Clonal Hematopoiesis and prediction of Progression to a Myeloid Neoplasm

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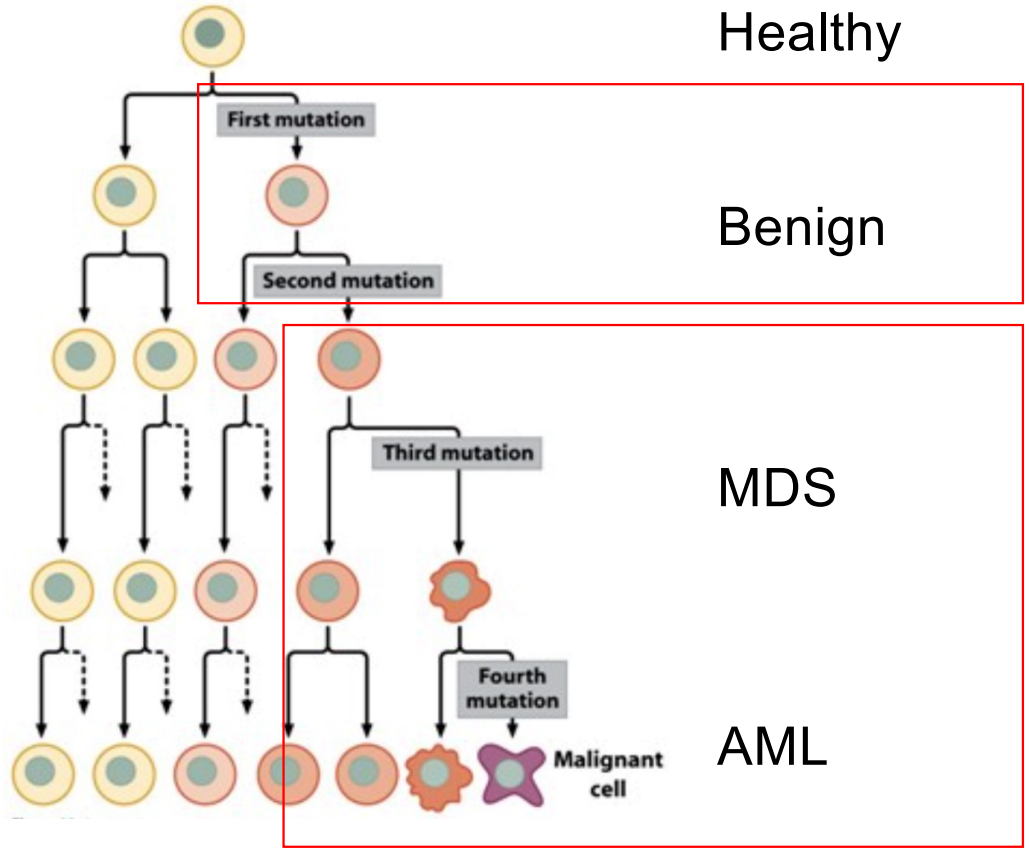
No relevant disclosures

Classical multi-hit model of leukemogenesis

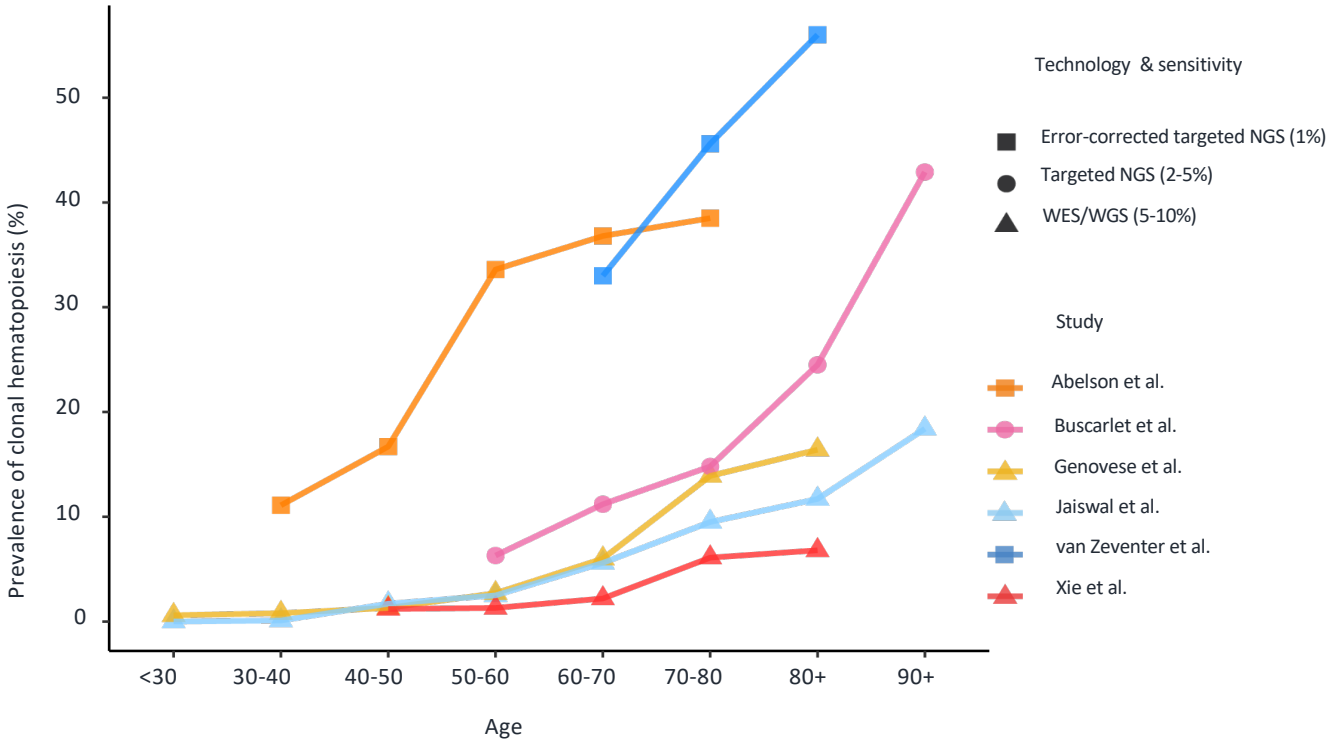


Characteristics of different phases of (premalignant) clonal evolution

	Normal	Clonal Hematopoiesis	CHIP	CCUS	MDS MPN	AML
Clonality (mutations)	-	Yes (any VAF)	VAF >2%	yes	yes	yes
Cytopenia	-	-	-	yes	yes	yes
Dysplasia	-	-	-	-	yes	Yes/no
Blasts	-	-	-	-	<20%	>20%
Overall Risk	-	overall low	overall low	variable	high	high
Treatment	-	-	-	If necessary	Supportive care/yes	yes

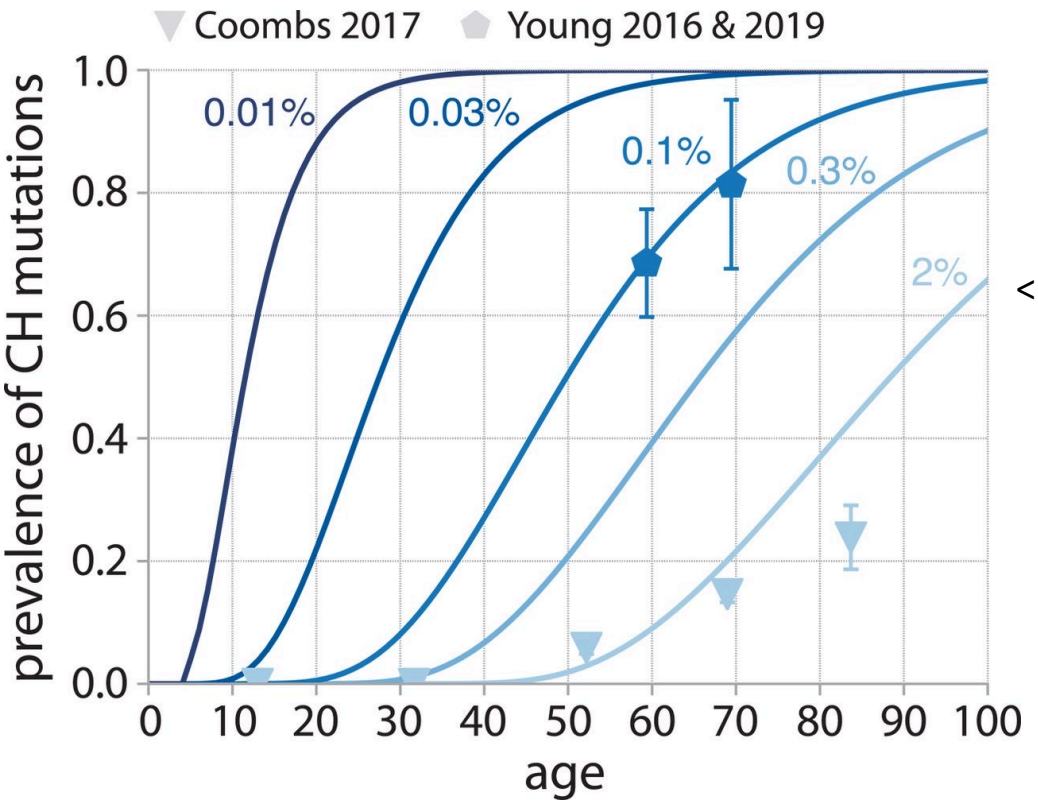
CH = Clonal Hematopoiesis: presence of a heatological clone carrying an acquired mutation, any clone size
CHIP = Clonal Hematopoiesis of Indeterminate Potential: mutated clone is present >4% of all cells (VAF >2%), no symptoms
CCUS = Clonal Cytopenia of Undetermined Significance: CHIP in the presence of one or more cytopenias

Incidence of clonal hematopoiesis is very common, arises early in life



In general: 5-10 fold increased risk of developing a myeloid malignancy
2-3 fold increased risk of cardiovascular disease

Theroretical prevalence of clonal hematopoieis at various detection limits
Assuming a constant growth rate during life

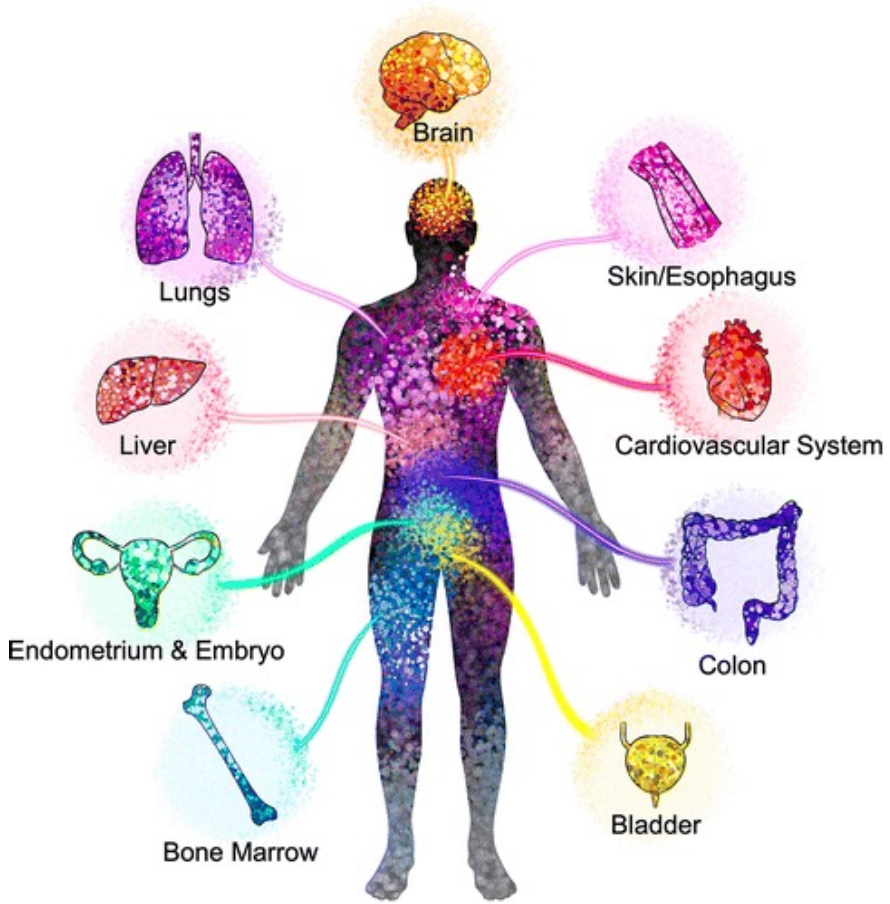


<= Clonal hematopoiesis measured using 2% detection limit (=CHIP)

Watson et al. Science 2020

- Clonal hematopoiesis
  - occurs very frequently, if not ubiquitously when measured at high sensitivity
  - Increases with age
  - can be driven by many, if not all, known leukemia-associated driver mutations
  - Associates with a 5-10 fold increased risk of developing a myeloid neoplasm
    (NB: even at a 5-10 fold increased risk, the chance of developing a myeloid neoplasm is still limited)

Clonally expanded, non-malignant cells with acquired mutations are common in many different tissues



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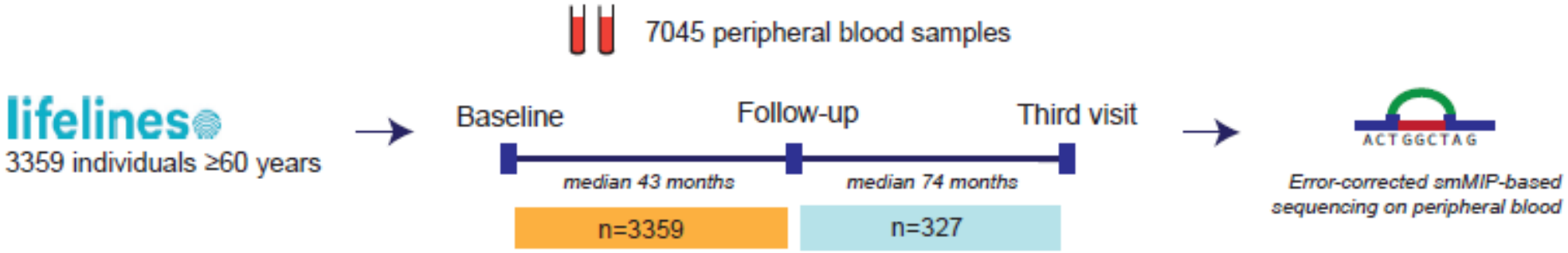
Clonal Hematopoiesis of **Indeterminate Potential** (CHIP)
and Clonal Cytopenia of **Unknown Significance** (CCUS)

are very unsatisfactory terms !

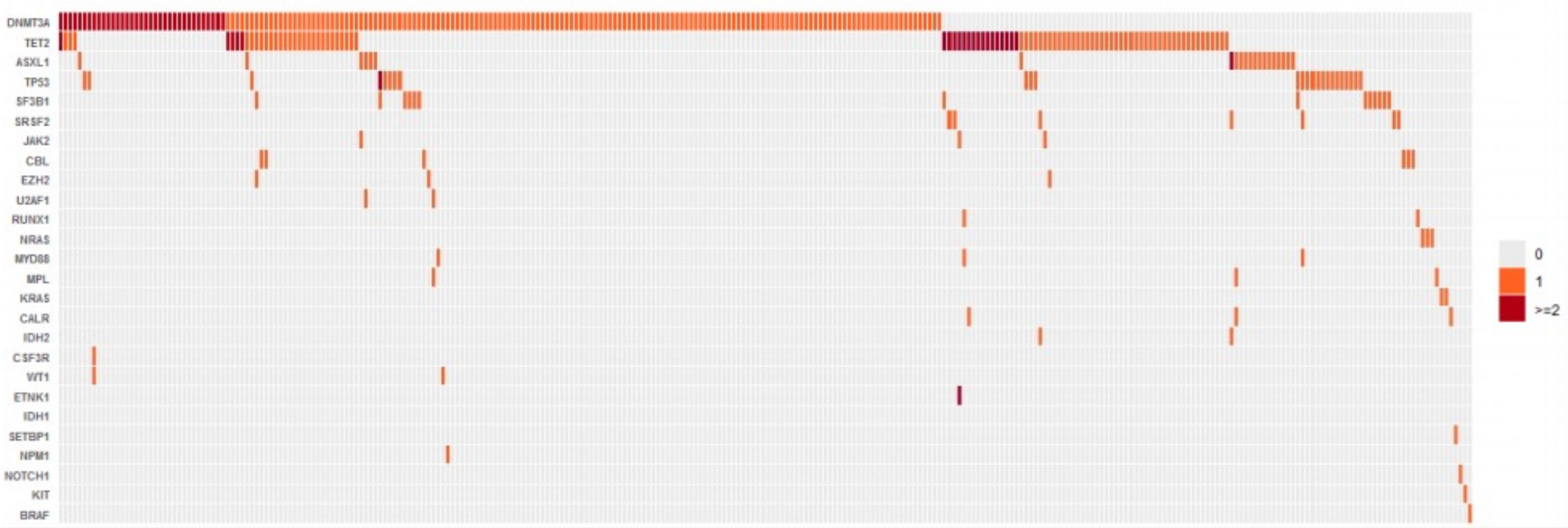
Lifelines: Population-based cohort (n=169.000) with extensive data on life-style, health, medication, profession, as well as routine blood analyses and biomaterials (blood cells and serum, saliva)



⇒ Coupling to national death registry and the National Cancer Registry allowing analysis of neoplastic diagnoses and causes of death

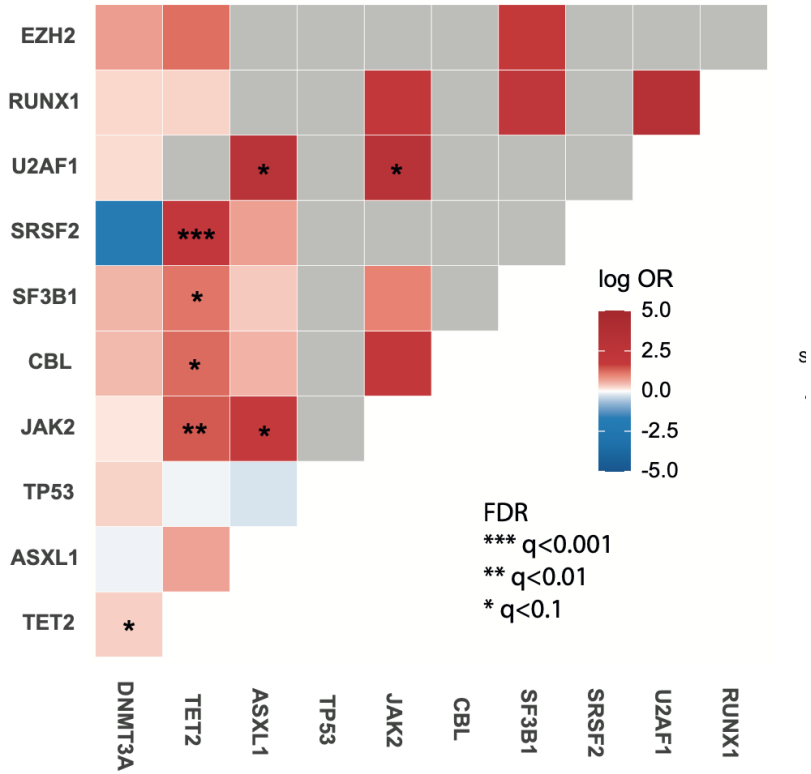
⇒ Availability of multiple samples from the same individual allowed longitudinal rather than cross-sectional analyses

Mutational spectrum in clonal hematopoiesis
most common: DNMT3A, TET2 & ASXL1 (DTA mutations)

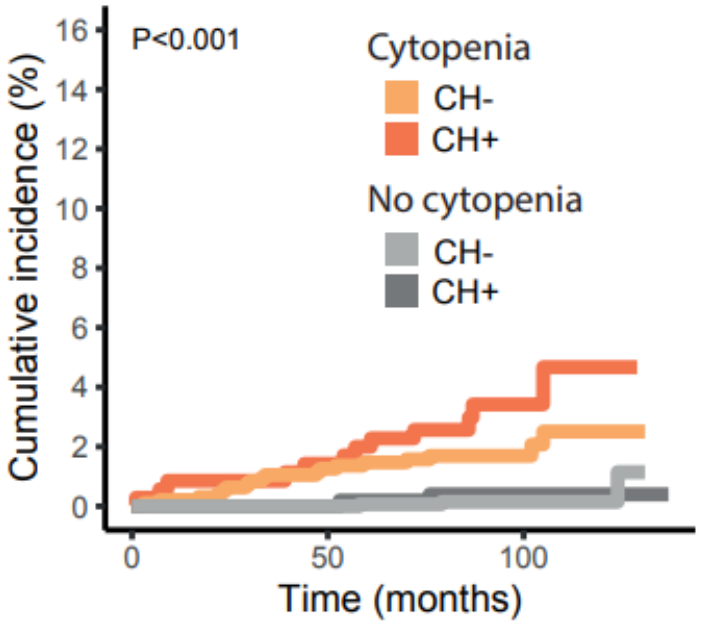


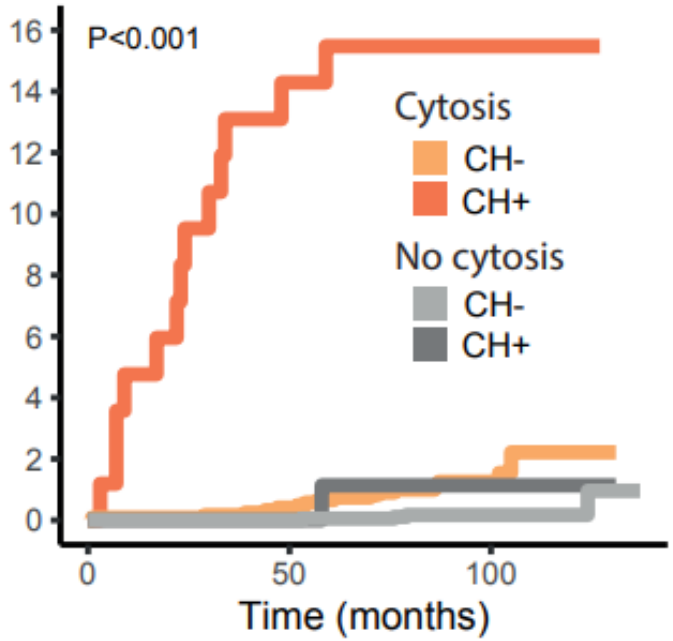
Zeventer & de Graaf et al. Evolutionary landscape of clonal hematopoiesis in 3,359 individuals from the general population (Cancer Cell 2023)

Co-mutational patterns in individuals with 2 or more mutations at baseline.

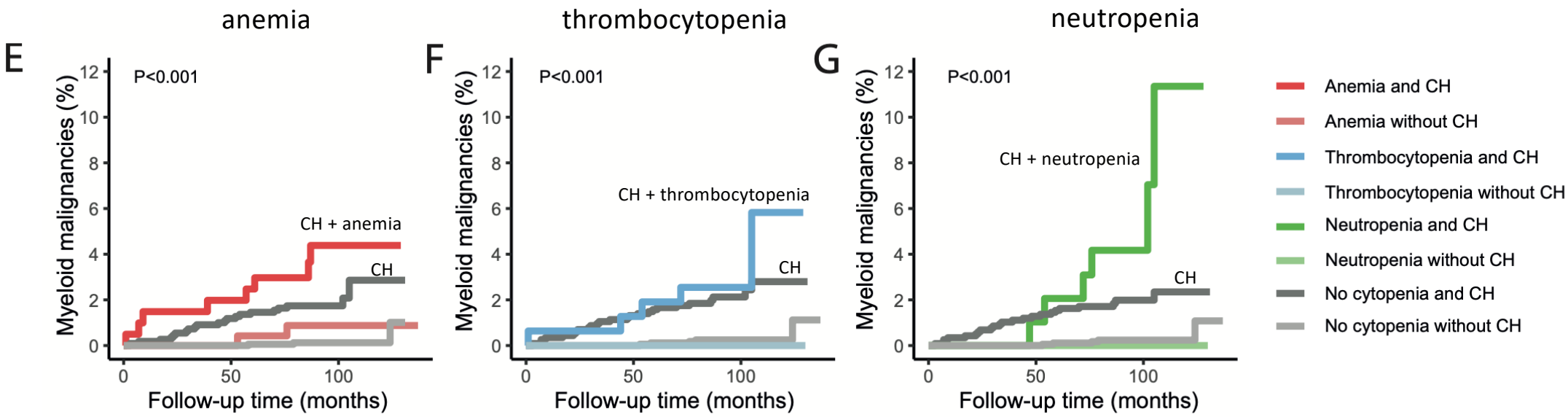


Risk of myeloid malignancy is enhanced by the combination of clonal hematopoieis and blood count abnormalities (cytopenia & cytosis)

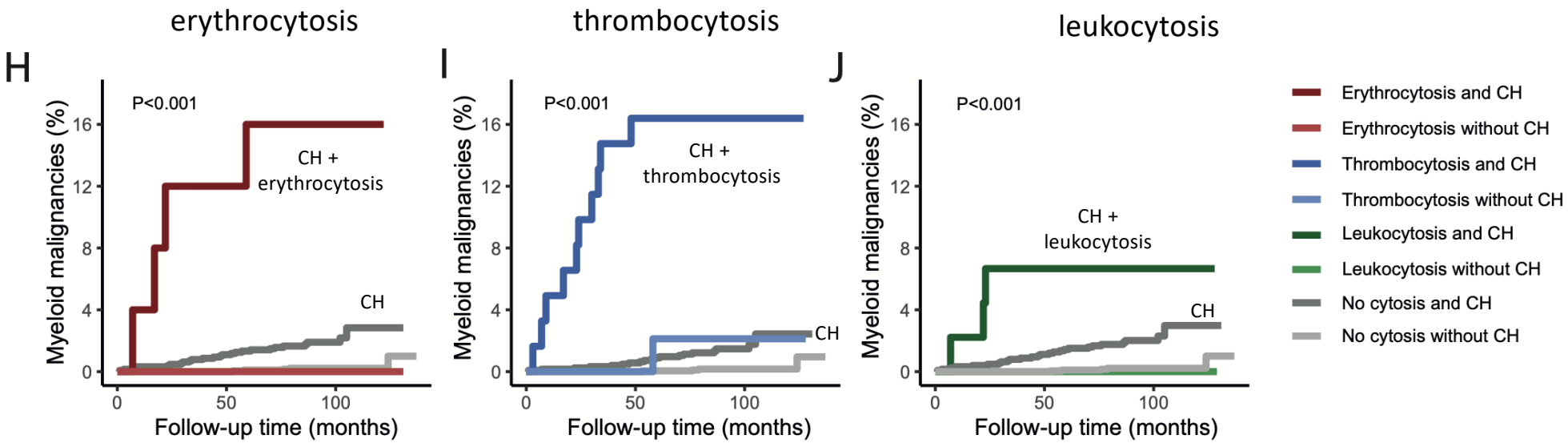




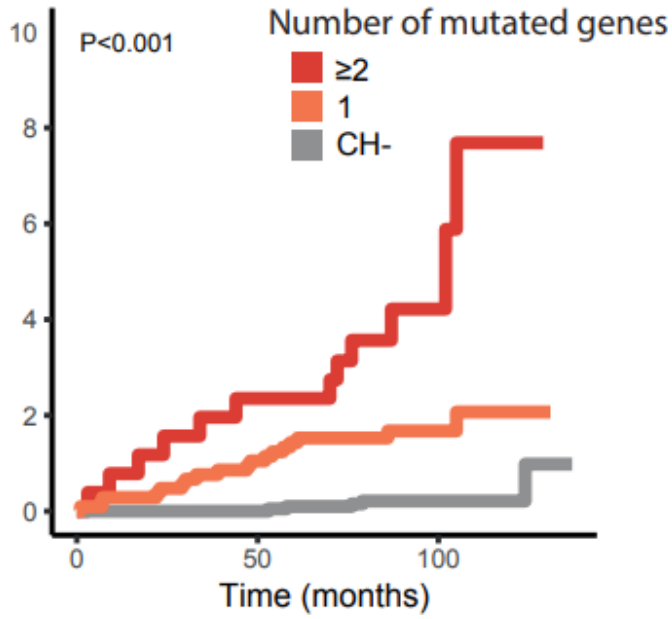
Enhanced risk of myeloid neoplasm in case of clonal hematopoiesis plus a cytopenia; most prominently in case of neutropenia

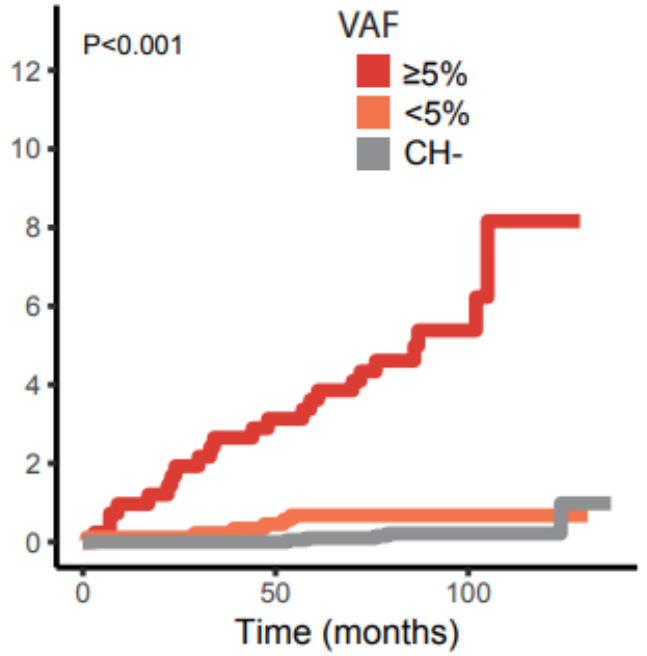


Enhanced risk of myeloid neoplasm in case of clonal hematopoiesis plus a cytosis: most prominently in case of erythrocytosis or thrombocytosis

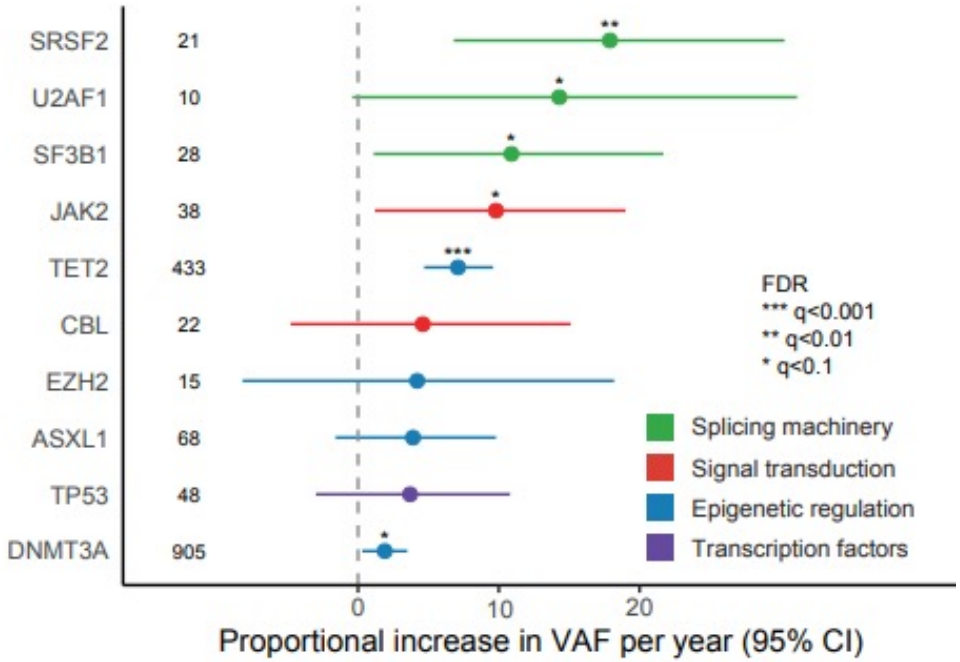


Risk of myeloid malignancy is also enhanced with higher number of mutations or large clone sizes (high VAF)





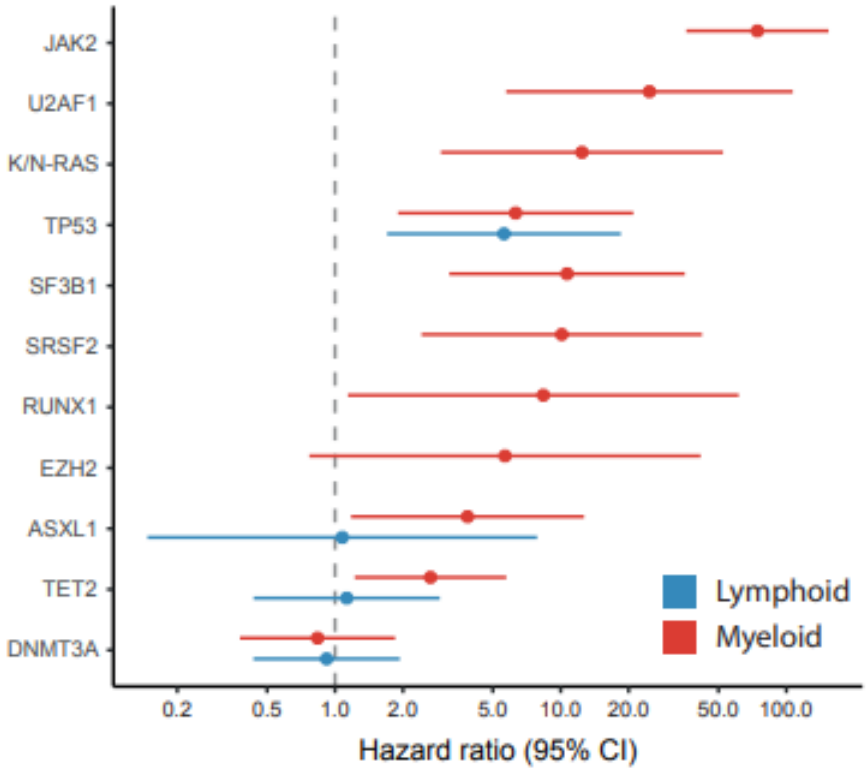
Clone growth is mutation-specific, clones with splicing factor mutations grow fastest



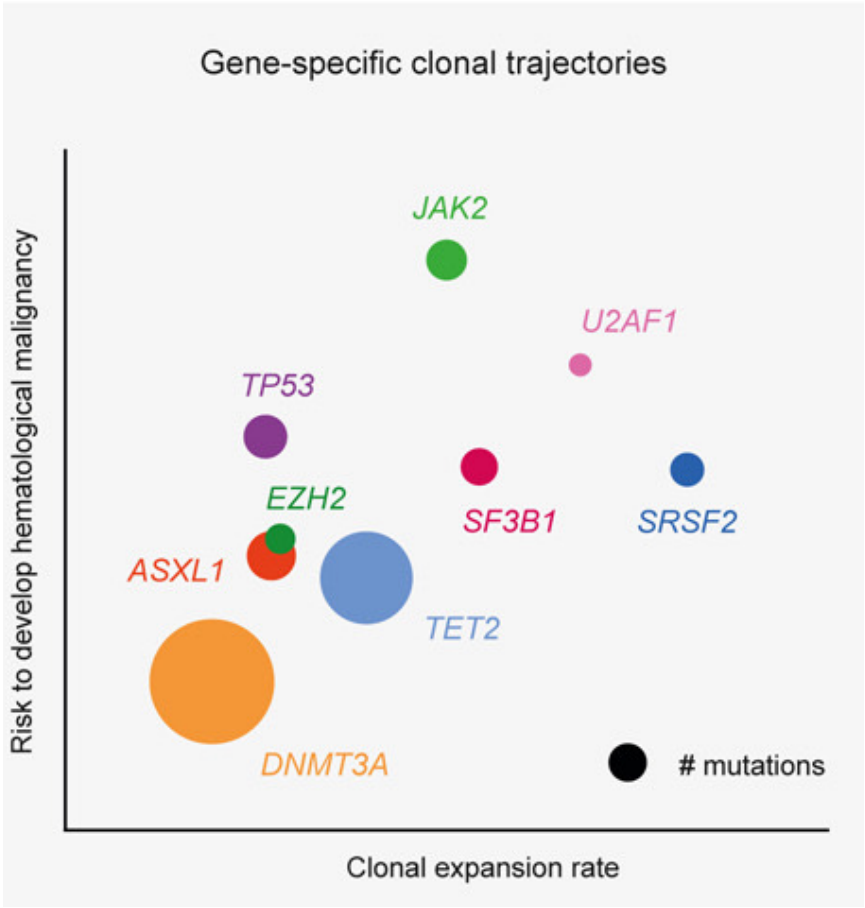
Counter-intuitively:

The most prevalent mutations (DNMT3A) associate with very slow growth

Transformation risk is mutation-specific,
HR DNMT3A mutation =1; HR risk JAK2 = 75



Growth rate and transformation risk are correlated



Weighted multiparameter transformation risk scoring system

Table 2. CHRS Values.*

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 (yr)		<65	≥65		

Total score defines risk category:
low (score ≤9.5), intermediate (score 10-12), and high (score ≥12.5).

L. Weeks, 2023 NEJM Evid 2023;2(5)

Weighted multiparameter transformation risk scoring system

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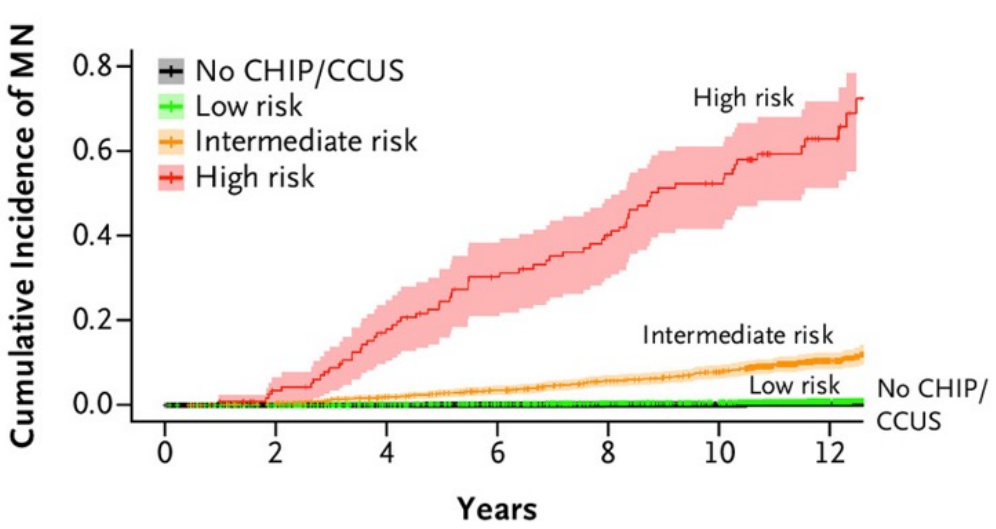
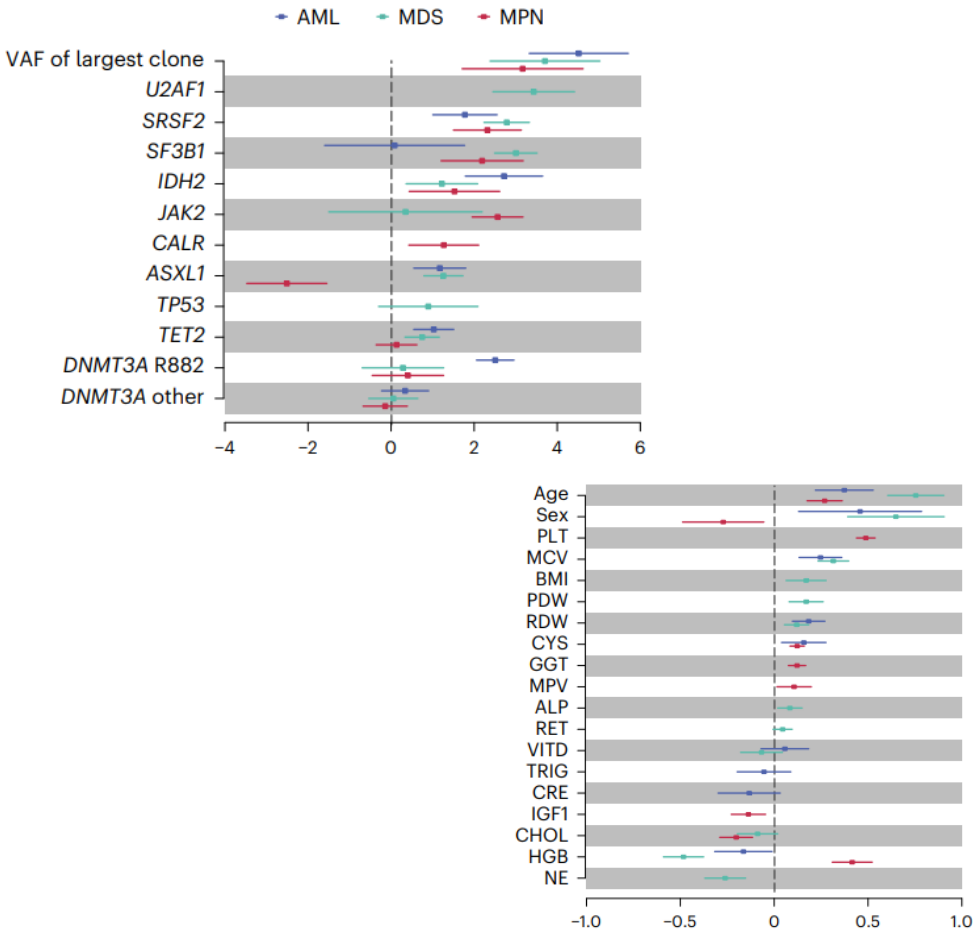


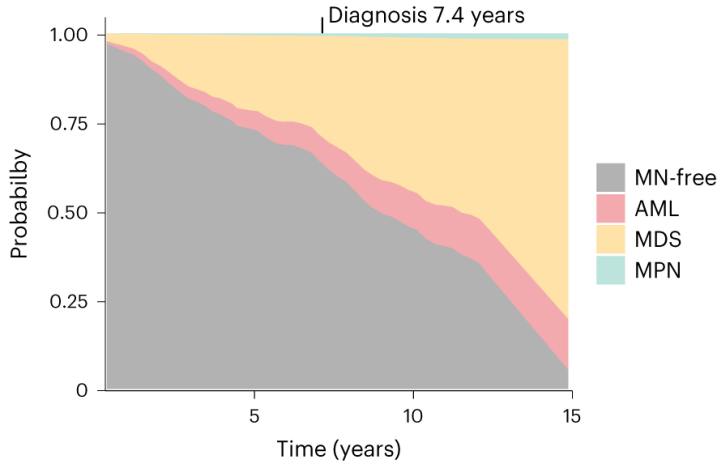
Number at Risk

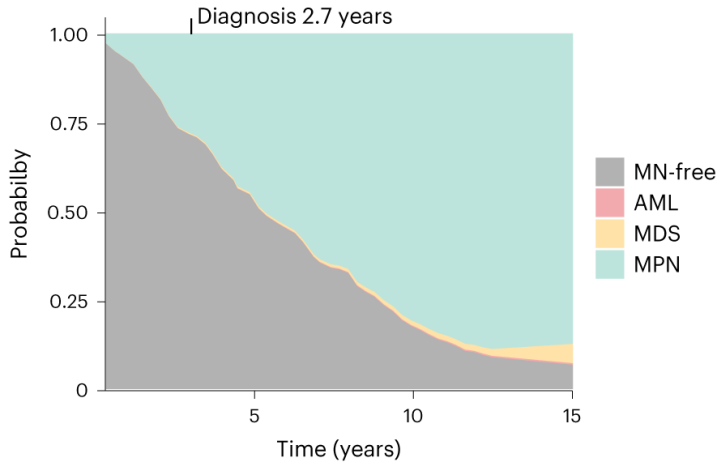
Time (yr)	0	2	4	6	8	10	12
High risk	123	109	90	72	60	43	15
Int. risk	1,196	1,174	1,125	1,080	1,016	961	336
Low risk	10,018	9,958	9,821	9,699	9,540	9,348	3,772
No CHIP/CCUS	182,406	181,674	180,407	178,734	176,174	174,455	72,254

L. Weeks, 2023 NEJM Evid 2023;2(5)

Second Integrated scoring system (MN-Predict)
https://bioinf.stemcells.cam.ac.uk/shiny/vassiliou/MN_predict/

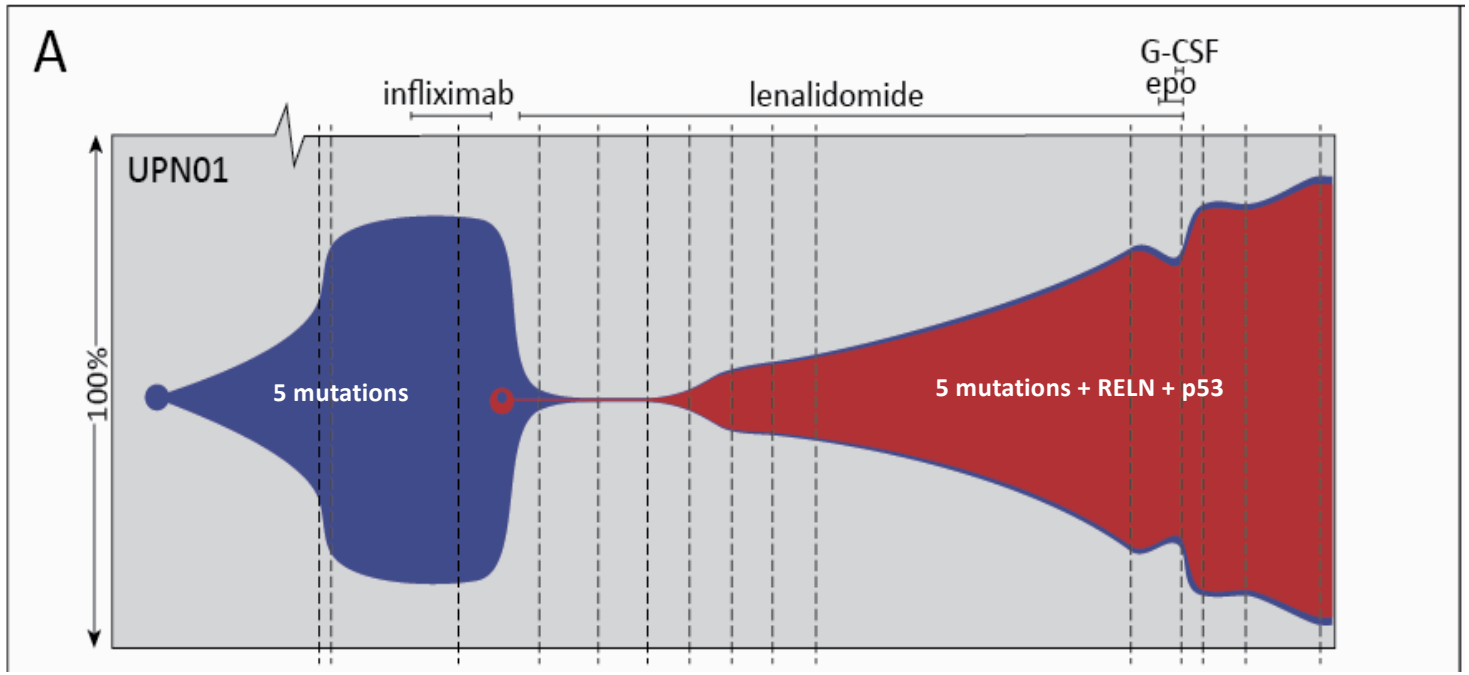






Gu et al. Nat Genetics Sept 2023; 55 1523-1530

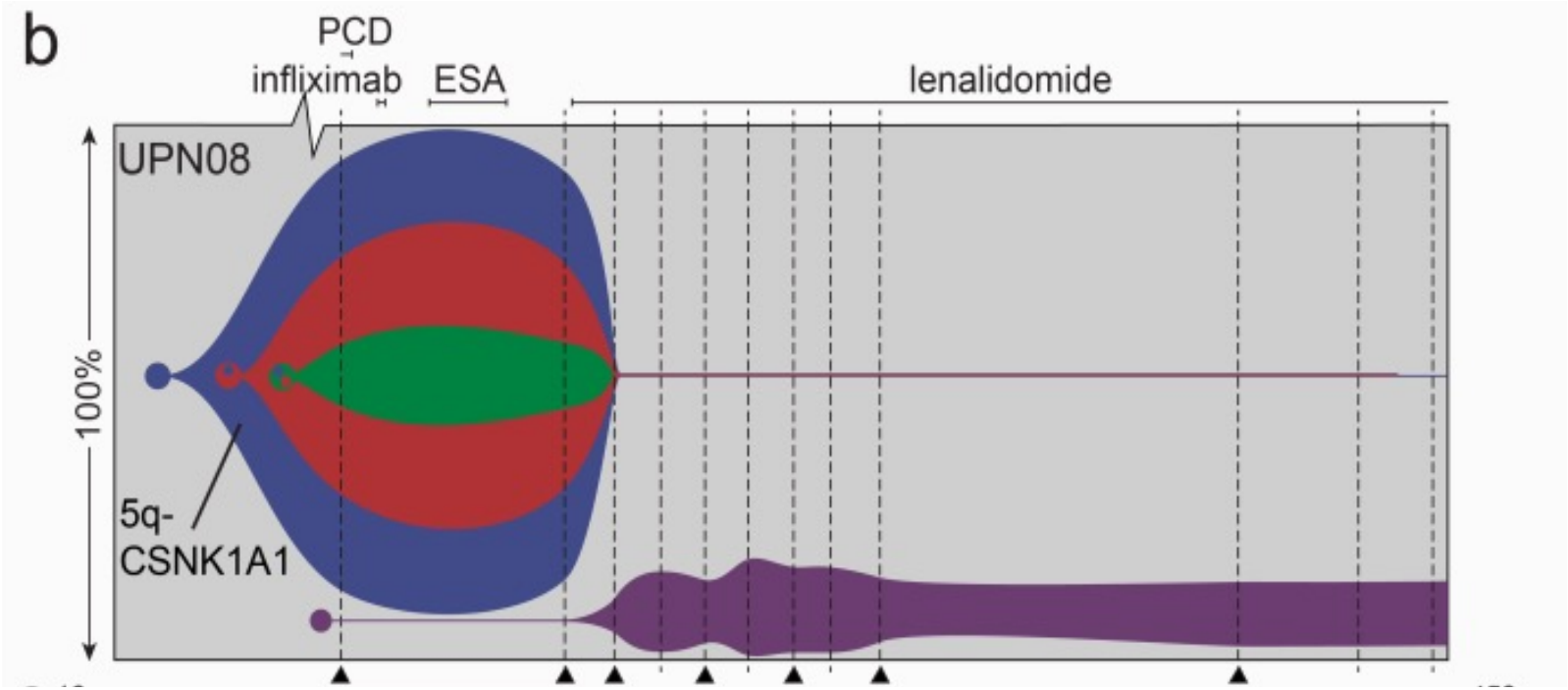
Implications for MRD determination:
Clonal development in MDS during lenalidomide treatment, acquisition of TP53 mutation



Clonal development during treatment, acquisition of TP53 mutation leading to len resistance in 5q- MDS

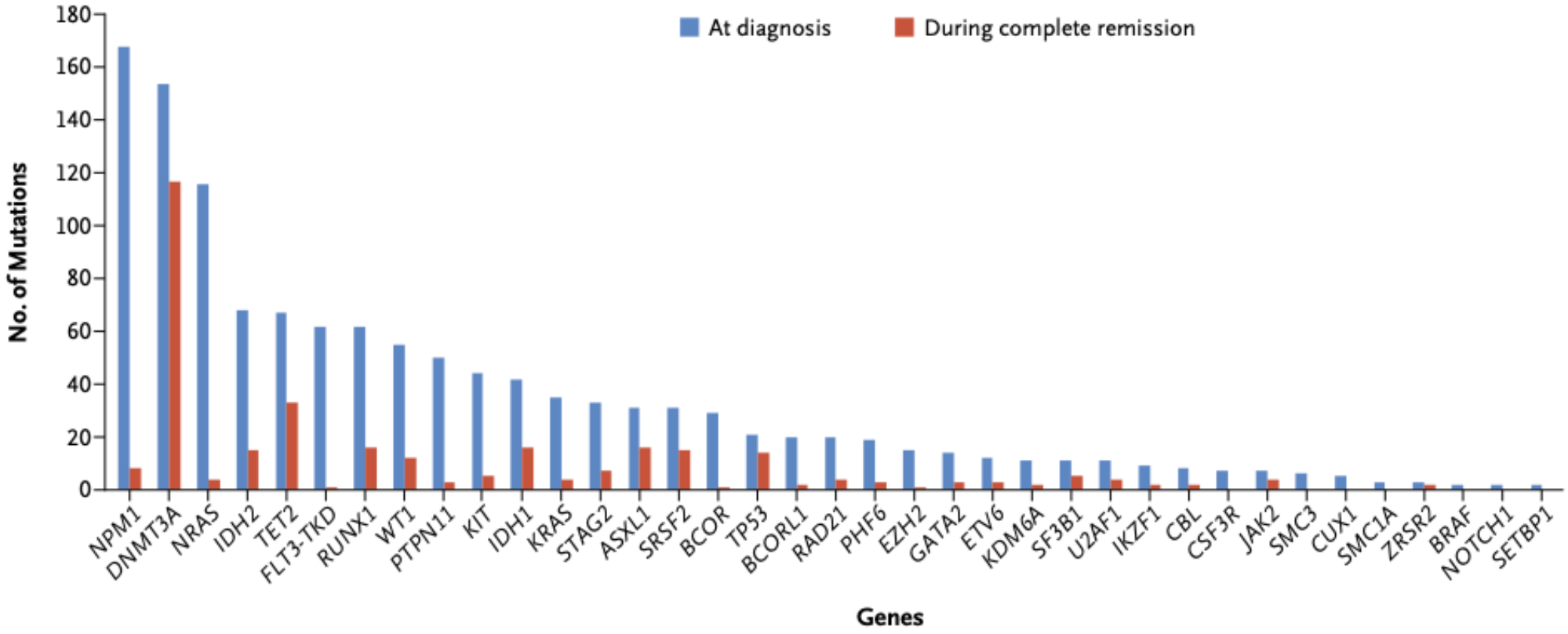
Da Silva-Coelho Nat. Comm. 2017

Implications for MRD determination:
Eradication of the original malignant clone and opportunistic outgrowth of an unrelated CHIP clone



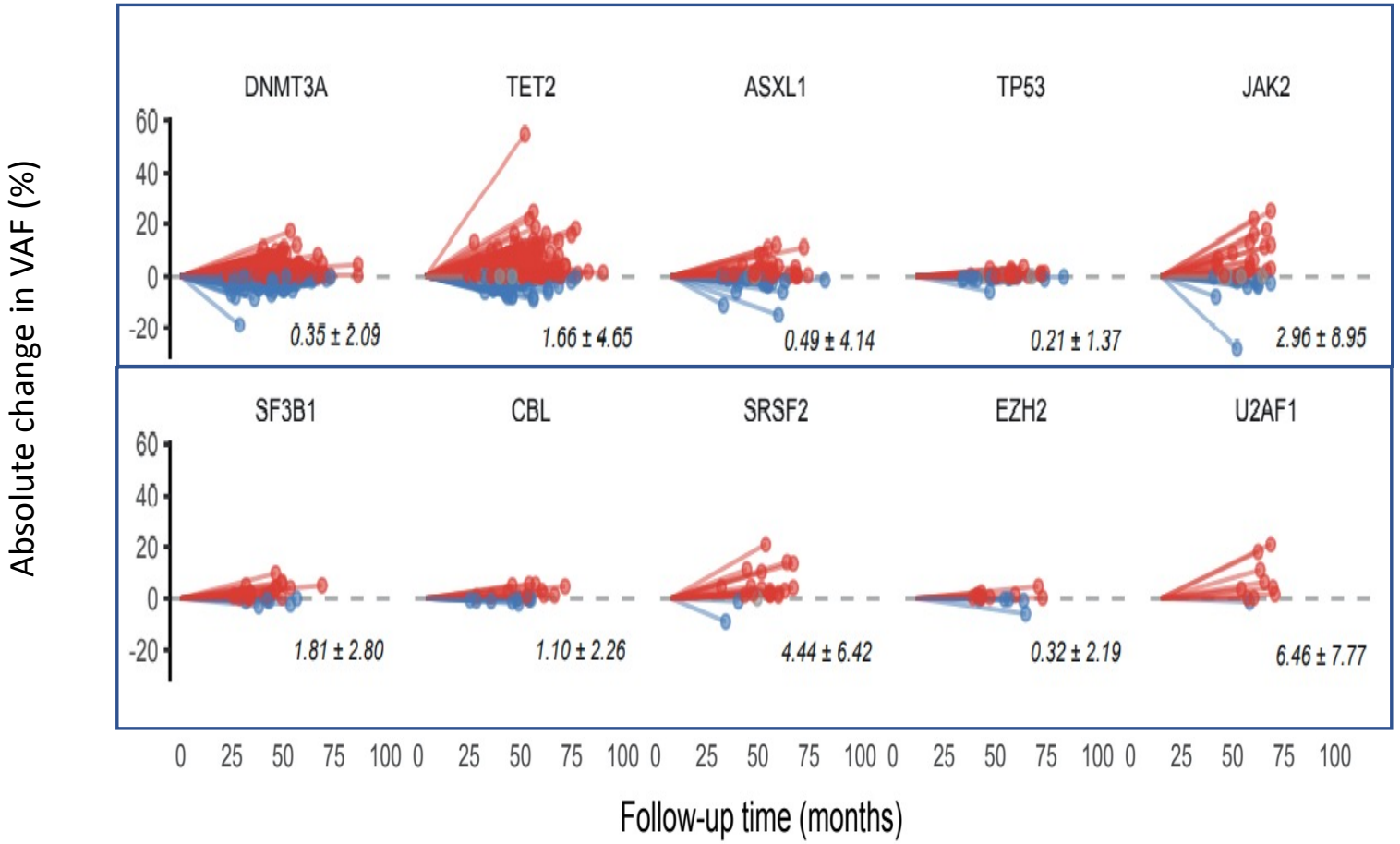
Da Silva-Coelho Nat. Comm. 2017

In AML, several mutations (most prominently DNMT3A) may remain in complete remission, which does not necessarily lead to relapse, in contrast to for instance NPM1

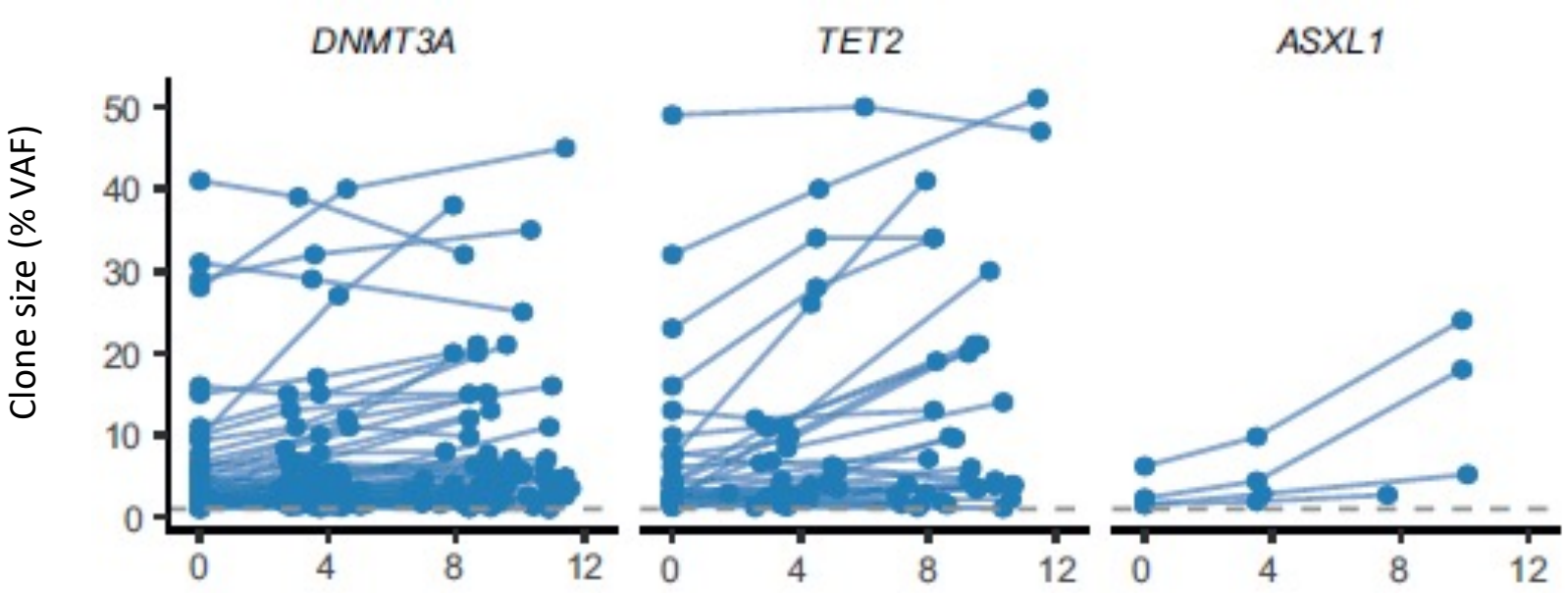


Jongen-Lavrencic et al. NEJMed 2018 378(13)

Different individuals with the exact same mutation may show very different growth rates in several individuals, significantly decreasing clones are observed (!)



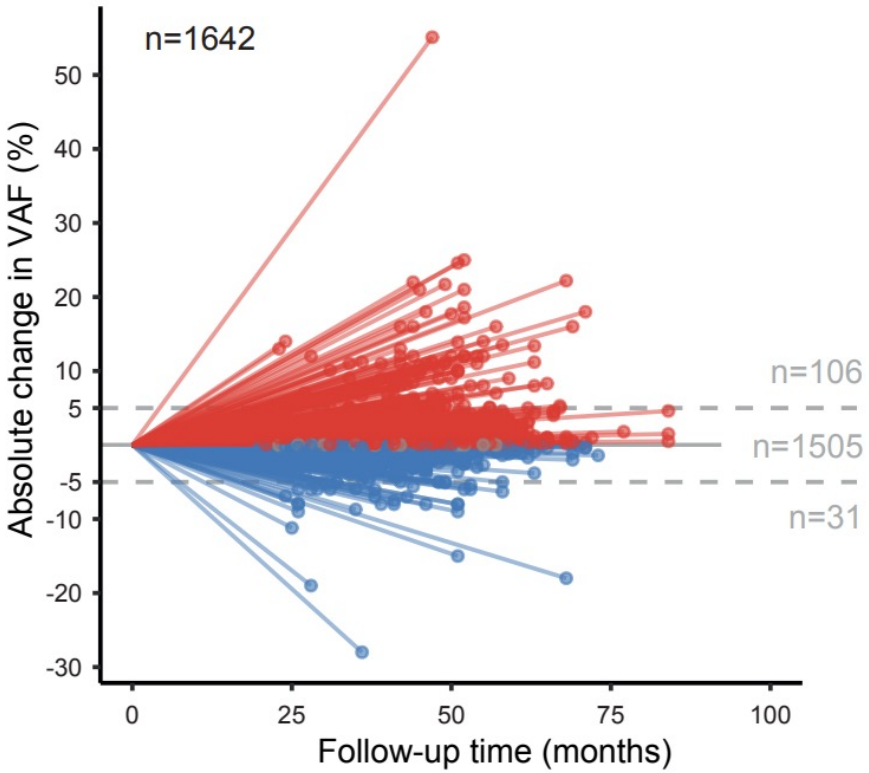
Growth and decline in a given individual is relatively stable not subject to short term effects (flu, common cold etc)



⇒ Growth is modulated by unknown host factors

⇒ As previously grown clones may stop growing or even significantly decline without changing mutational content: non-genetic mechanisms must be operational

Longitudinal clonal expansion data of 1642 individuals with CH
Most individual clones grow slowly, some grow fast but some have stopped growing or even decline



Clone stabilization / shrinkage is possible

As these clones have grown at some point in life: which factors cause them to slow down or decline ?

Road to actionable targets potentially allowing development of intervention strategies for very high risk individuals

⇒ Effect of various factors such as acquired diseases (eg chronic inflammation), puberty, menopause, medication etc will be analysed, as well as full proteomic analysis of growers and decliners

Conclusions

- Clonal Hematopoiesis is very common
- Evolution to a myeloid neoplasm is enhanced with
  - Cytopenia / Cytosis
  - High risk mutations
  - Faster growth rates
  - Large clone size
  - Multiple mutations
  - Blood values (RDW, PDW, MCV)
  - Biochemistry values
- High risk profiles can now be defined
- Clone sizes may stabilize and even decline. Identification of factors that drive this could potentially provide clues for intervention strategies in high-risk individuals

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