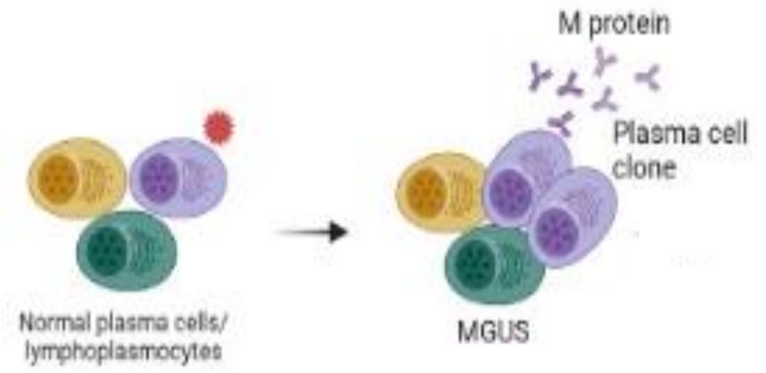
- CHIP: **C**lonal **H**ematopoiesis of **I**ndeterminate **P**otential
  - characterized by low frequency mutations
- T-CUS: **T**-cell **C**lones of **U**nknown **S**ignificance
  - no evidence yet for somatic mutations (Semenzato et al., Haematologica 2025)
- MGUS: **M**onoclonal **G**ammopathy of **U**ndetermined **S**ignificance
  - same mutations as multiple myeloma orginating from the MGUS (combination of SNVs, copy-number alterations and chromosomal translocations (Alberge et al., Nature Genetics 2025))
- MBL: **M**onoclonal **B**-cell **L**ymphocytosis
  - same mutations as CLL originating from the MBL

Precursor hematologic conditions
MGUS, MBL, CHIP & TCUS

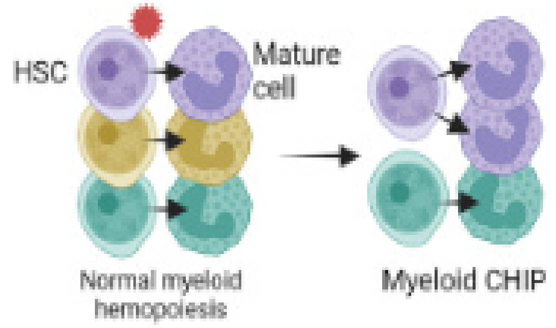
- **Asymptomatic clonal expansion** of either plasmacells, lymphoid or myeloid cells
- **Not meeting criteria** for active hematologic **malignancy** (myeloma, lymphoma, leukemia, MDS)
- **Often incidental** finding based on abnormalities on routine laboratory assessment in **otherwise healthy** asymptomatic adults
- **May** develop into cancer

Precursor hematologic conditions

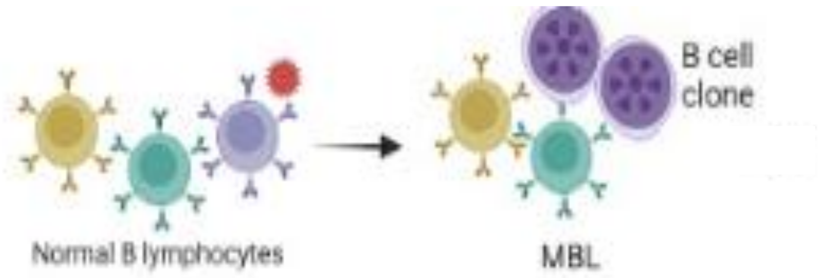
- **Asymptomatic clonal expansion** of either plasmacells, lymphoid or **myeloid cells**



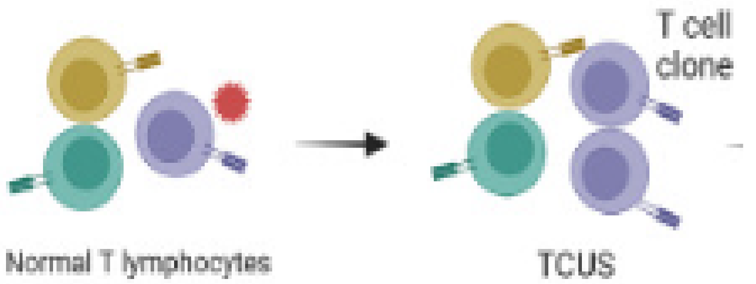
MGUS: monoclonal gammopathy of undetermined significance



CHIP: clonal hematopoiesis of indeterminate potential



MBL: monoclonal B-cell lymphocytosis



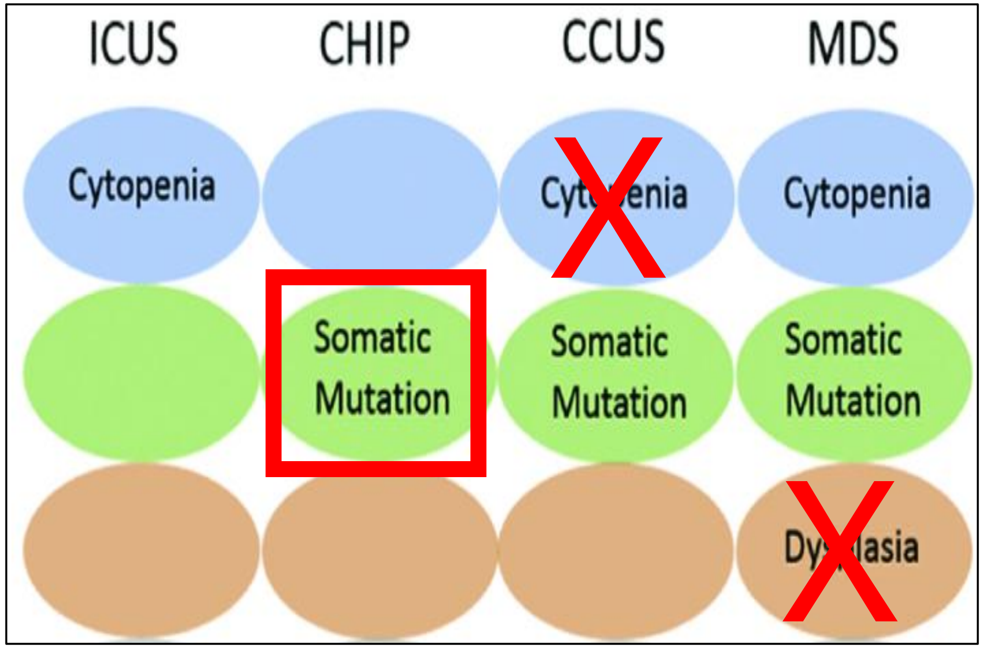
TCUS: T-cell clones of uncertain significance

Clonal hematopoiesis of indeterminate potential (CHIP)

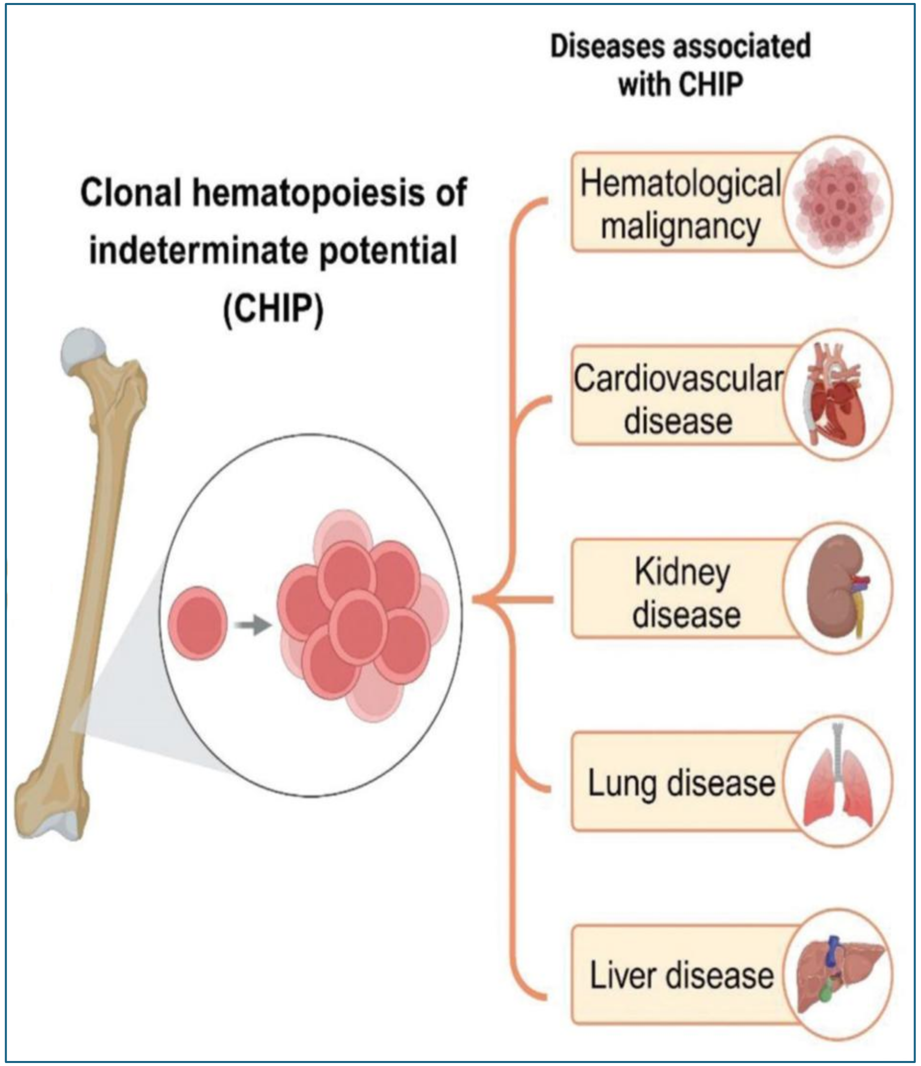
- detection of **≥1 somatic mutations** in genes associated with hematological malignancies in hematopoietic cells of **healthy** individuals (with variant allele frequency (VAF) ≥2%)

- **absence** of **unexplained cytopenias**

- **absence** of diagnostic **criteria** for defined (myeloid) **neoplasms**

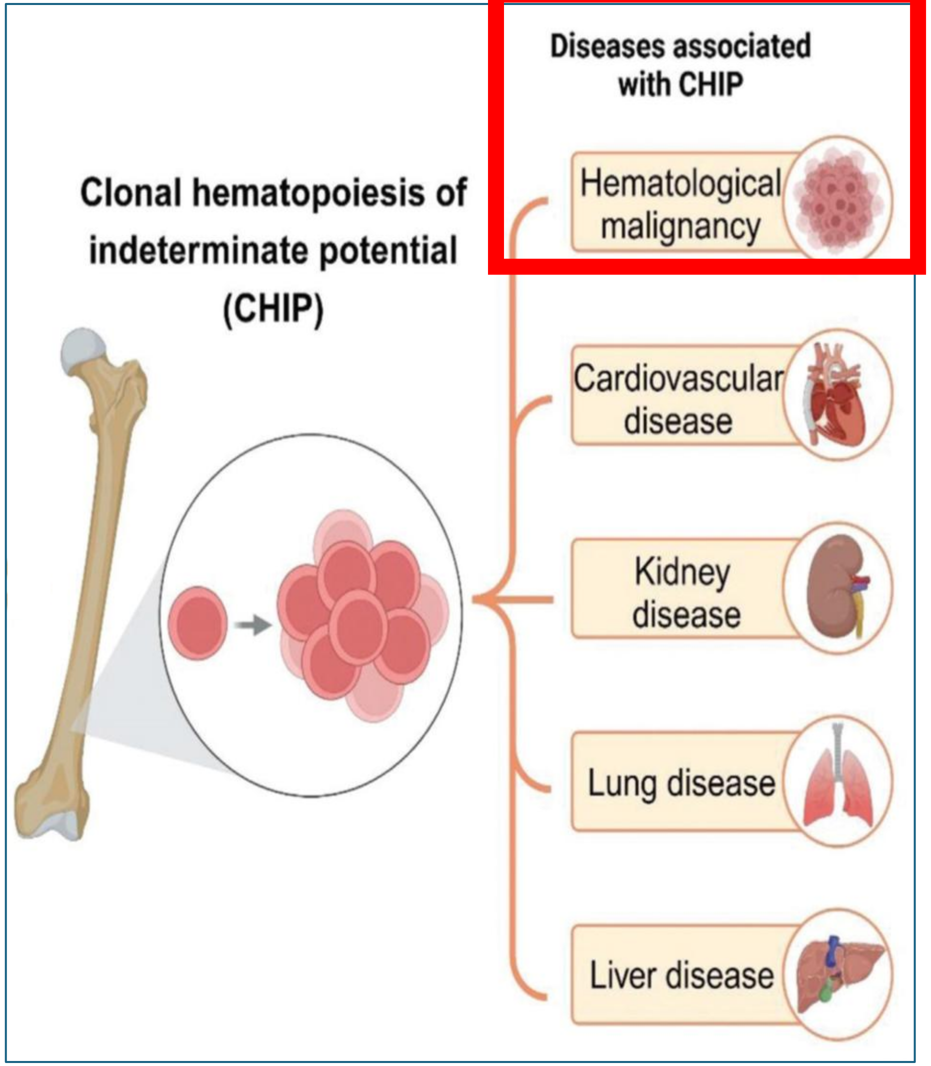


Clinical implications of CHIP



Guo, Meiqi Curr Opiin Hemato, 2025.

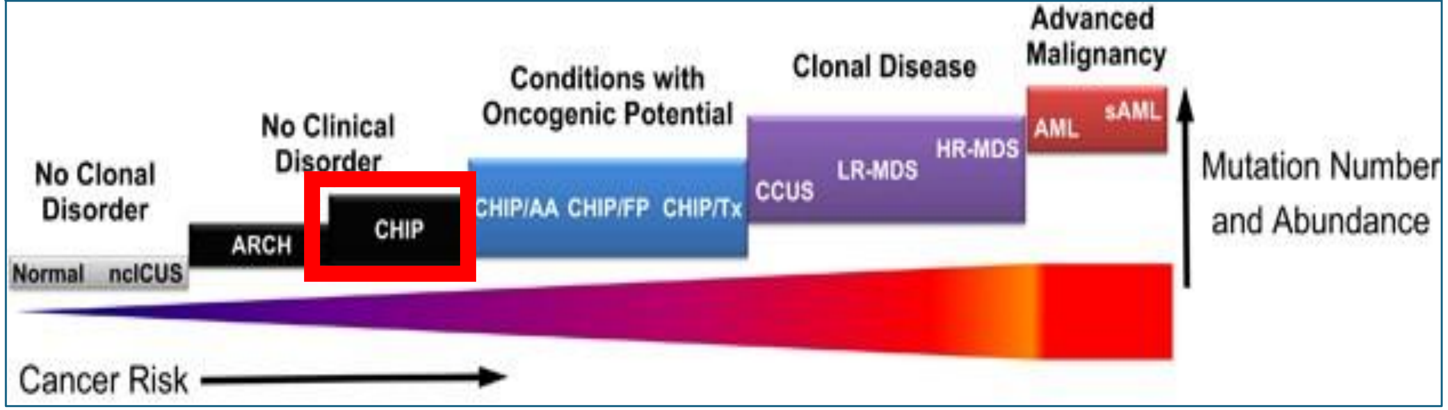
Clinical implications of CHIP



Increased risk of

- hematologic neoplasms (absolute risk of 0.5-1% per year)

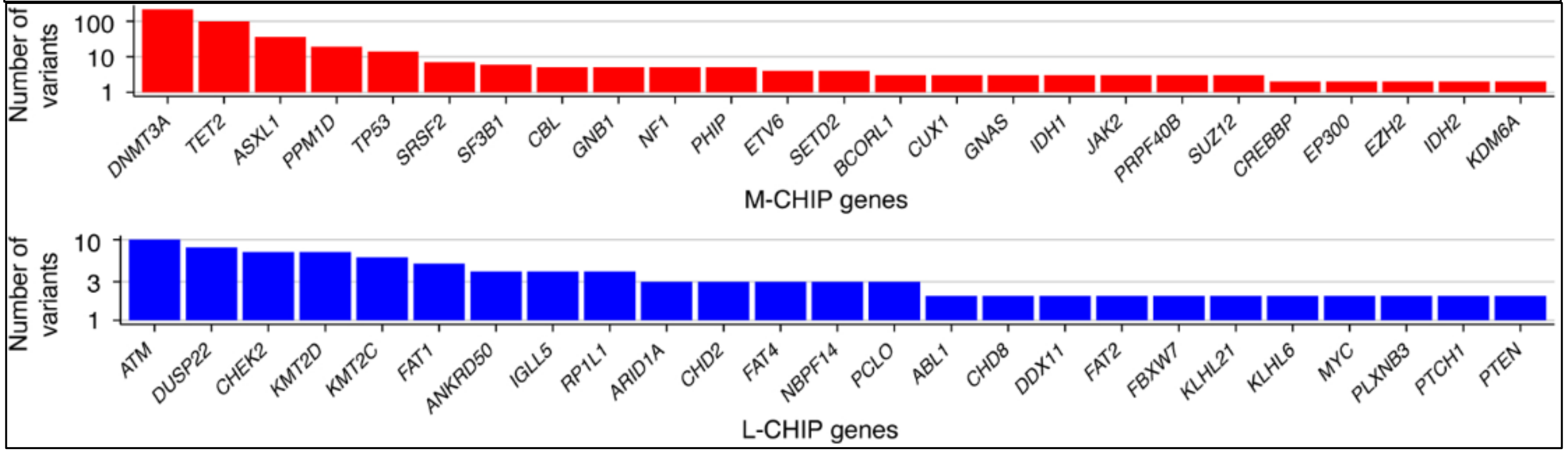
VARIATION OF RISK ASSOCIATED WITH CLONAL HEMATOPOIESIS IN DIFFERENT CLINICAL CONTEXTS

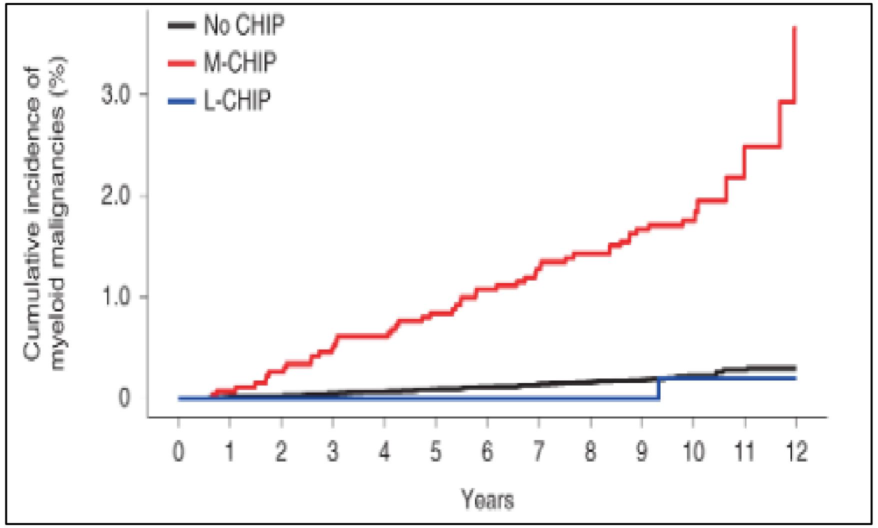


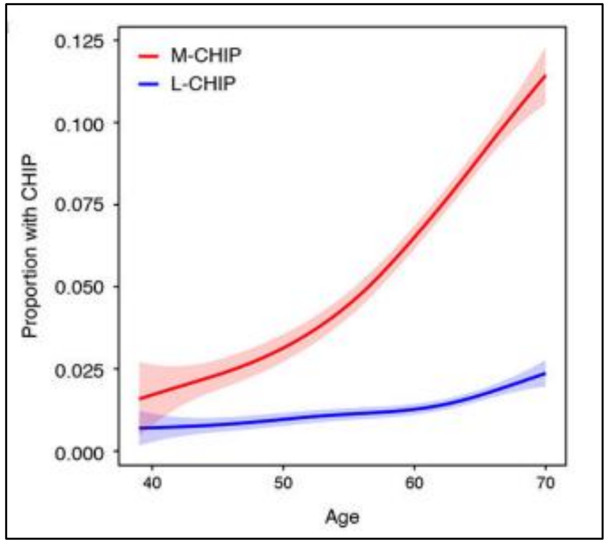
Bejar R, Leukemia, 2017. Guo, Meiqi Curr Opiin Hemato, 2025.

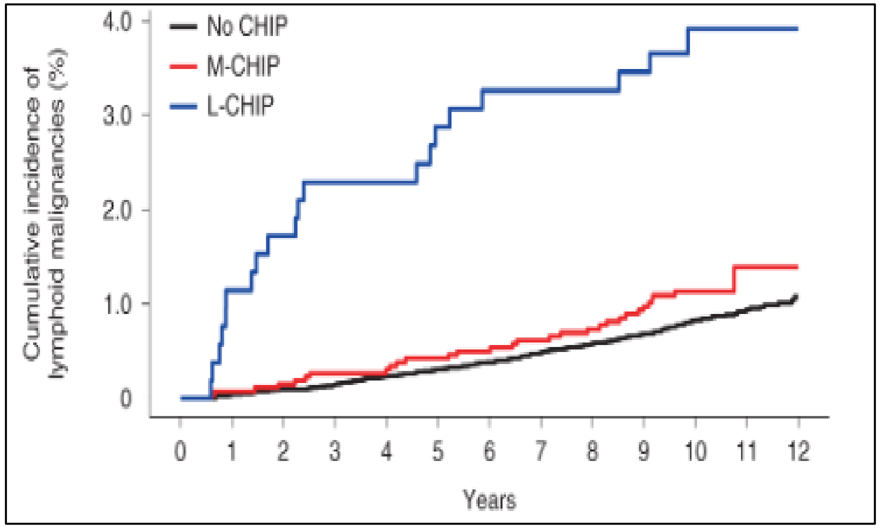
CHIP

Top 25 myeloid and lymphoid driver genes mutated in MGBB cohort



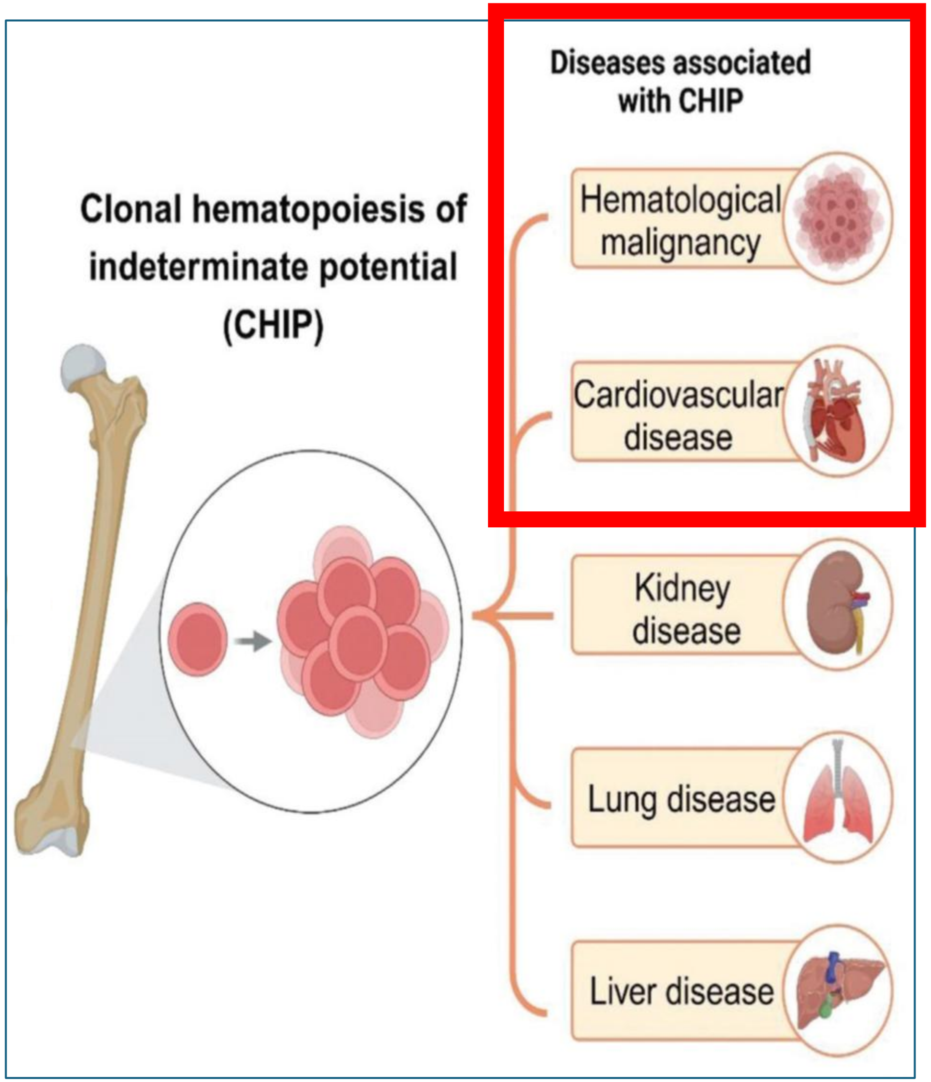






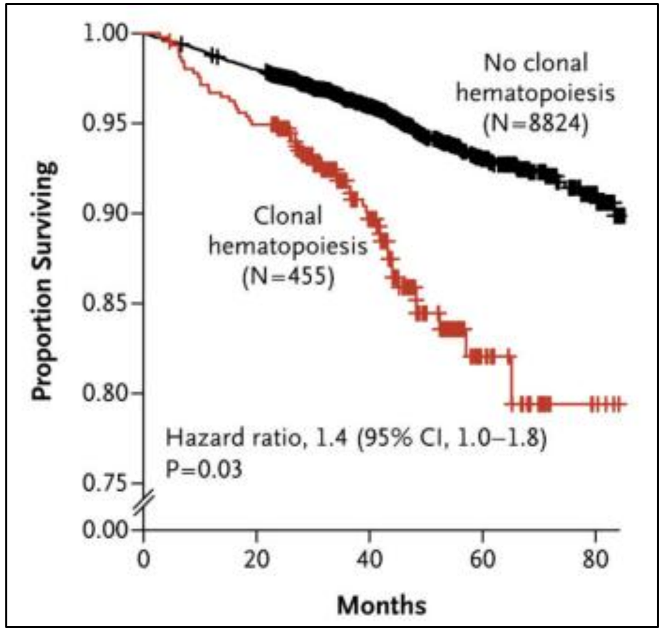
Genovese G., NEJM 2014; Niroula A., Nat. Med. 2021

Clinical implications of CHIP



Increased risk of

- hematologic neoplasms (absolute risk of 0.5-1% per year)
- cardiovascular disease (acute myocardial infarction, ischemic stroke)



Guo, Meiqi. Curr Opin Hemato, 2025.

Precursor hematologic conditions

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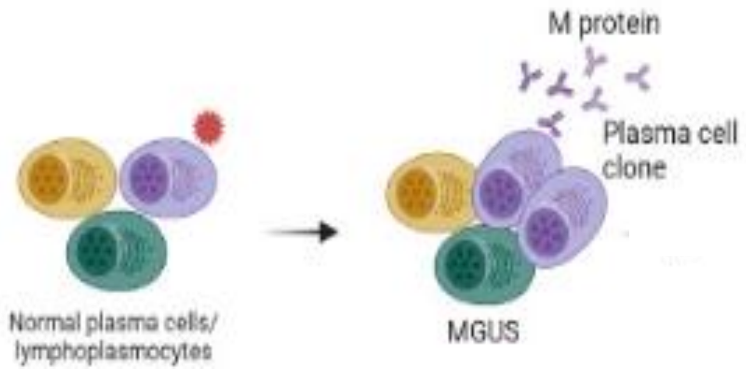
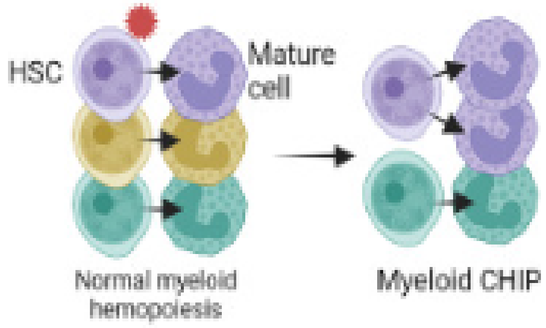
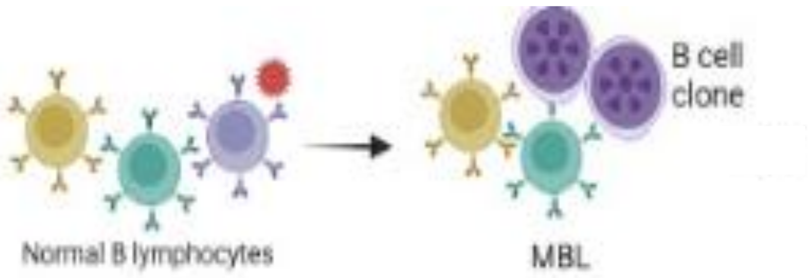


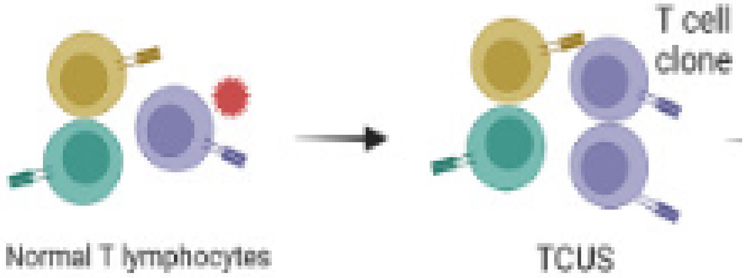
MGUS: monoclonal gammopathy of undetermined significance



CHIP: clonal hematopoiesis of indeterminate potential



MBL: monoclonal B-cell lymphocytosis



TCUS: T-cell clones of uncertain significance

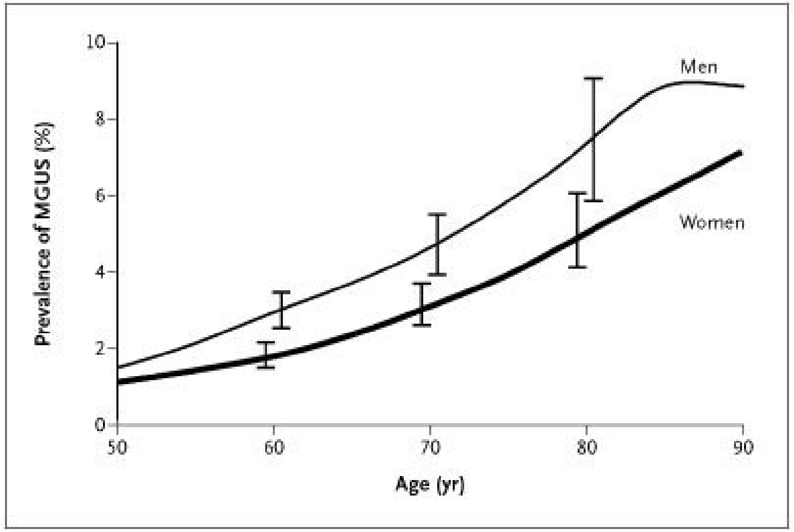
Definition of MGUS

- Serum monoclonal protein (M protein) of <3 g/dL
- Clonal bone marrow plasma cells <10%
- Absence of CRAB symptoms
  - ✓ hypercalcemia
  - ✓ renal insufficiency
  - ✓ anemia
  - ✓ bone lesions

- 3 clinical subtypes
  - ✓ IgM MGUS
  - ✓ non-IgM MGUS
  - ✓ (light chain) LC-MGUS

Based on heavy chain:
70% IgG, 15% IgM, 12% IgA, 3% biclonal

Prevalence of MGUS



- 3% of general population >50y
- 1,7% in 50-59y
- >5% in over 70y
- M>F

Serum protein electrophoresis, and confirmation by immunofixation if any abnormality detected	3.5%
Serum protein electrophoresis plus serum-free light-chain assay	4.2%
Serum immunofixation plus serum-free light-chain assay	4.4%
miRAMM plus serum-free light-chain assay	5.1%[a]

miRAMM monoclonal immunoglobulin rapid accurate mass measurement
[a]This estimate represents the lower limit of the estimated prevalence of MGUS

Kyle RA. et al. N Engl J Med 2006; Murray D Blood Cancer 2019

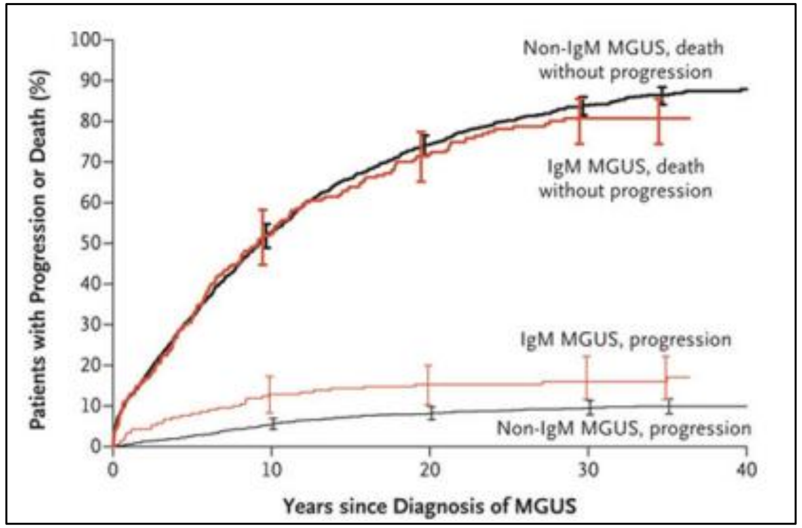
UZ LEUVEN

Clinical impact of MGUS

Risk of malignant progression

- MGUS: +/-1% risk of progression
- subtypes of MGUS have different progression phenotypes

Type of MGUS	Type of progression	Risk of progression
Non-IgM MGUS	Multiple myeloma Solitary bone or extramedullary plasmocytoma	1% per year
IgM MGUS	Waldenström macroglobinemia	1.5% per year
LC-MGUS	Light chain multiple myeloma Solitary bone or extramedullary plasmocytoma	0.3% per year

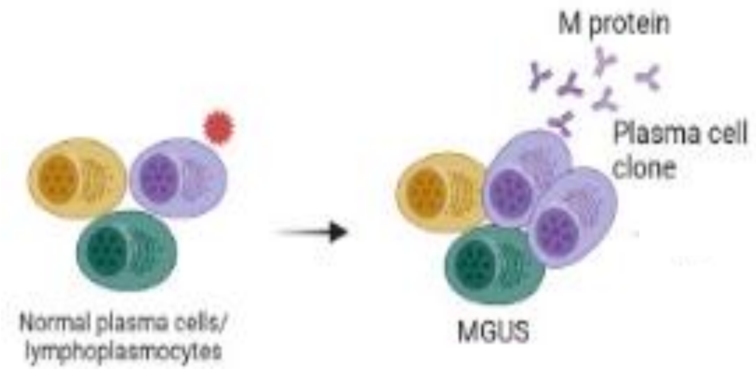


- risk of progression of MGUS to myeloma or related disorder over a lifetime is only 10%
- 90% NEVER progress until death

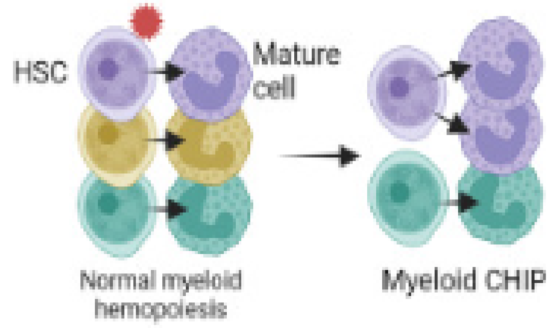
Landgren O. Blood 2009. Rajkumar SV. NEJM, 2025. Kyle RA, NEJM, 2018

Precursor hematologic conditions

- **Asymptomatic clonal expansion** of either plasmacells, **lymphoid** or myeloid cells



MGUS: monoclonal gammopathy of undetermined significance



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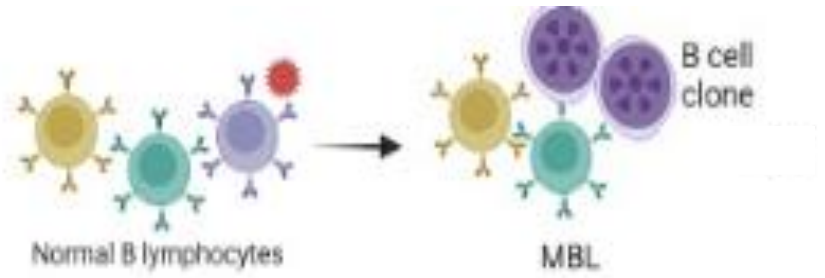
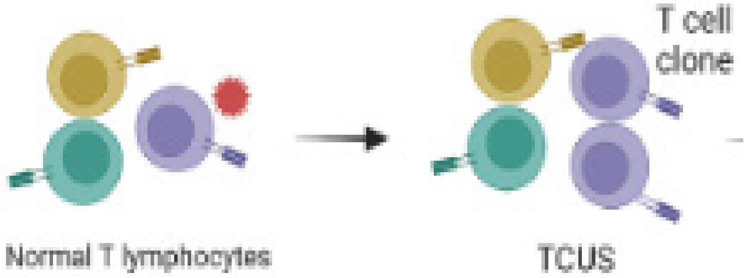


MBL: monoclonal B-cell lymphocytosis

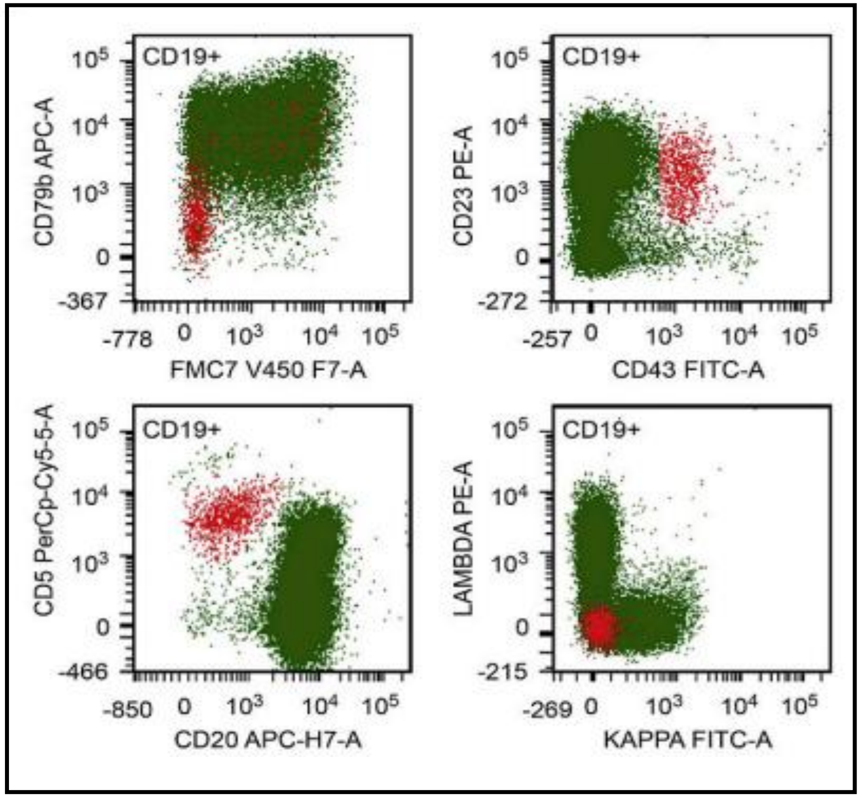


TCUS: T-cell clones of uncertain significance

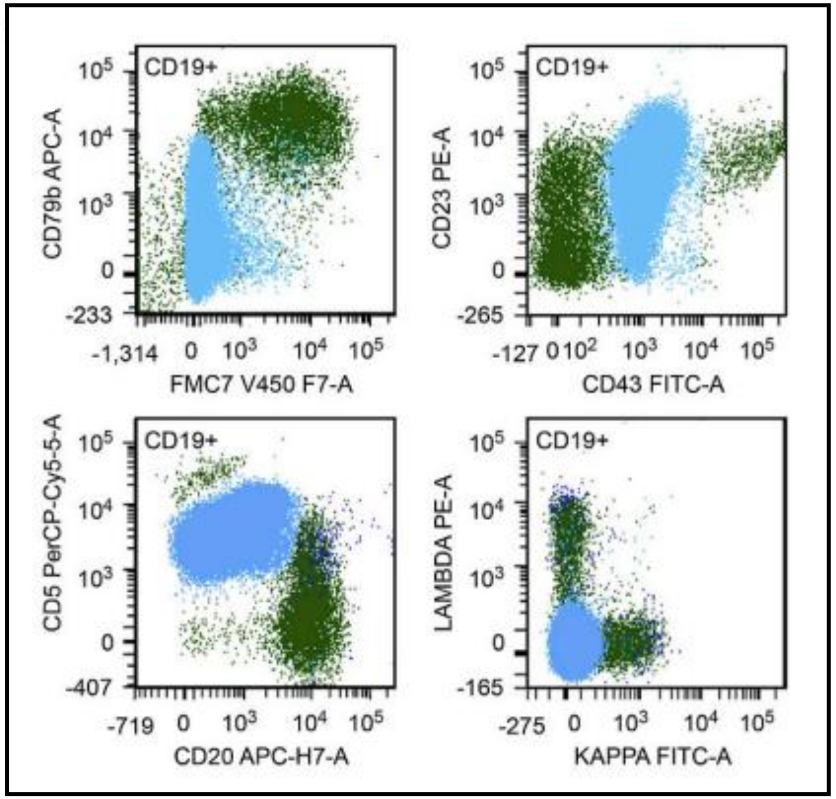
Diagnosis of MBL

Classification of MBL ⇒ immunophenotype

⇒ clone size



0.4% of total lympho, abs. abn. B-cells 0.08 × 10^9/L



88% of total lympho, abs. abn. B-cells 4.44 × 10^9/L

Definition and classification of MBL

Classification of MBL ⇒ immunophenotype

⇒ clone size

WHO 2022

- Low-count MBL
  - clone size <0.5×10^9/L
  - CLL/SLL-like phenotype (CD5+, CD20dim)
- CLL/SLL-type MBL
  - clonal B-cell count 0.5-5 ×10^9/L
  - CLL/SLL-like phenotype
- Non-CLL/SLL-type MBL
  - clonal B-cell expansion without typical CLL/SLL phenotype (CD20+, CD5-)
  - often markers associated with MZL

ICC 2022 (cfr WHO 2018)

- CLL-type MBL
  - low count
  - high count
- Non-CLL type MBL
- Atypical CLL-type MBL (CD5-)

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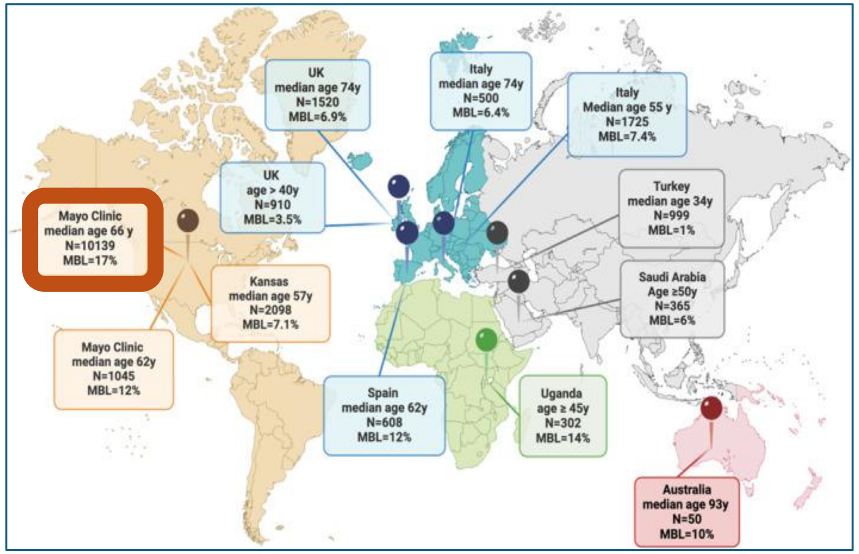
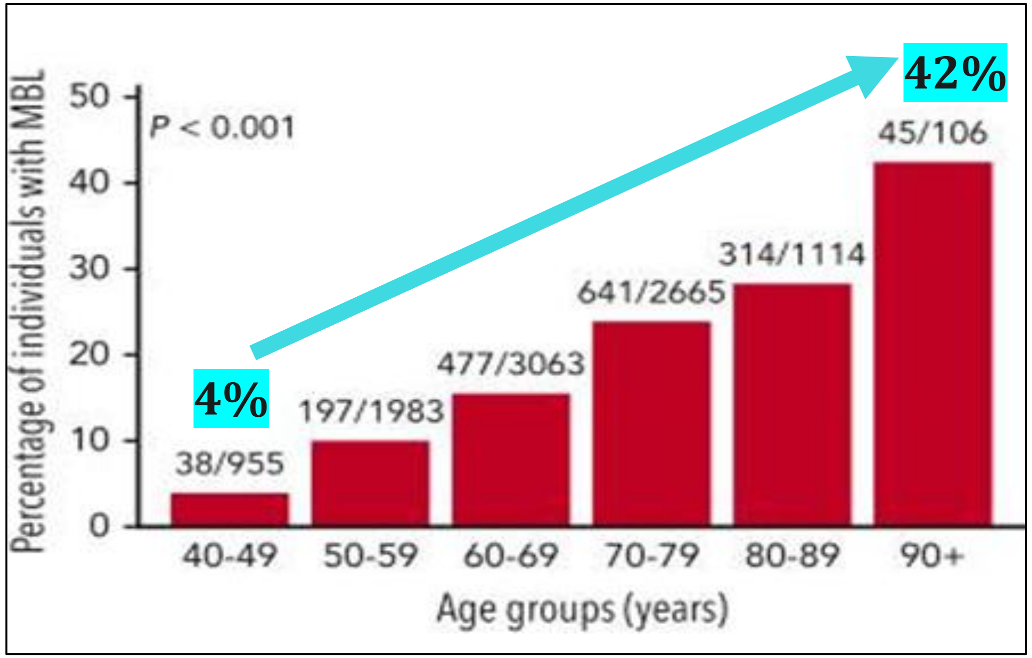
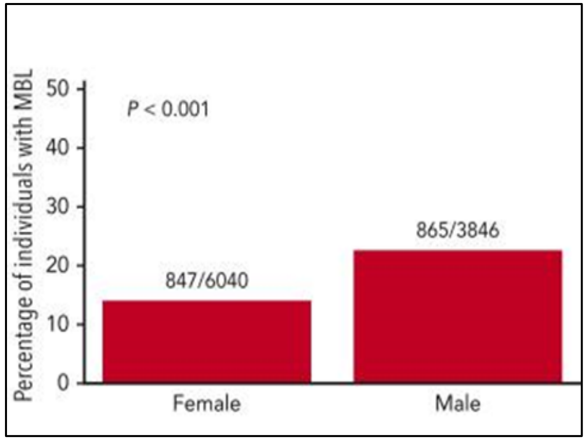
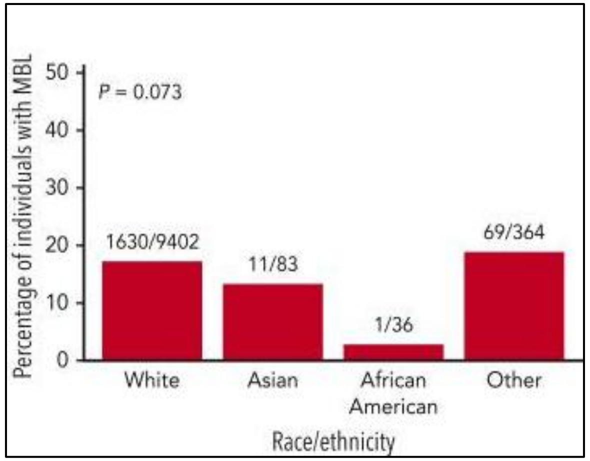
Prevalence of MBL



Remark: differences in size, age, assay sensitivity

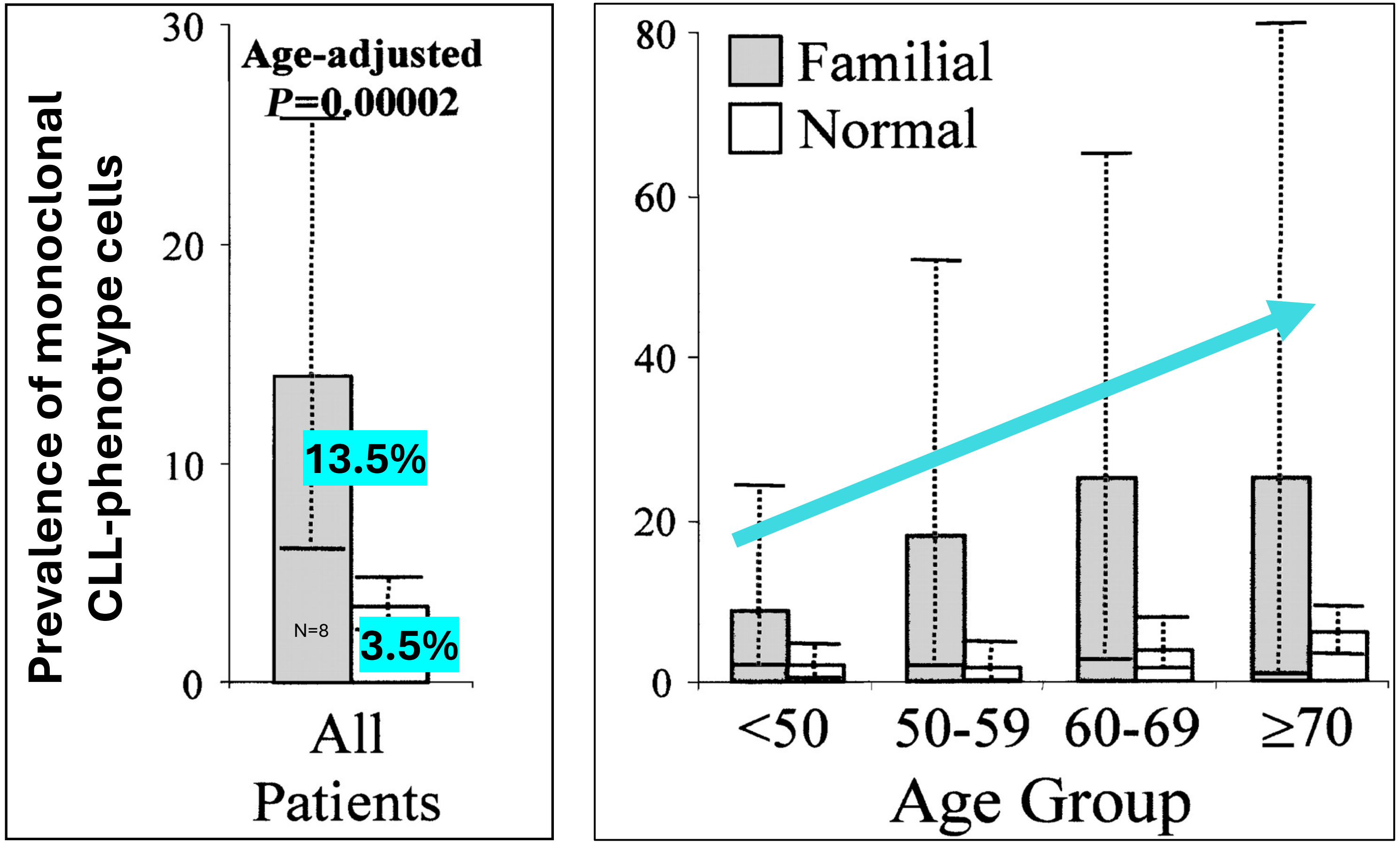






Slager SL, et al. Blood 2022, Serafin A, et al. Hem Onc 2025

Prevalence of MBL



Familial aggregation of MBL and CLL

Higher prevalence of MBL in first degree relatives of CLL patients / families

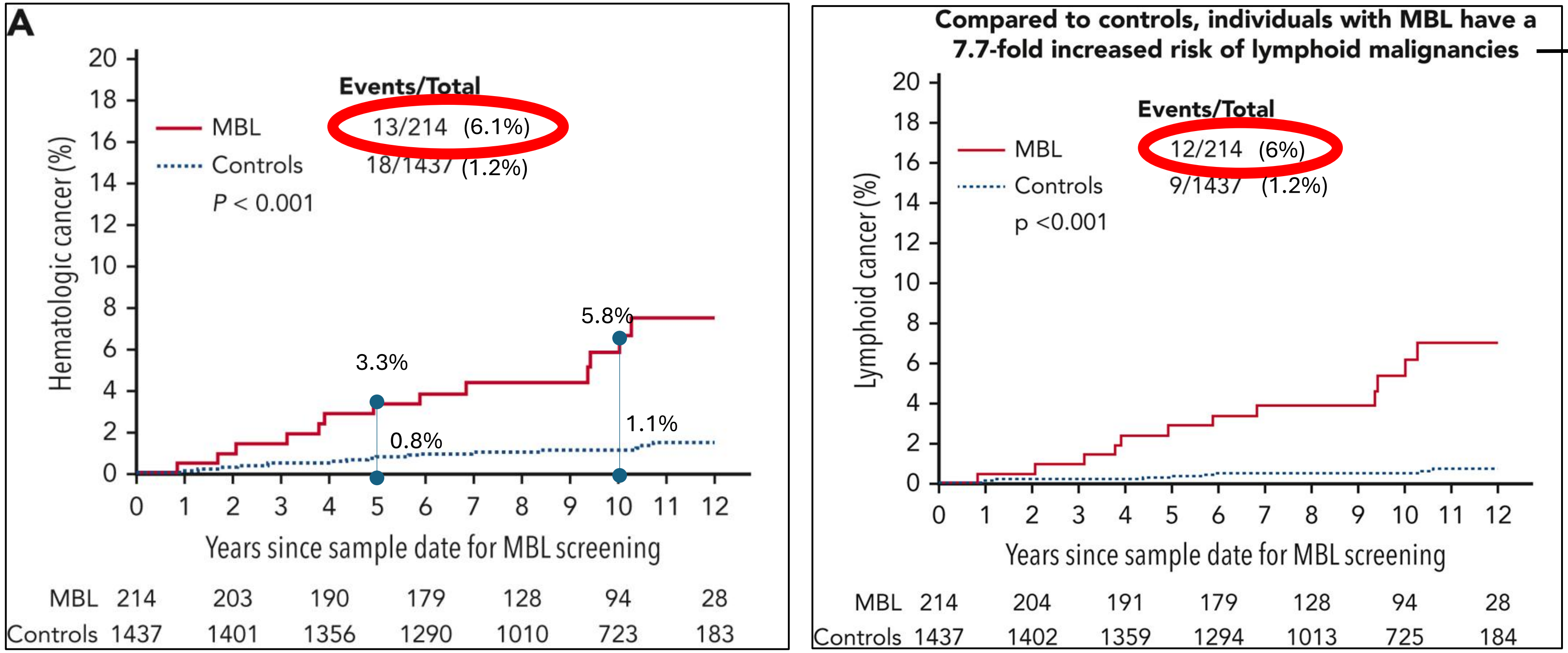
healthy controls (n=910)
59 healthy first-degree relatives of CLL patients

Rawstron AC , et al. Blood 2002

Clinical implications of MBL

Risk of progression to a hematological malignancy

Progression of MBL: a screening study of 10 139 individuals



→ Including CLL, DLBCL, MCL, MZL, ...

Risk in HC-MBL >> LC-MBL

(74 fold increased risk *versus* 4.3 fold)

Slager SL. Blood, 2022

Clinical implications of MBL

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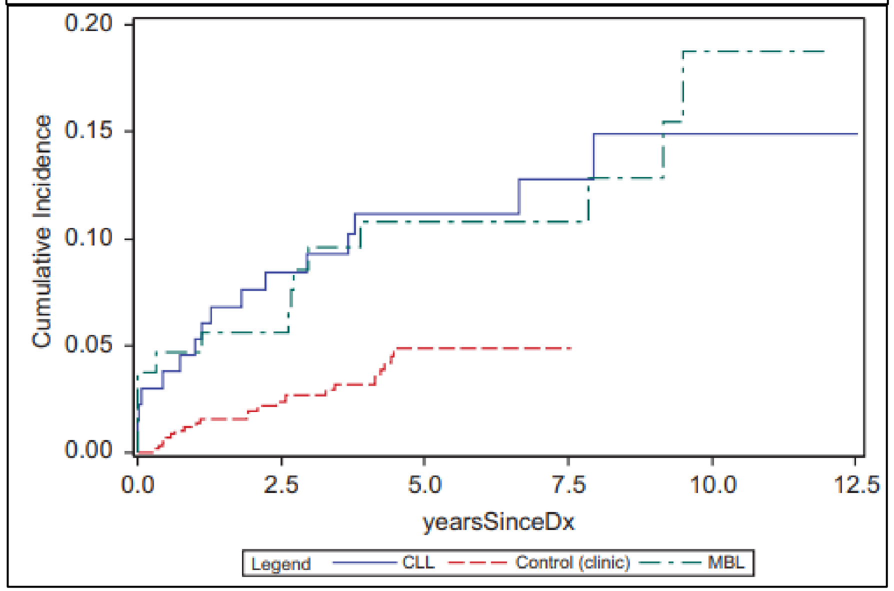
Risk of second neoplasia

Time from diagnosis to non-hematologic cancer

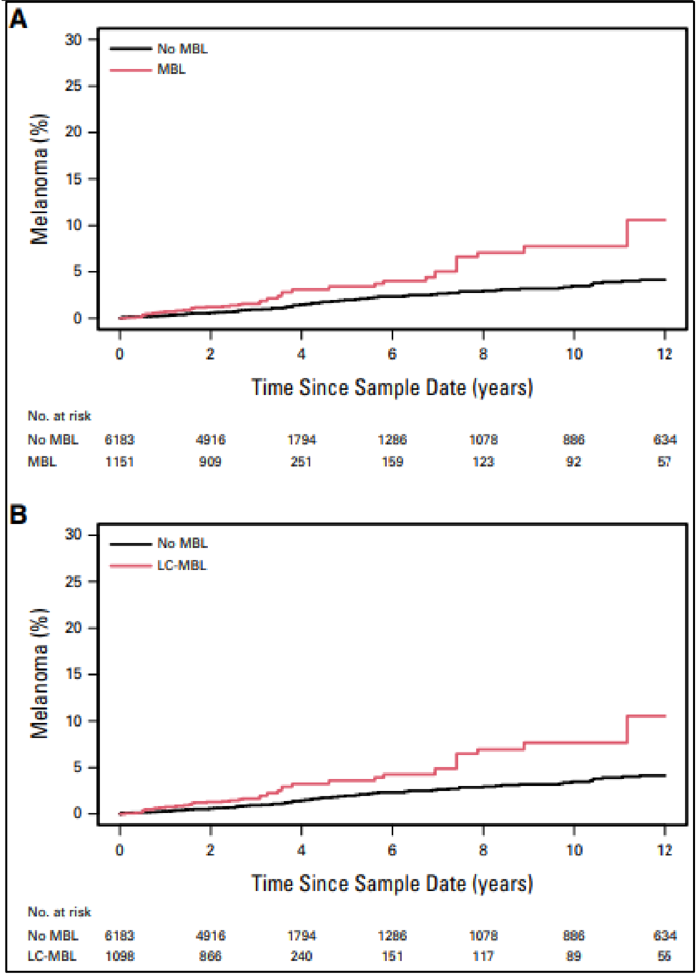


MBL associated with increased risk of solid tumors and skin cancers

Non-hematologic cancer in individuals with CLL and HC-MBL compared with controls

Cancer	*CLL, n = 132* n *(%)*	*MBL, n = 107* n *(%)*	*Flow controls, n = 482* *n (%)*	*P-value*
Any cancer	16 (12)[a]	14 (13)[b]	18 (4)[c]	< 0.0001
Breast	0/44 (0)	3/43 (7)	3/298 (1)	0.01
Lung	4 (3)	4 (4)	1 (0.2)	0.002
Gastrointestinal	5 (4)	2 (2)	4 (1)	0.046
Pancreas	0 (0)	0 (0)	0 (0)	
Colorectal	4 (3)	1 (1)	2 (0.4)	
Liver	1 (1)	1 (1)	2 (0.4)	
Stomach	0 (0)	0 (0)	0 (0)	
Esophagus	0 (0)	0 (0)	0 (0)	
Genitourinary	2 (2)	1 (1)	3 (1)	0.60
Bladder	1 (1)	0 (0)	3 (1)	
Kidney	1 (1)	1 (1)	0 (0)	
Ureter	0 (0)	0 (0)	0 (0)	
Prostate	2/88 (2)	3/64 (5)	3/184 (2)	0.38
Gynecologic	1/44 (2)	1/43 (2)	0/298 (0)	0.03
Endometrial	1/44 (2)	1/43 (2)	0/298 (0)	
Ovarian	0/44 (0)	0/43 (0)	0/298 (0)	
Peritoneum	0/44 (0)	0/43 (0)	0/298 (0)	
Nervous system	1 (1)	2 (2)	1 (0.2)	0.11
Brain	0 (0)	1 (1)	1 (0.2)	
Peripheral nerve (acoustic)	1 (1)	0 (0)	0 (0)	
Meningioma	0 (0)	1 (1)	0 (0)	
Head and neck	1 (1)	0 (0)	1 (0.2)	0.48
Tongue	1 (1)	0 (0)	0 (0)	
Tonsil	0 (0)	0 (0)	0 (0)	
Neck	0 (0)	0 (0)	1 (0.2)	
Melanoma	3 (2)	1 (1)	2 (0.4)	0.11
Thyroid	0 (0)	1 (1)	0 (0)	0.06

Cumulative incidence for melanoma in MBL

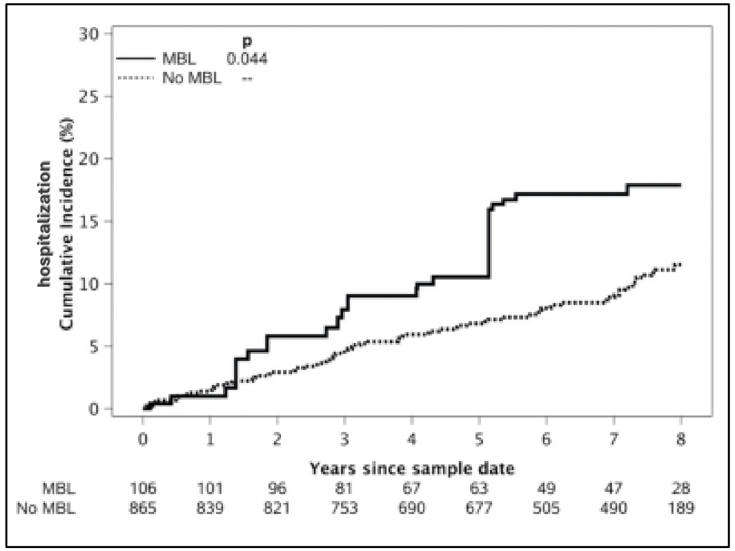


Solomon BM, et al. Leukemia 2016; Vallejo BA, et al. J.Clin Onc 2024

Clinical implications of MBL

Risk of serious infection

	All participants (*n* = 971)	CLL phenotype MBL (*n* = 106)	No MBL (*n* = 865)	Unadjusted *p* value
Other[d]	47	7	40	
8-year cumulative incidence estimate (95% confidence interval)				
All Sites		23% (13–32%)	11% (9–13%)	<0.001
Specific Sites				
Pneumonia		9% (4–18%)	2% (2–4%)	0.002
Blood stream		9% (4–18%)	2% (1–4%)	0.002
UTI		7% (3–16%)	3% (2–5%)	0.10
Cellulitis		2% (1–8%)	3% (2–5%)	0.79



Shanafelt et al. Leukemia. 2021

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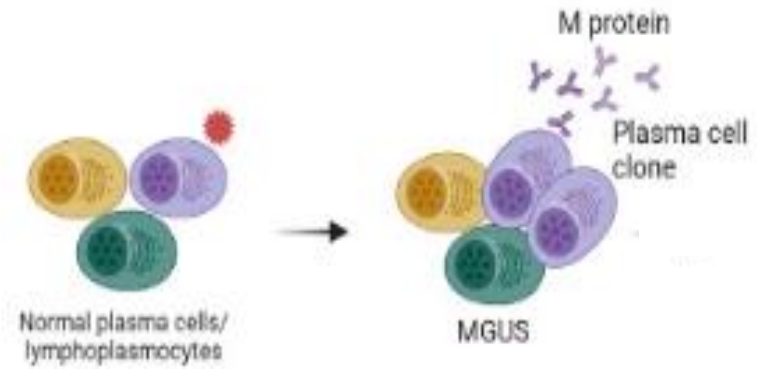
- **Asymptomatic clonal expansion** of either plasmacells, **lymphoid** or myeloid cells



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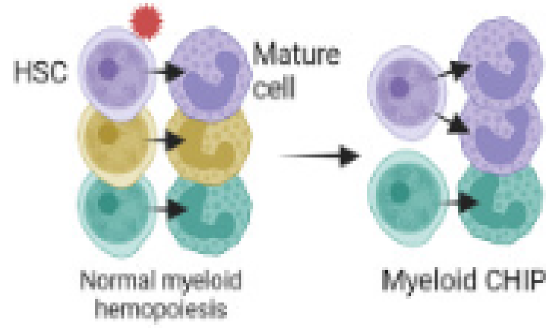

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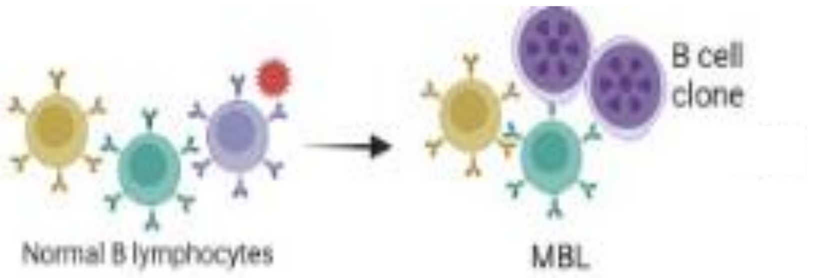

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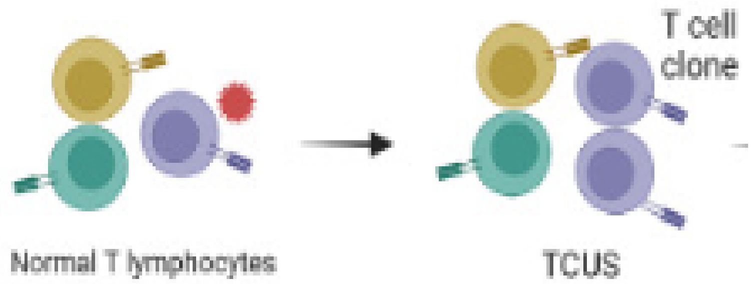

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Definition T-CUS

- Presence of persistent circulating **monoclonal** T-cells in blood, in otherwise **healthy subjects**, ie. in the **absence** of data of **T-cell malignancy**

Shi M. et al. Mod. Path, 2020

T-CUS: clonality

T-cell clonality assay
PCR-based techniques of TCR gene rearrangements
NGS of TCR gene rearrangements
Flow cytometer analysis of TCRVβ expression[15,16]
Flow evaluation of the constant regions 1 and 2 of the T-cell receptor β chain (TRBC1 and TRBC2)[7,17,18]

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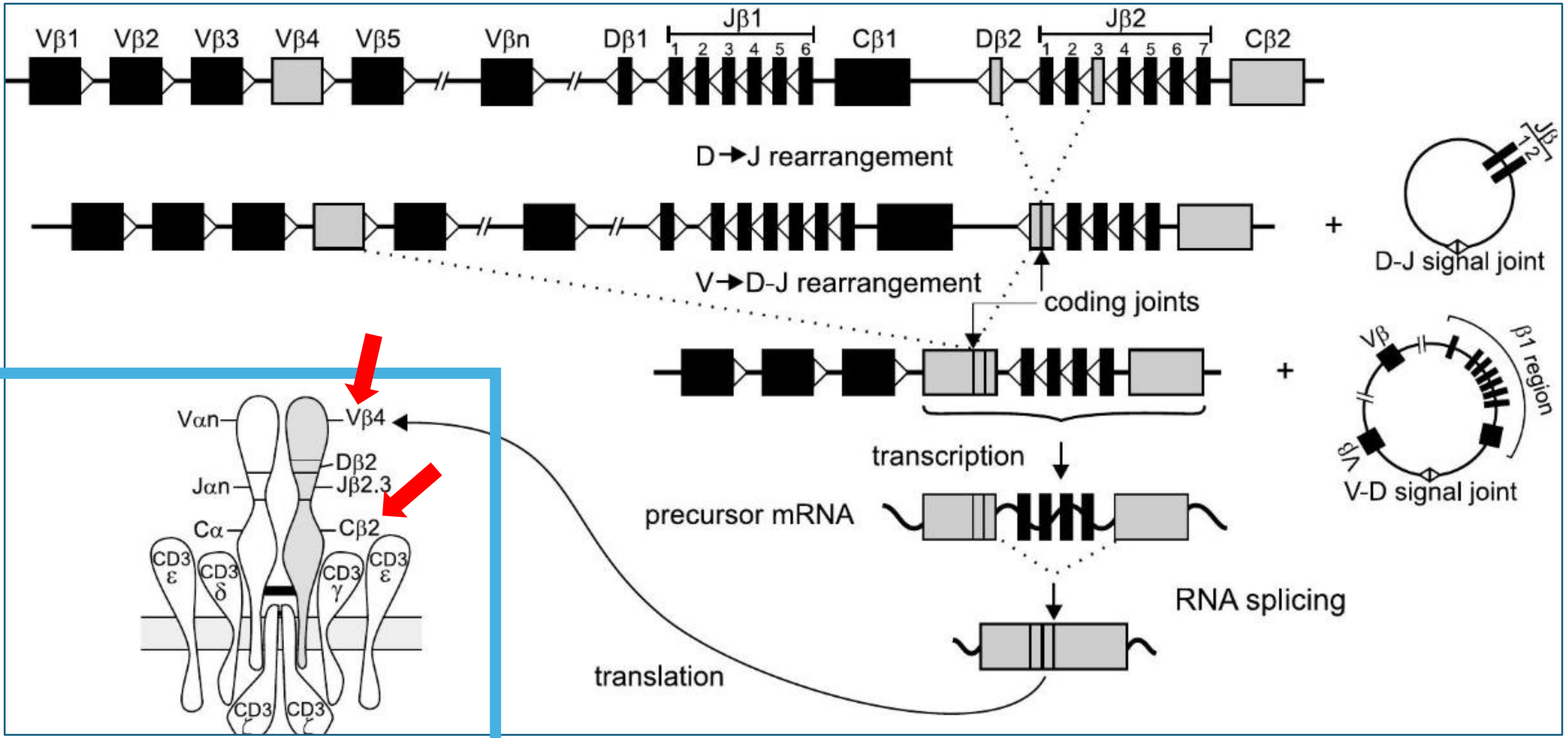

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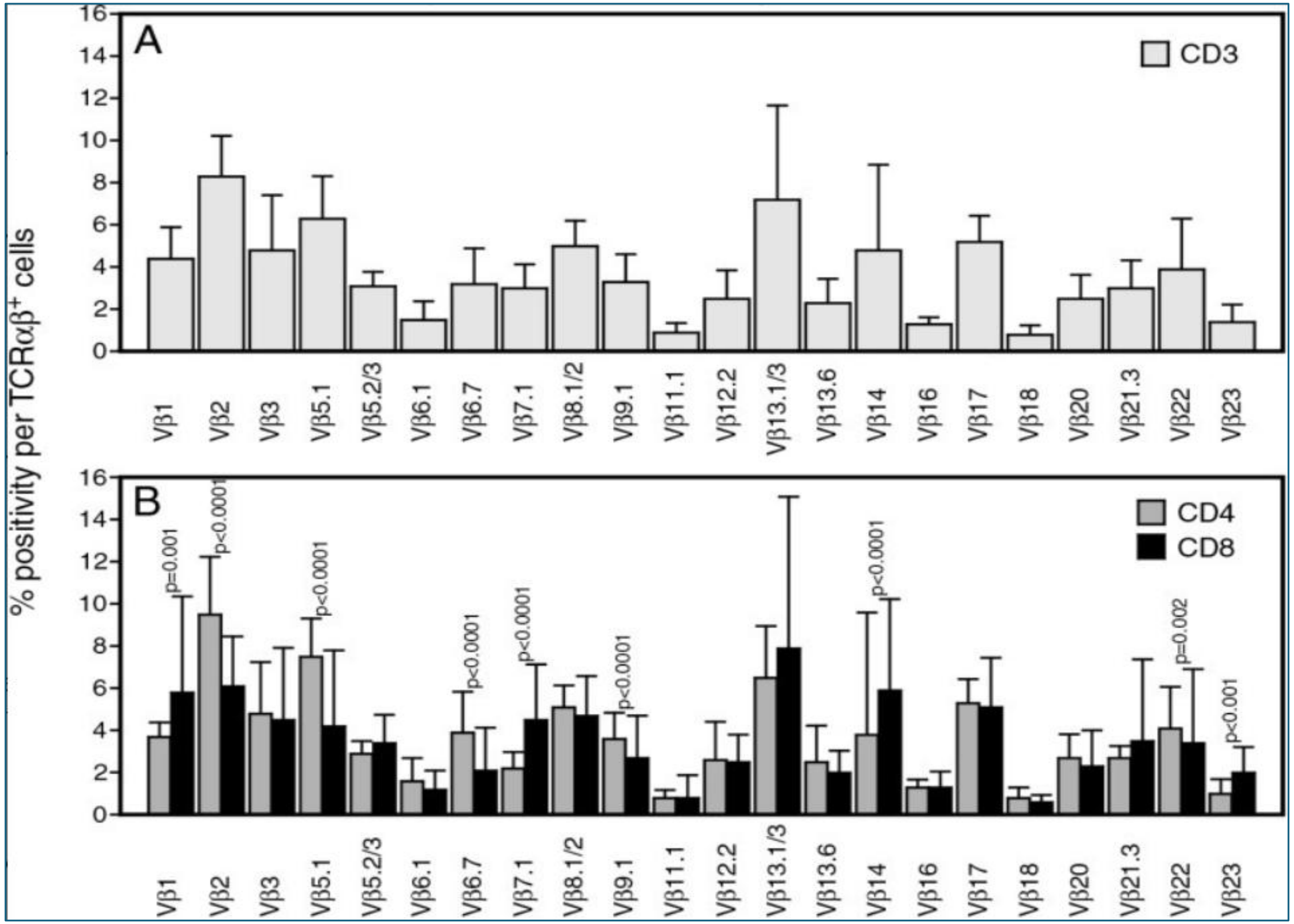

Van der Beemd R, et al; Cytometry A, 2000

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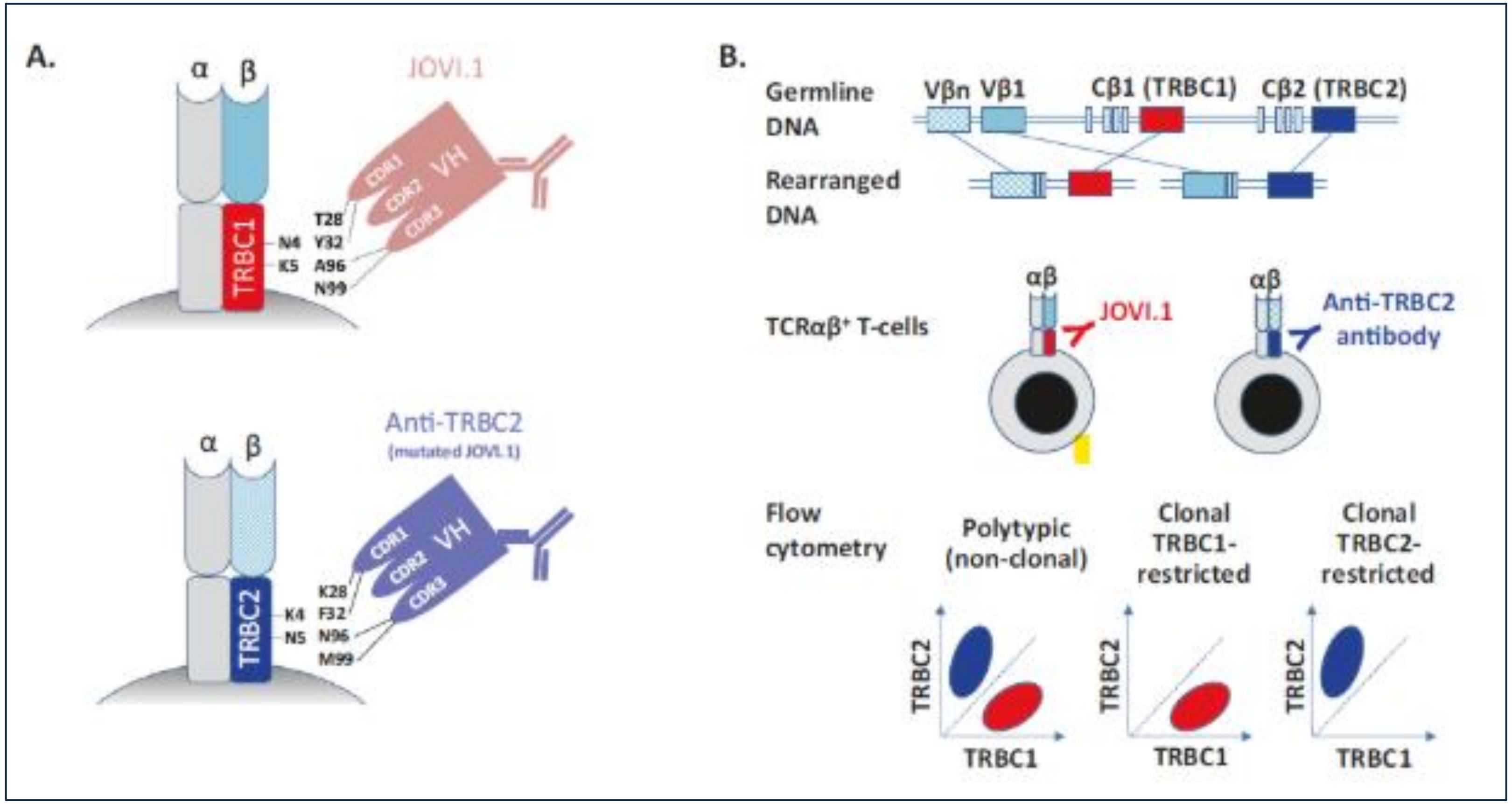

G Semenzo, Haematologica. 2025. P. Horna, Blood Cancer 2024

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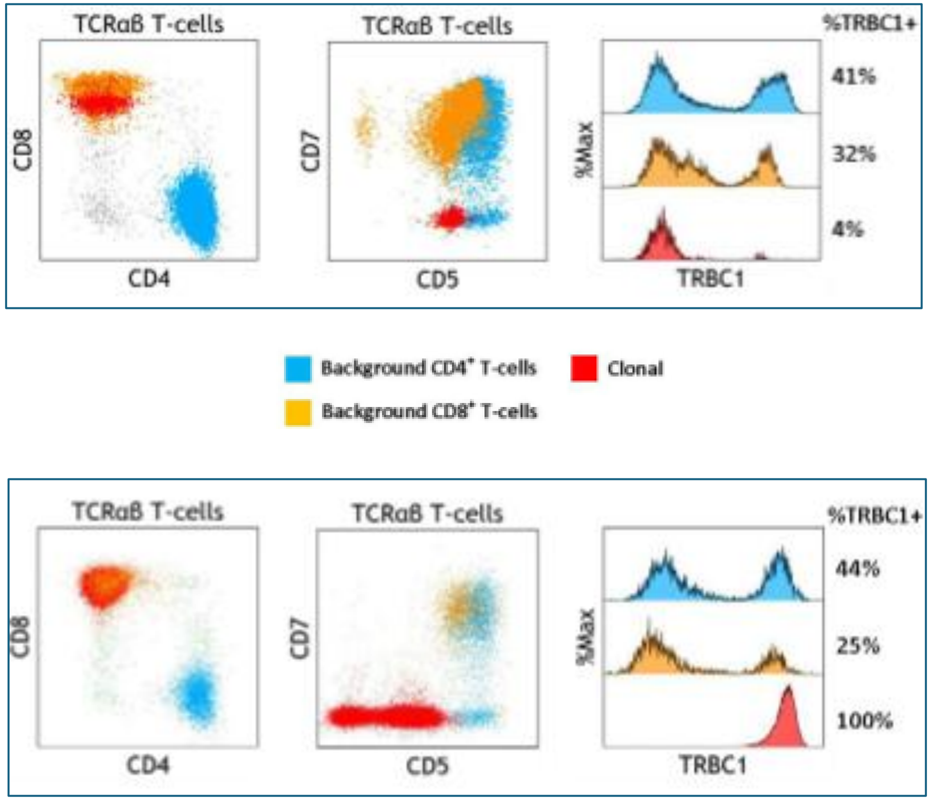

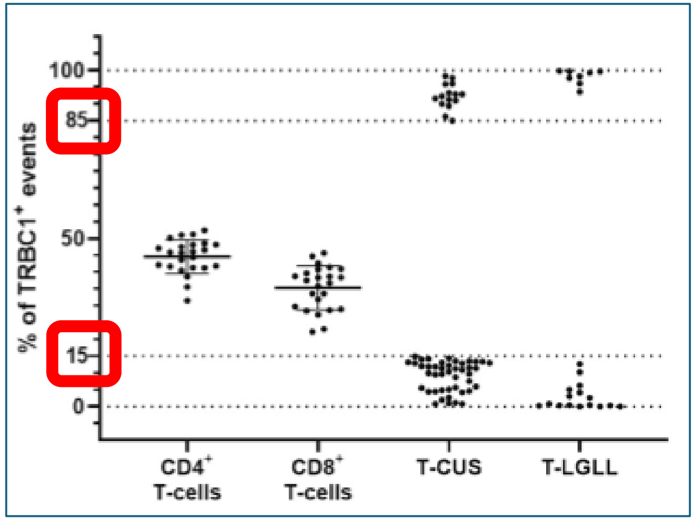

Shi M et al., Mod, Path 2020

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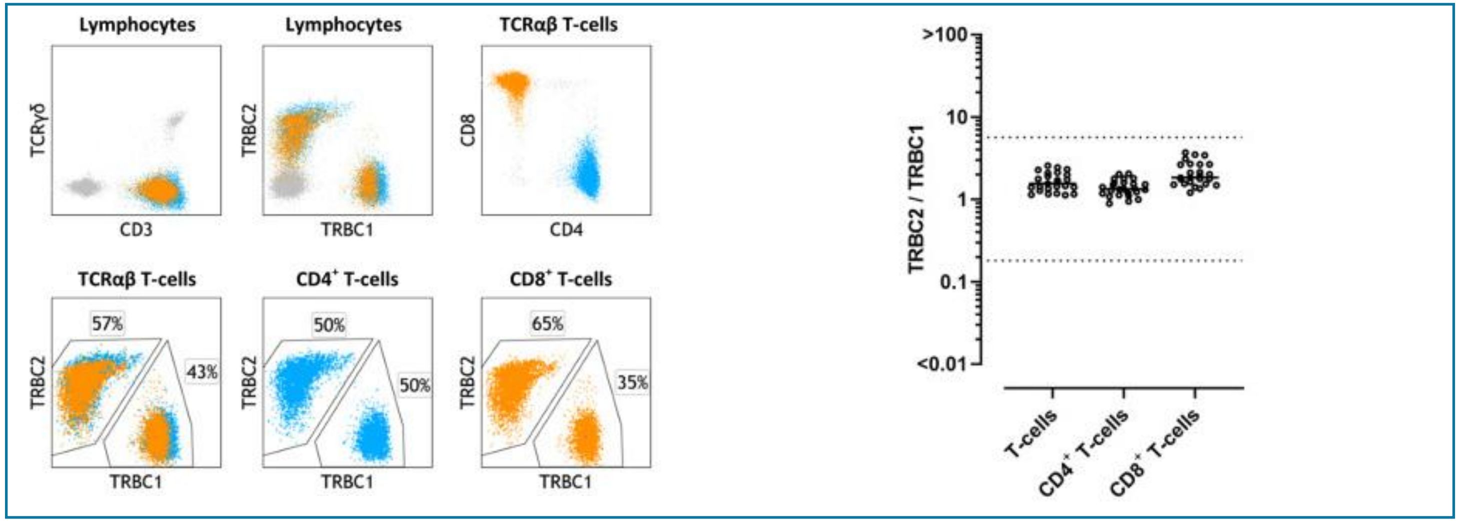

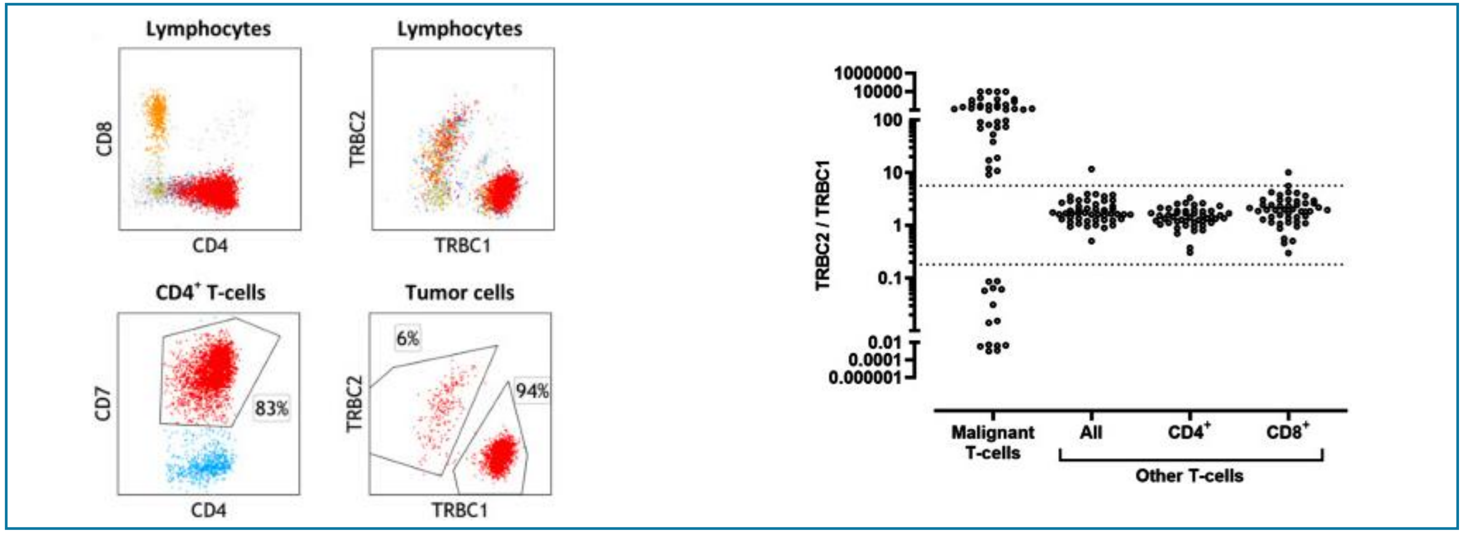

Horna P et al., Blood Canc J. 2024

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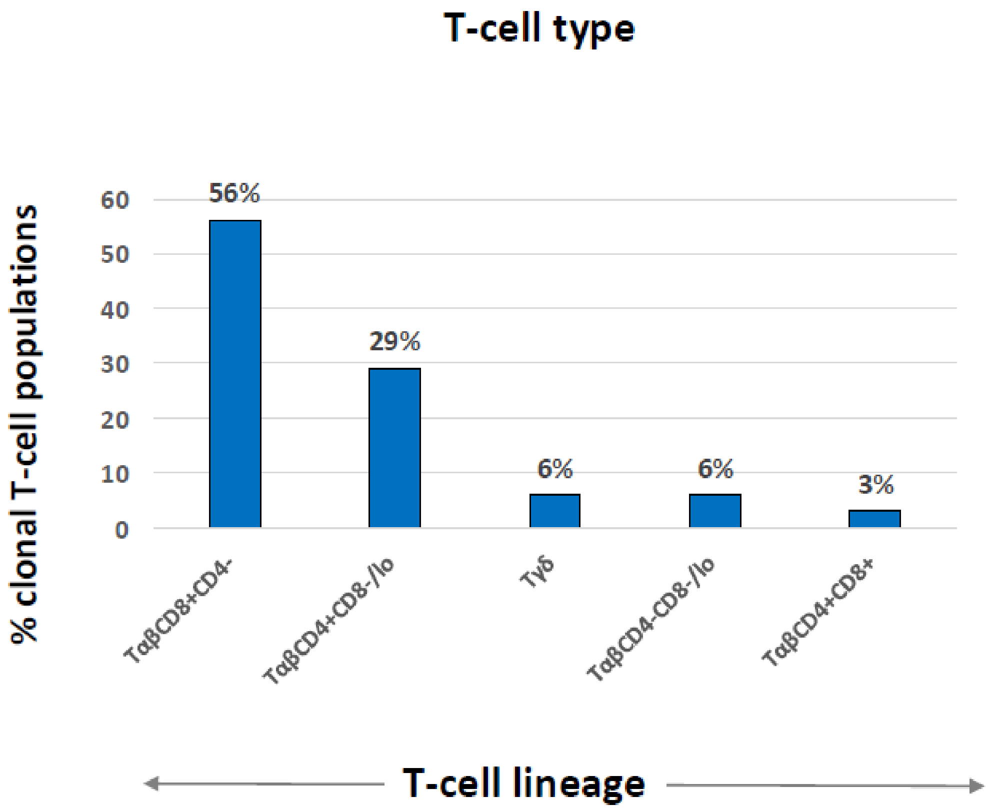
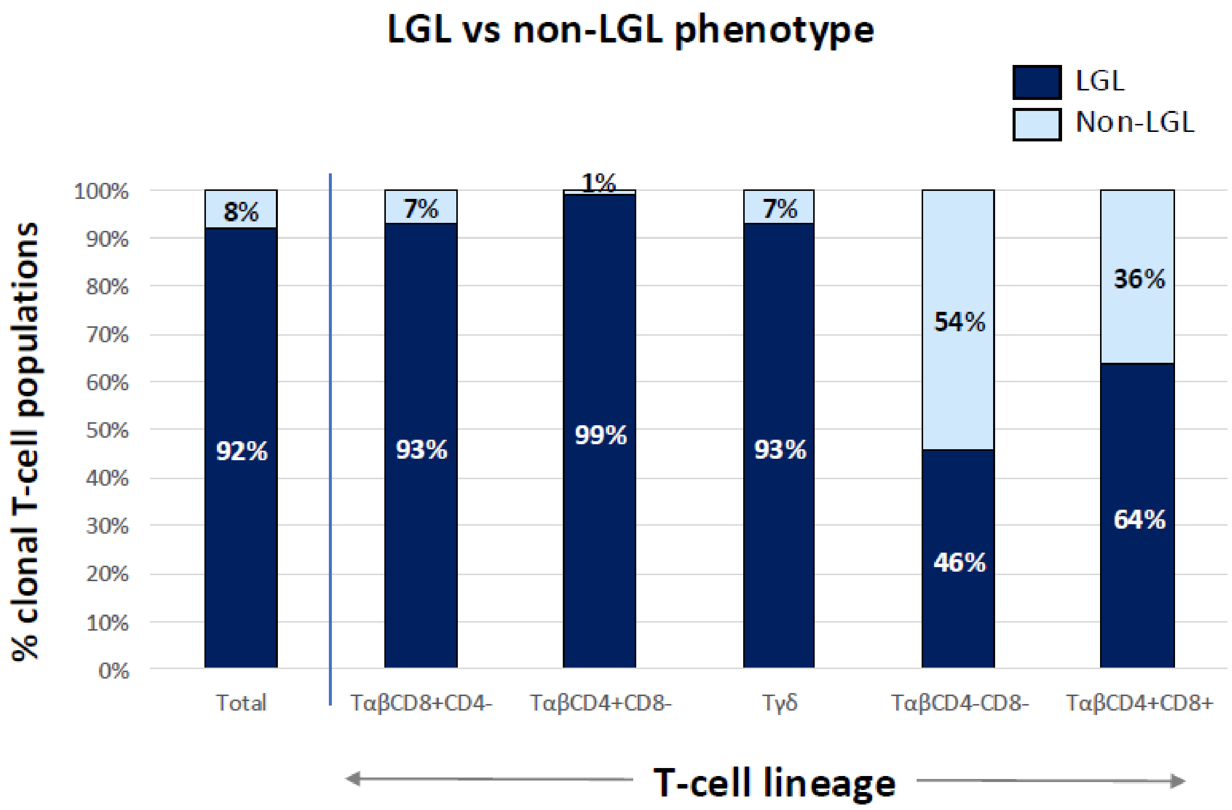
- Presence of **persistent** circulating **monoclonal** T-cells in blood, in otherwise **healthy subjects**, ie. in the **absence** of clonical and biological **data of T-cell malignancy**

- T-CUS exhibit **immunophenotypic features closely resembling those of T-LGLL**

In-depth characterization of clonal T-cell populations in T-CUS cases

Classification of T-cell populations (N=560) from T-CUS (N=339) according to the T-cell type and phenotypic profile (LGL vs. non-LGL)





Analyses restricted to those T-CUS cell populations with mokecular confirmation of T-cell clonality (N=560 populations)

Carretero-Domínguez et al (manuscript in preparation)

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Variables	T-CUS	T-LGLL
Clone size	≤0.5 LGL $x10^9/L$	>0.5 LGL $x10^9/L$
Clinical manifestations	Absent	From mild to aggressive
Associated diseases	Absent	Detectable in a variable proportion of cases
Mutational pattern	Preliminary data indicate lack of somatic mutations	Somatic mutations are detected in approximately >50% of cases
Bone marrow involvement[#]	Absent	Present
Disease subtypes	$CD8^+$ $T\alpha/\beta$, $CD4^+$ $T\alpha/\beta$ and $T\gamma/\delta$. Frequency to be defined	$CD8^+$ $T\alpha/\beta$ (~65%), $CD4^+$ $T\alpha/\beta$ (~25%) and $T\gamma/\delta^-$ (~10%)
Treatment	None	Indications for treatment include severe cytopenias, particularly neutropenia associated with recurrent infections

G Semenzo, Haematologica. 2025; Teramo A. et al IJLH, 2025

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G Semenzo, Haematologica. 2025

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Essential criteria 5^{th} WHO : increase in circulating cytotoxic T-cells (often 2x10e9/L, but may be lower)

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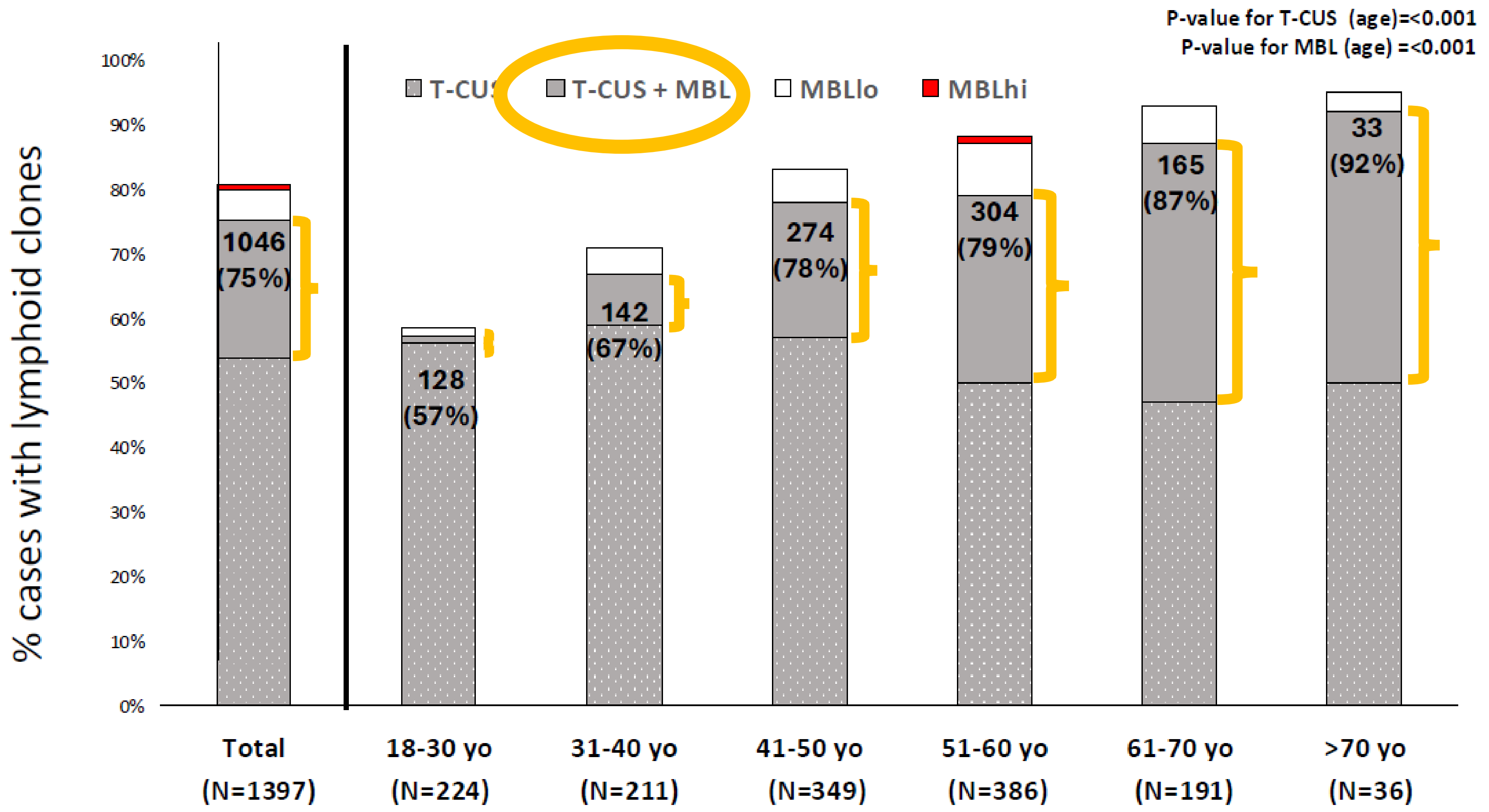
Treatment	None	

desirable criteria 5^{th} WHO : *STAT3* or *STAT5B* mutation

G Semenzo, Haematologica. 2025

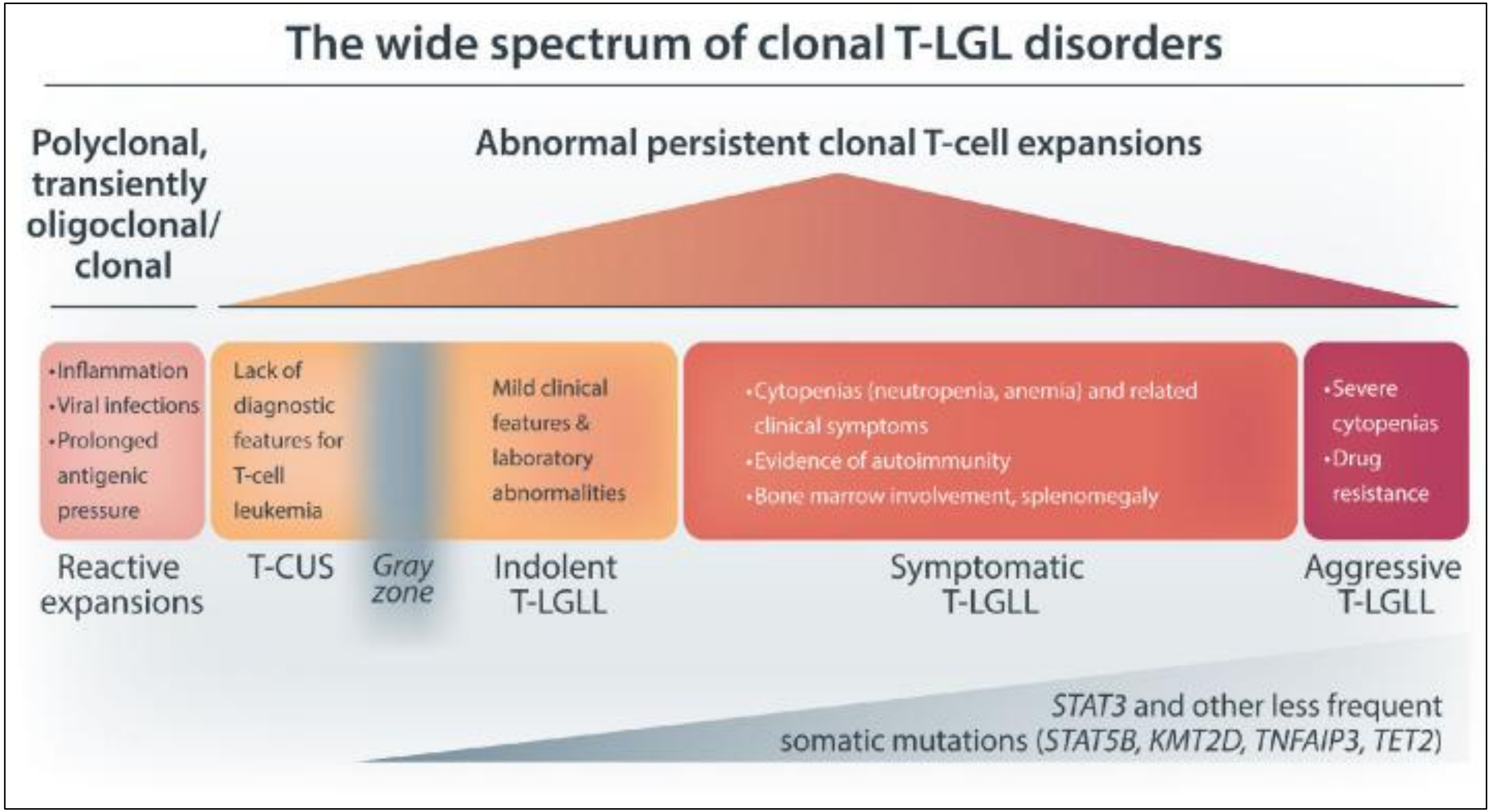
Prevalence of T-CUS in healthy adults (≥18y) healthy donors from the general population by NGF (n= 1397)

T-CUS (N=1046/1397; 75%)



Carretero-Domínguez et al (manuscript in preparation)

Clinical impact of T-CUS



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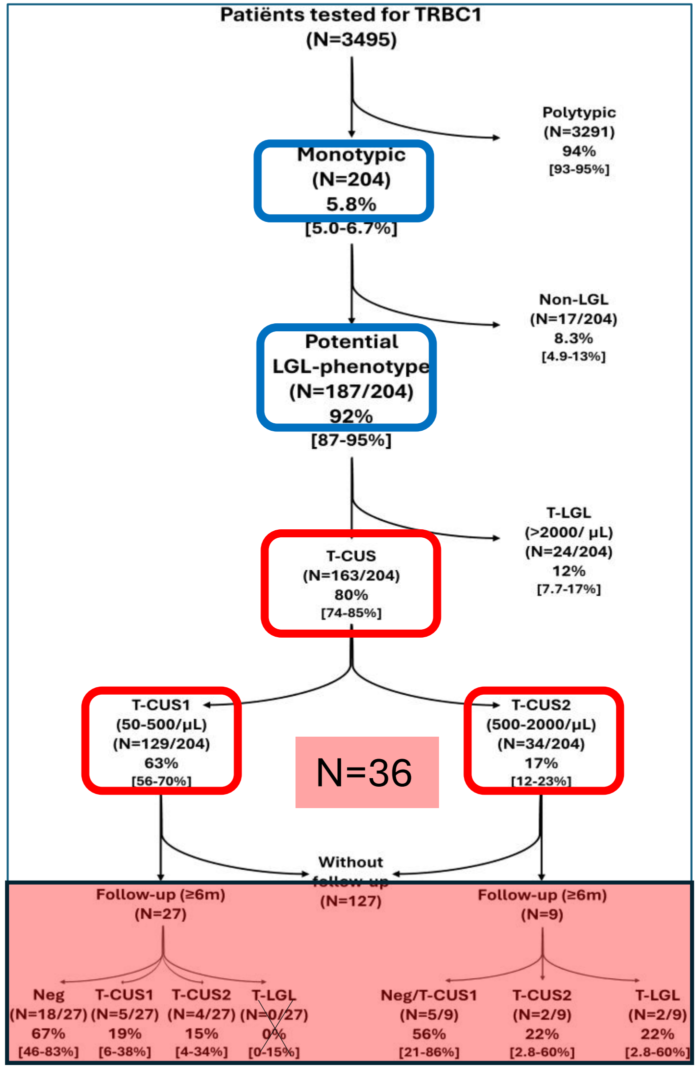

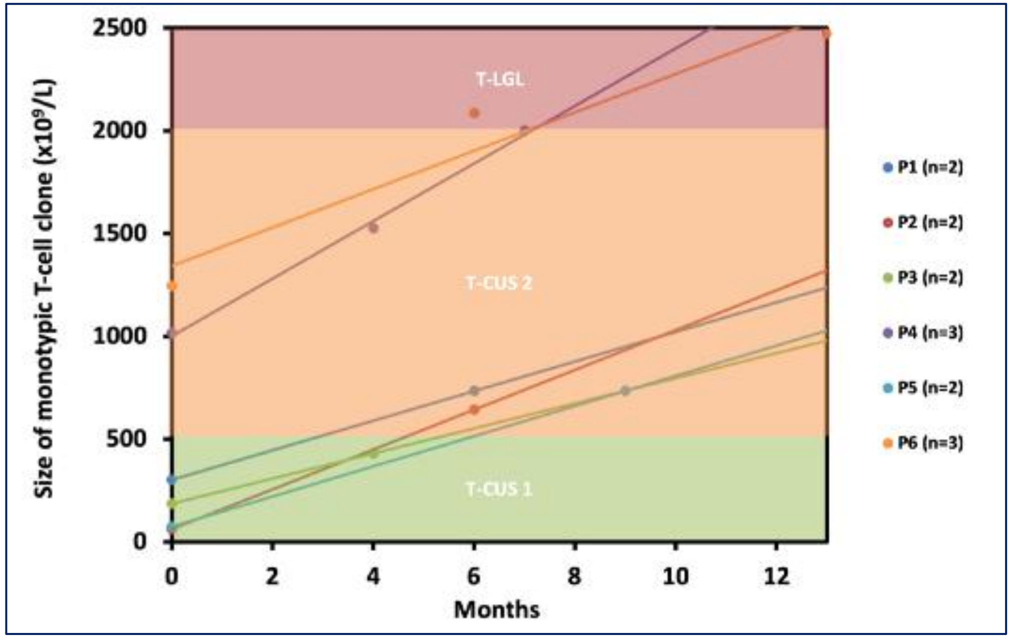

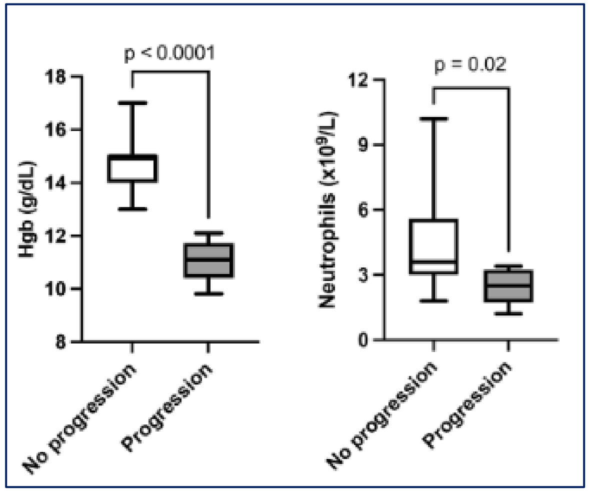


THANK YOU!