

# **KLONALE HÄMATOPOESE ALS PRÄMALIGNE ENTITÄT**

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**Klinik m.S. für Hämatologie, Onkologie und Tumorummunologie**

# Disclosures

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**Research funding:**

**Novartis**

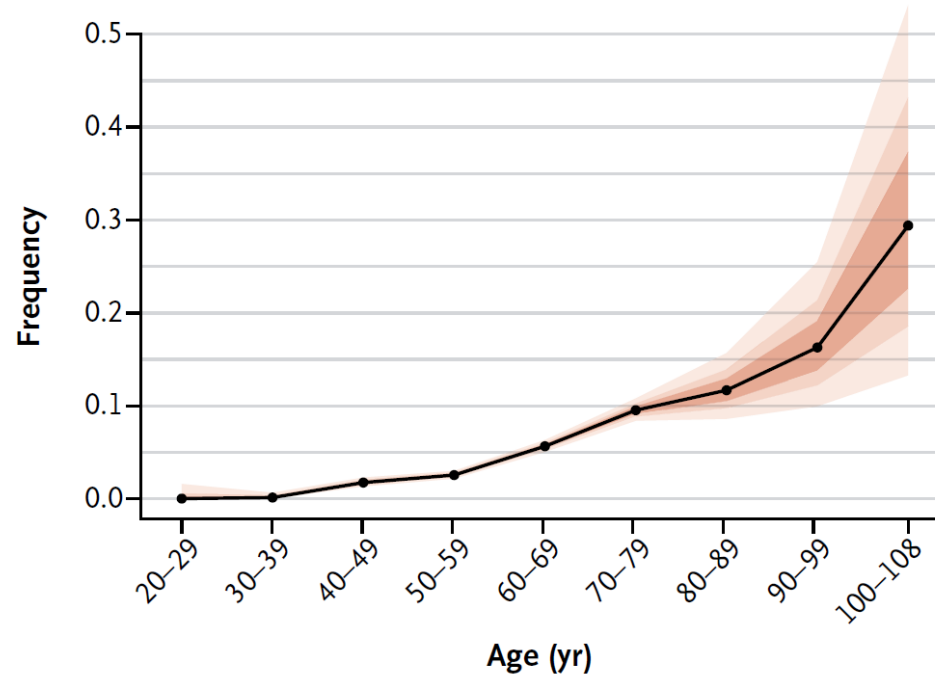
**Honoraria, Advisory Board:**

**AbbVie, Amgen, Astra Zeneca, BeiGene, Gilead, Incyte, Novartis, Roche**

**Travel, Accommodations, Expenses:**

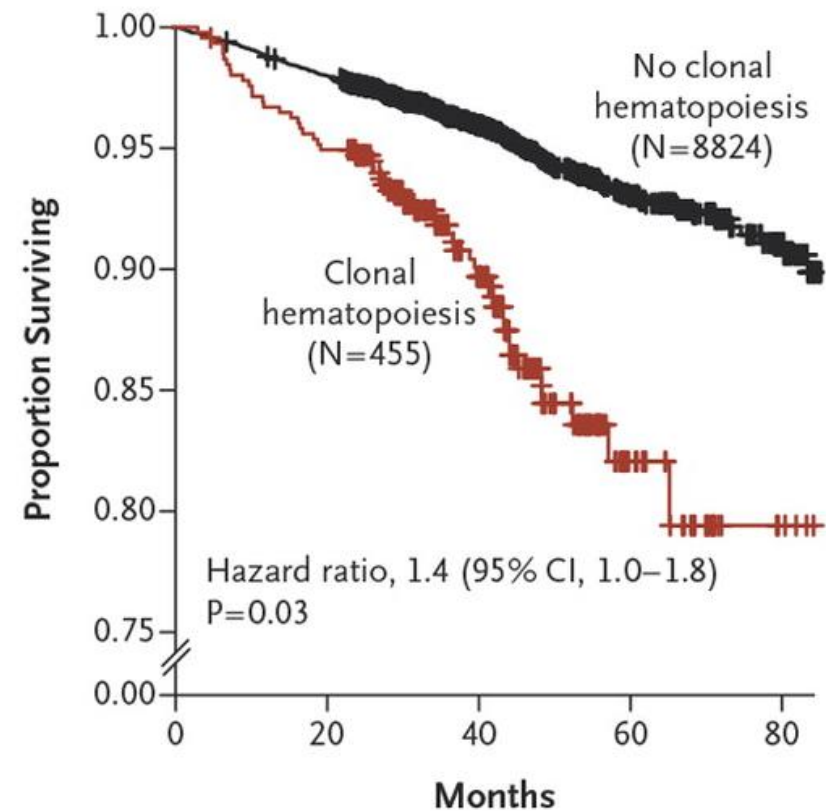
**AbbVie, Astra Zeneca, BeiGene, Gilead, Jazz Pharmaceuticals, Roche**

# Was ist Klonale Hämatopoese?



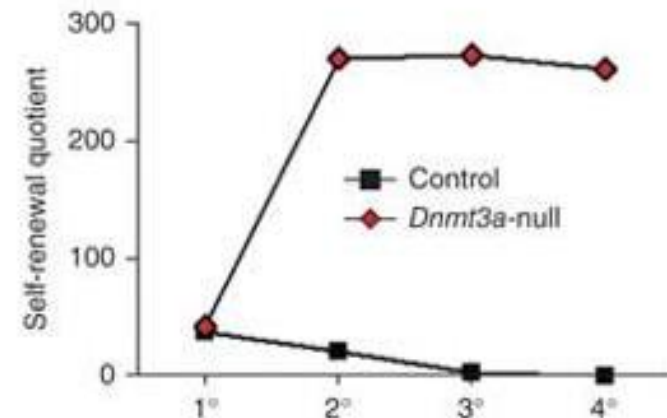
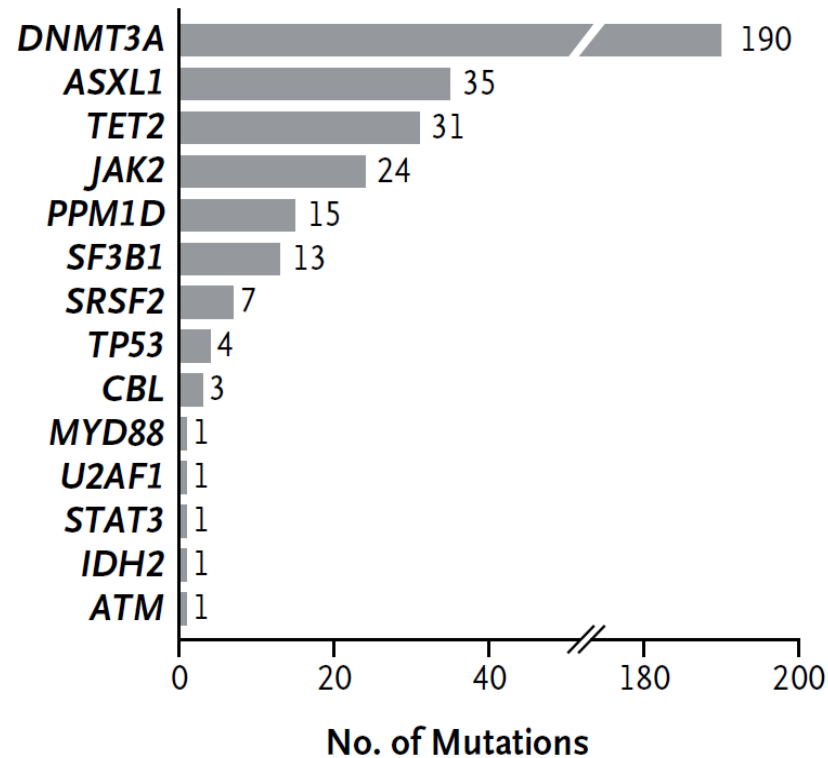
No. with Mutation  
Total

0	1	50	138	282	219	37	14	5
240	855	2894	5441	5002	2300	317	86	17

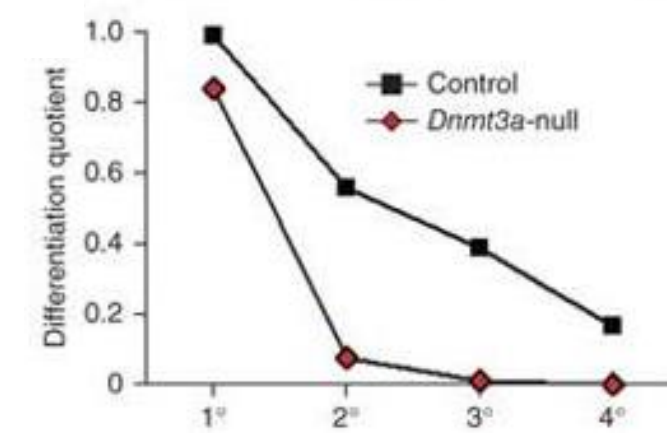


# Was ist Klonale Hämatopoese?

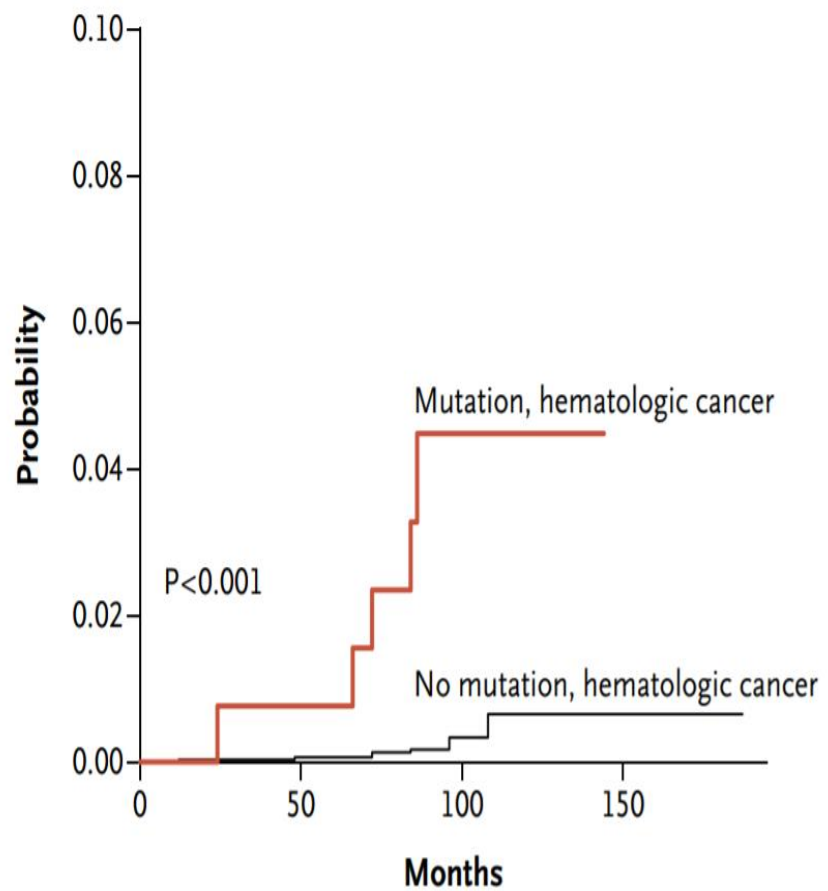
- Mutations occur non-randomly in the human genome and mainly affect three epigenetic regulators of transcription (*DNMT3A*, *ASXL1*, and *TET2*).



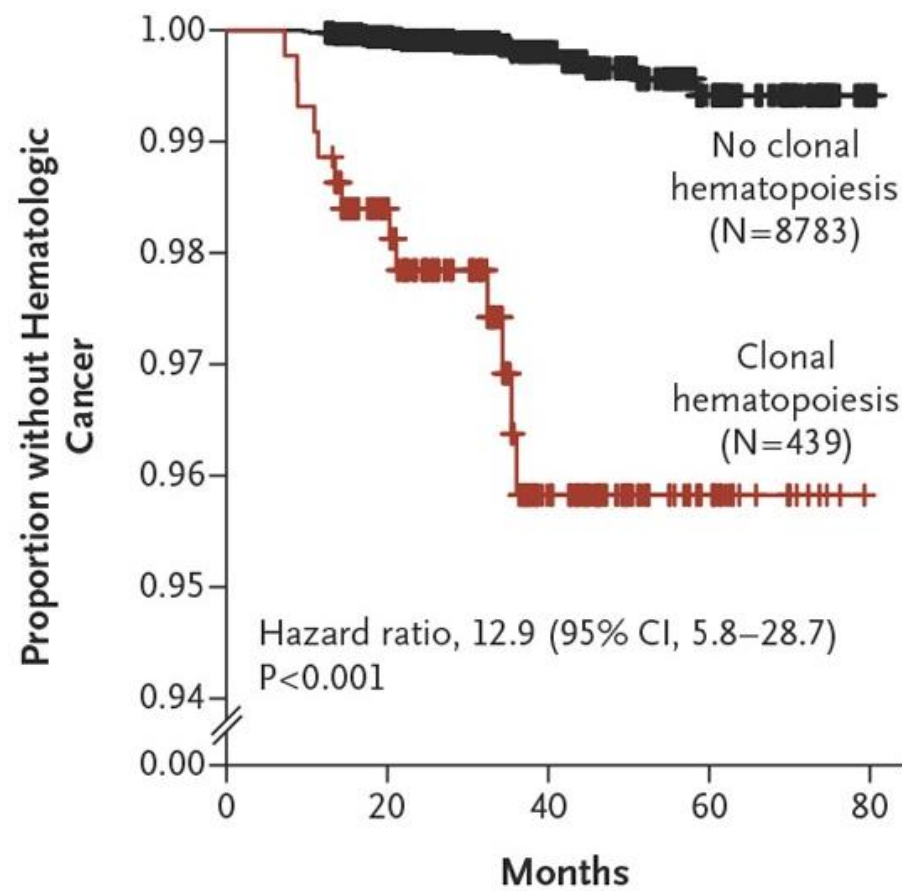
Self-renewal ↑



Differentiation ↓

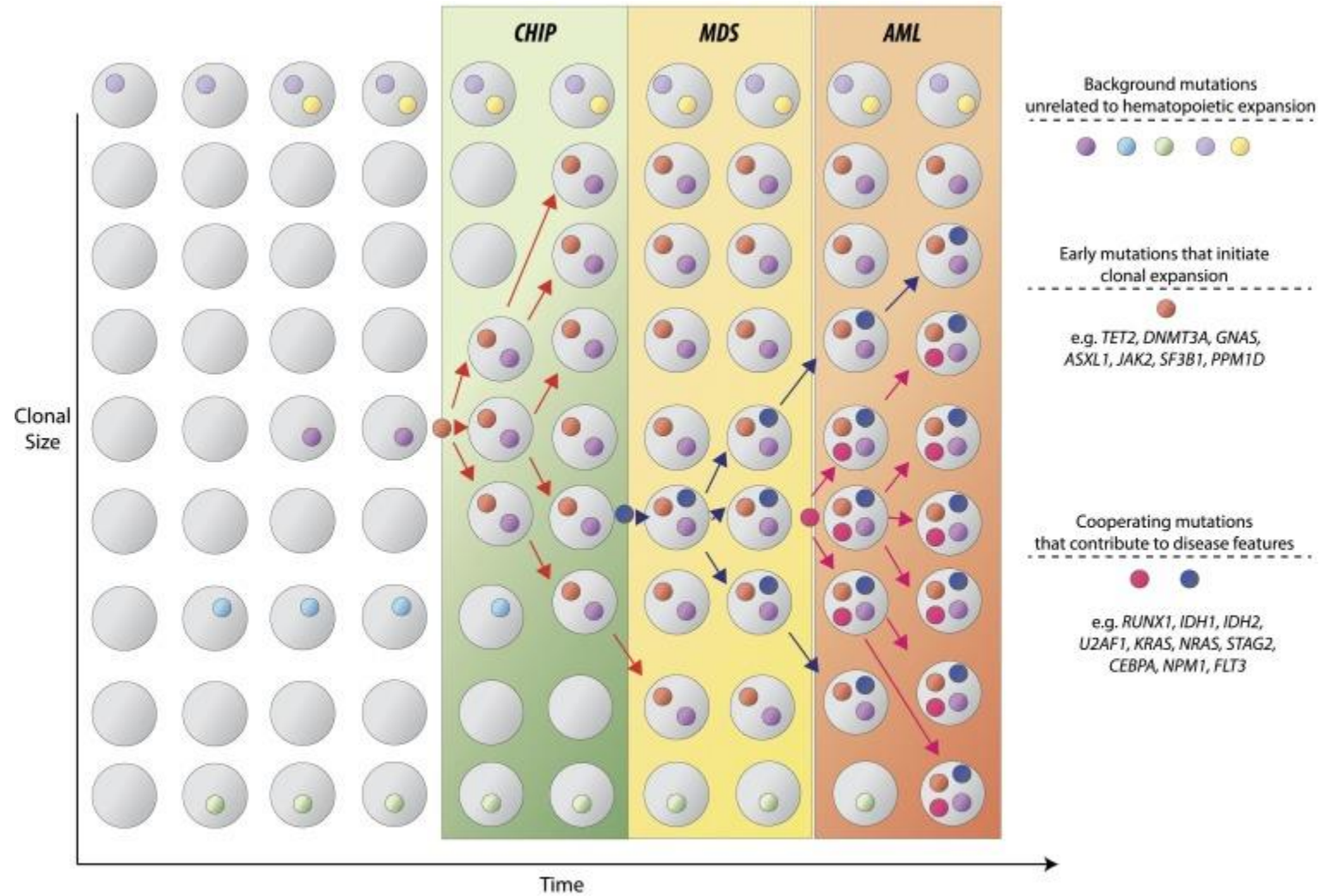


Jaiswal *et al.*, NEJM 2014



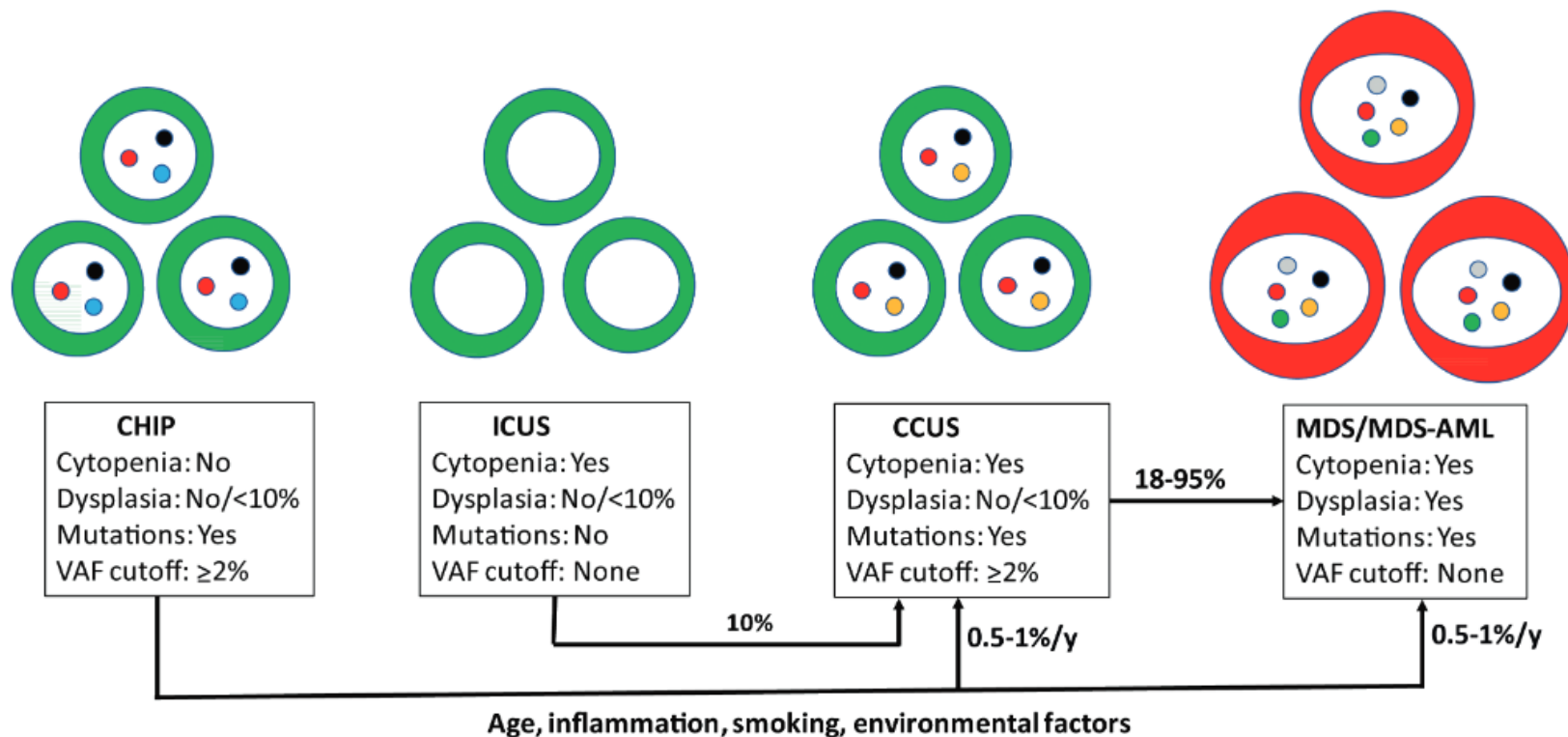
Genovese *et al.*, NEJM 2014

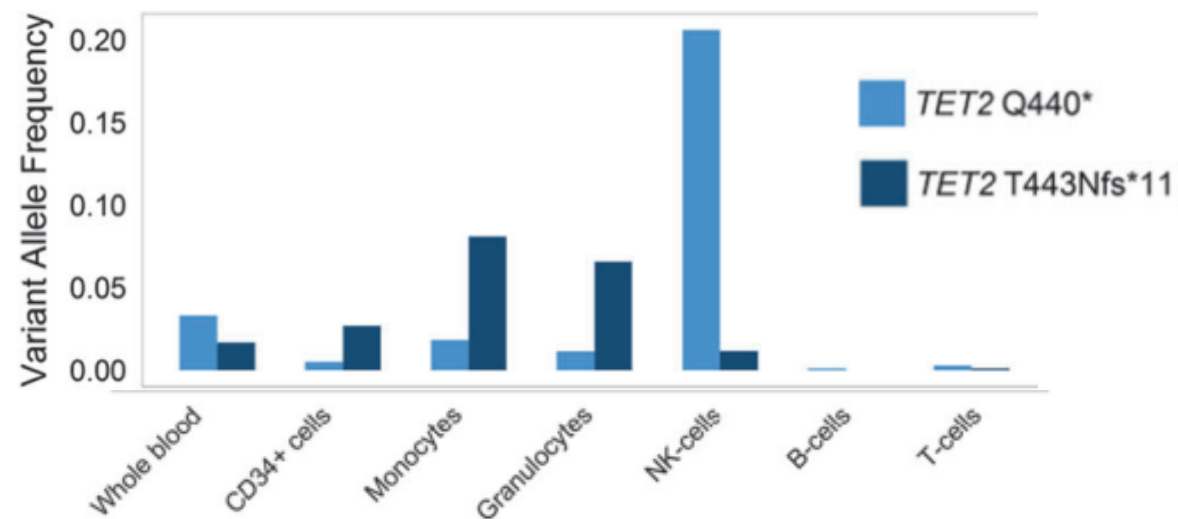
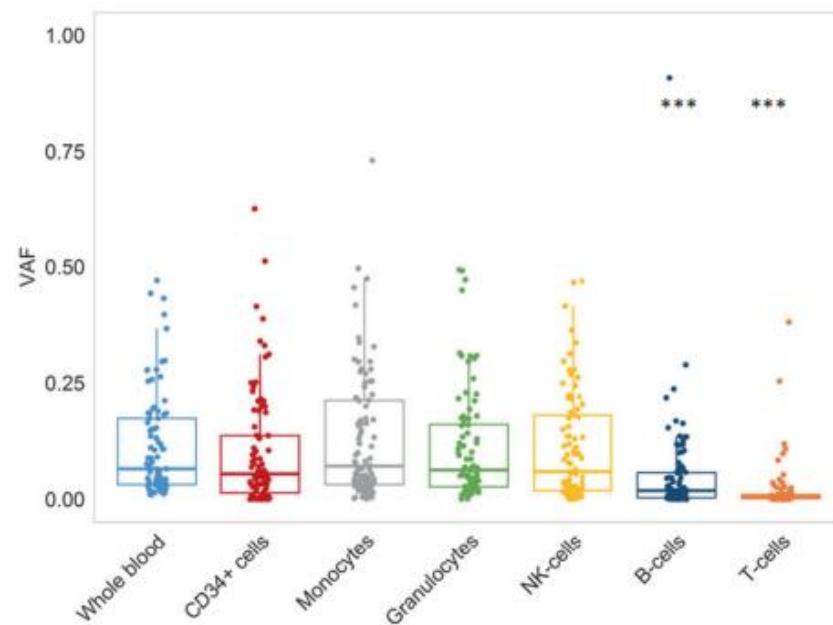
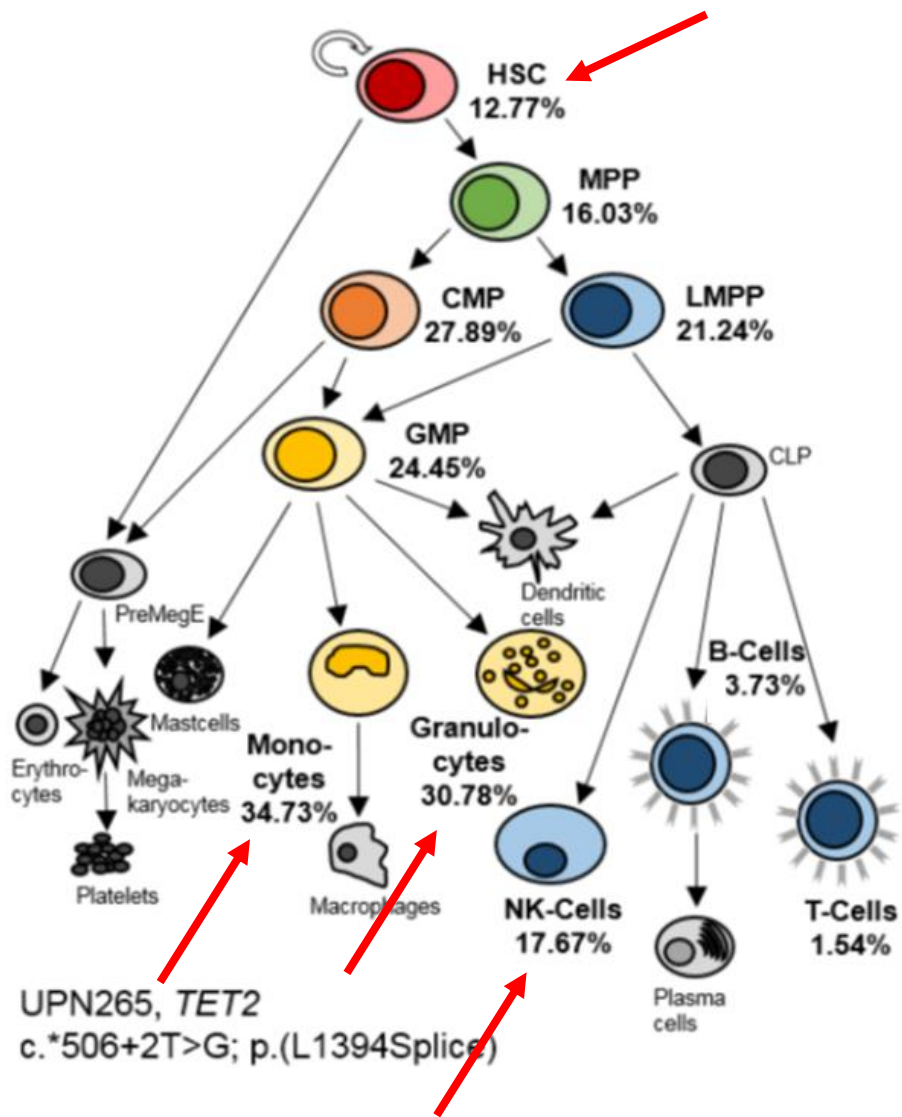
# KH: ein prä-maligner Status für hämatologische Neoplasien



- “*Clonal hematopoiesis of indeterminate potential (CHIP)*”:

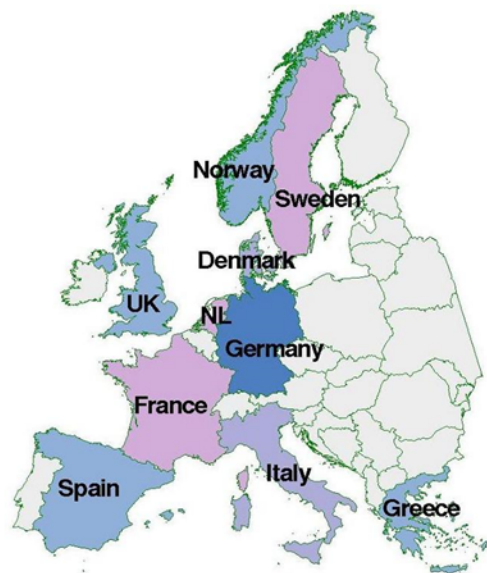
Acquisition of somatic mutations in hematopoietic cells in the absence of cytopenias and dysplastic hematopoiesis (allele burden: VAF  $\geq 2\%$ ).



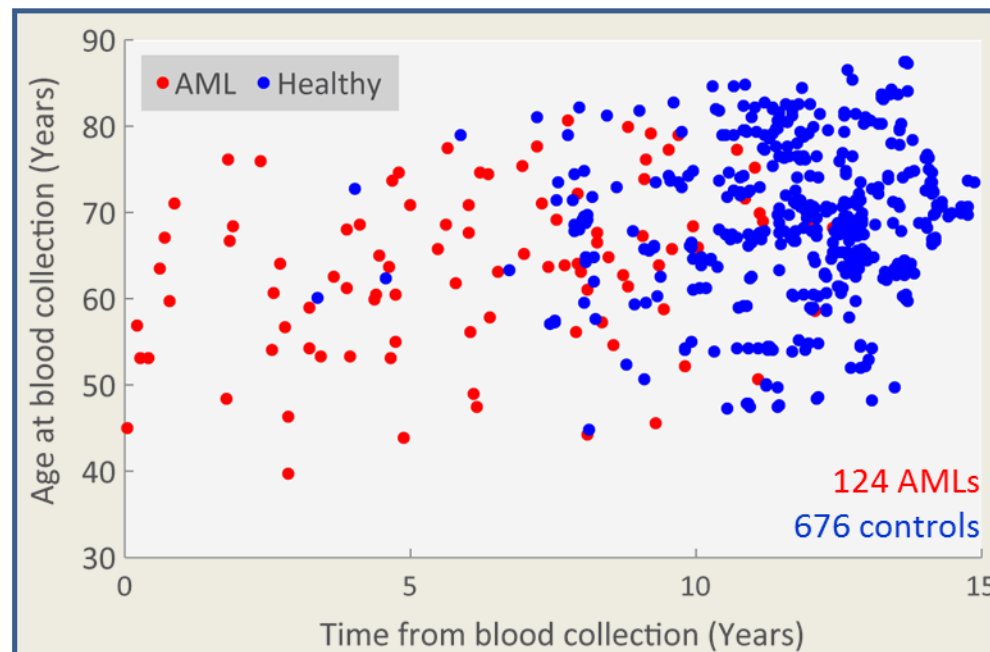




## EPIC European Prospective Investigation into Cancer and Nutrition



- >500,000 participants
- 10 countries
- 15-year follow-up
- Enrolled 1992-2000



### Discovery cohort (DC)

95 Pre-AMLs  
414 controls

Median to AML: 6.4 yrs

Error-corrected sequencing  
Detection cut-off: VAF  
≥0.5%

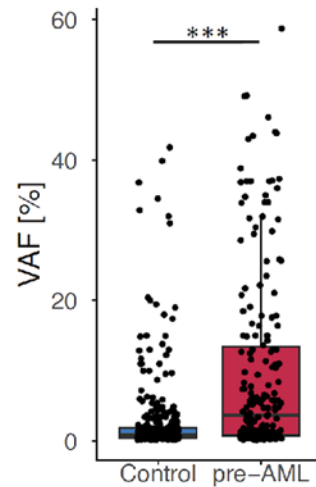
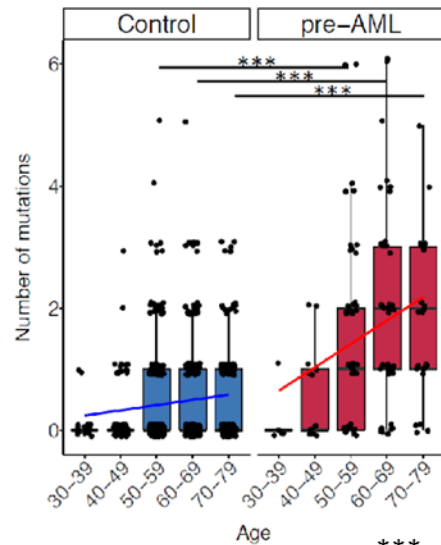
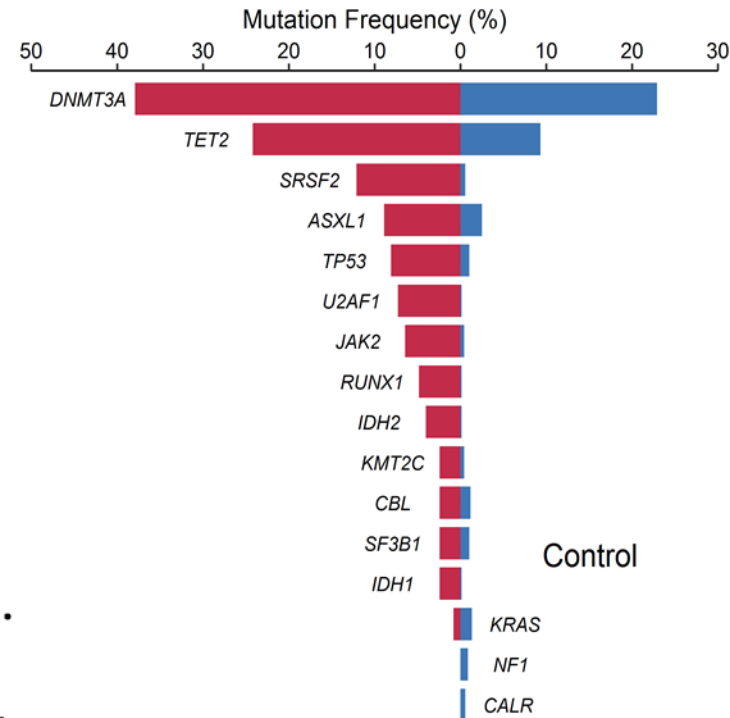
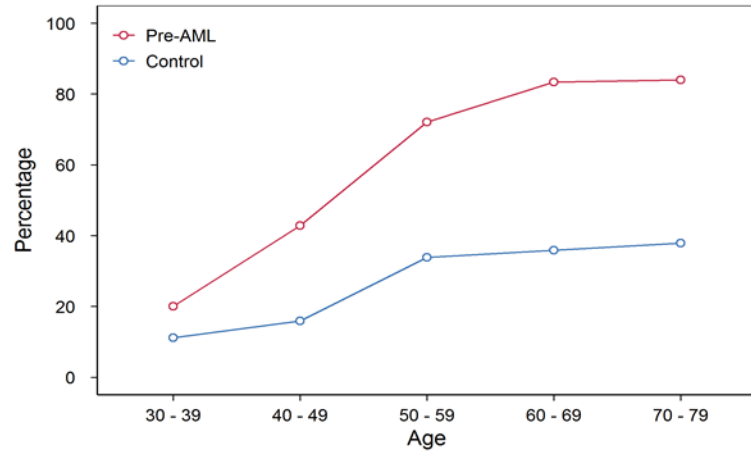
### Validation cohort (VC)

29 Pre-AMLs  
262 controls

Median to AML: 10.4 yrs

Conventional cRNA baits  
Detection cut-off: VAF  
≥0.5%

# KH und AML-Prädiktion in gesunden Individuen



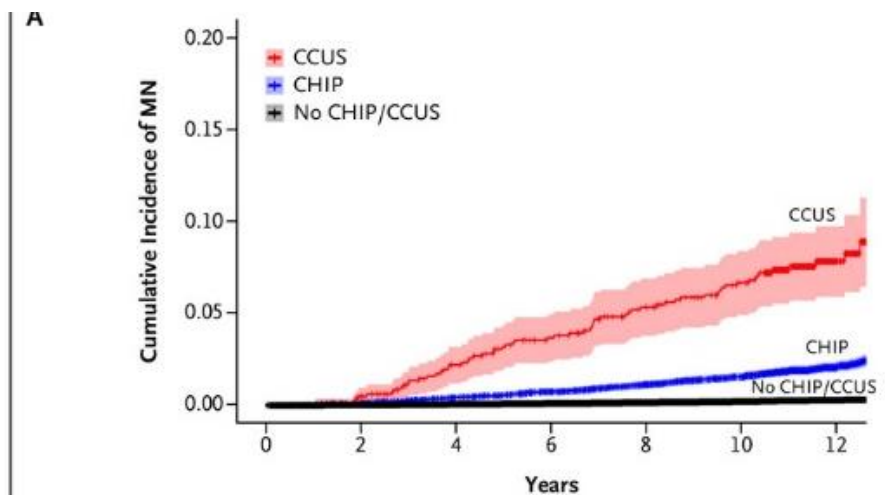
\*\*\* p<0.0005

**Pre-AMLs:**

- CH more common
- More mutations
- Bigger clones
- High risk mutations

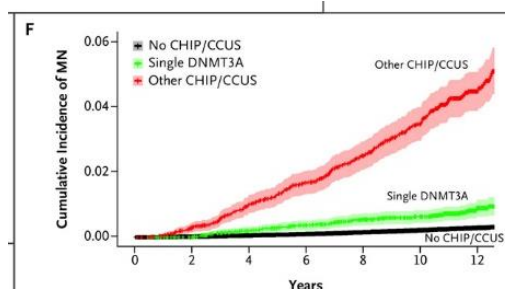
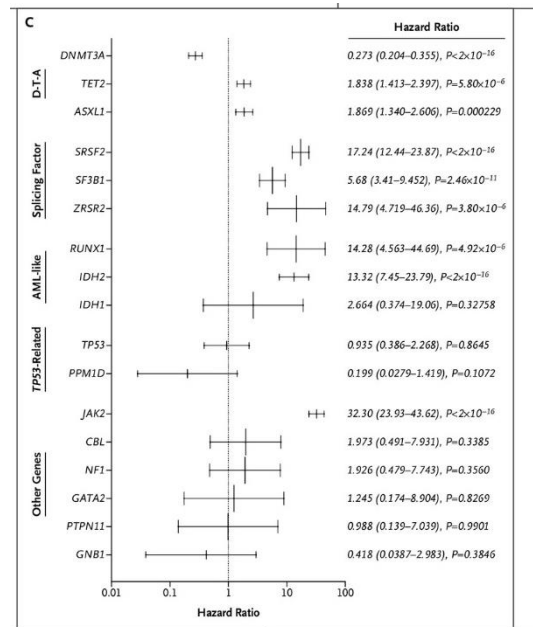
Characteristic	No CHIP/CCUS (n=182,406)	All CHIP/CCUS (n=11,337)	CHIP (n=10,479)	CCUS† (n=858)
Sex — no. (%)				
Female	100,200 (54.9)	6,235 (55.0)	5,818 (55.5)	417 (48.6)
Male	82,206 (45.1)	5,102 (45.0)	4,661 (44.5)	441 (51.4)
Age — median (IQR), yr				
	57.0 (50–63)	62.0 (57–66)	62.0 (57–66)	62.0 (56–66)
Follow-up — median (IQR), yr‡				
	11.7 (10.8–12.5)	11.6 (10.8–2.4)	11.6 (10.8–12.4)	11.2 (10.6–12.1)
Any smoking history — no. (%)				
Yes	102,085 (56.0)	5,703 (50.3)	5,272 (50.3)	431 (50.2)
No	80,322 (44.0)	5,634 (49.7)	5,207 (49.7)	427 (49.8)
Cancer history — no. (%)§				
Prior malignancy	9,844 (5.4)	908 (8.0)	818 (7.8)	90 (10.5)
No prior malignancy	172,562 (94.6)	10,429 (92.0)	9,804 (92.2)	768 (89.5)
Laboratory values and cytopenias¶				
White blood cell count (×10 <sup>9</sup> cells/l) — median (IQR)	6.68 (5.69–7.85)	6.84 (5.77–8.10)	6.90 (5.82–8.10)	6.28 (4.87–7.64)
Hemoglobin — median (IQR), g/dl	14.1 (13.3–15.0)	14.1 (13.4–15.0)	14.2 (13.5–15.1)	12.6 (11.7–14.0)
Platelets (×10 <sup>9</sup> cells/l) — median (IQR)	247 (213–286)	249 (213–289)	250 (216–290)	216 (142–284)
Neutrophil count (×10 <sup>9</sup> cells/l) — median (IQR)	4.03 (3.30–4.95)	4.16 (3.36–5.13)	4.20 (3.40–5.15)	3.67 (2.59–4.83)
No. of cytopenias — no. (%)				
0	169,801 (93.1)	10,479 (92.4)	10,479 (100)	0 (0)
1	12,106 (6.6)	797 (7.0)	0 (0)	797 (92.9)
2	464 (0.3)	57 (0.5)	0 (0)	57 (6.6)
3	35 (0.0)	4 (0.04)	0 (0)	4 (0.5)
Anemia — no. (%)				
No	174,878 (95.9)	10,837 (95.6)	10,479 (100)	358 (41.7)
Yes	7,528 (4.1)	500 (4.4)	0 (0)	500 (58.3)
Thrombocytopenia — no. (%)				
No	178,330 (97.8)	11,040 (97.4)	10,479 (100)	561 (65.4)
Yes	4,076 (2.2)	297 (2.6)	0 (0)	297 (34.6)
Neutropenia — no. (%)				
No	18,0871 (99.2)	11,211 (98.9)	10,479 (100)	732 (85.3)
Yes	1,535 (0.8)	126 (1.1)	0 (0)	126 (14.7)
Mean corpuscular volume — median (IQR), fl	91.3 (88.6–93.9)	91.4 (88.8–94.1)	91.4 (88.9–94.1)	90.6 (86.7–94.1)
Mean platelet volume — median (IQR), fl	9.20 (8.58–9.94)	9.18 (8.51–9.92)	9.15 (8.50–9.90)	9.47 (8.70–10.60)
Red cell distribution width — median (IQR), %	13.3 (12.9–13.9)	13.4 (13.0–14.0)	13.4 (12.9–13.9)	14.0 (13.3–15.1)

- UK Biobank: > 400.000 Individuen
- CHIP screening basierend auf whole-exome Daten
- Aufgeteilt in Discovery- und Validierungs-Kohorte
- Prävalenz von CHIP/CCUS: 6.5%



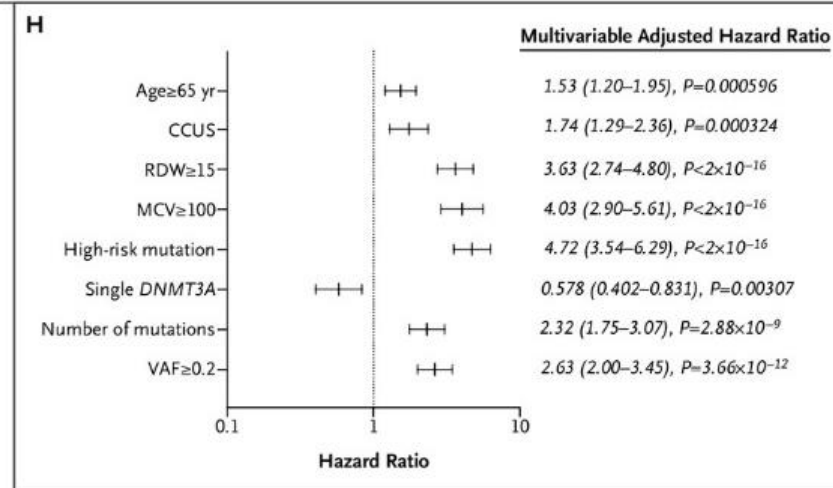
**Number at Risk**

Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254

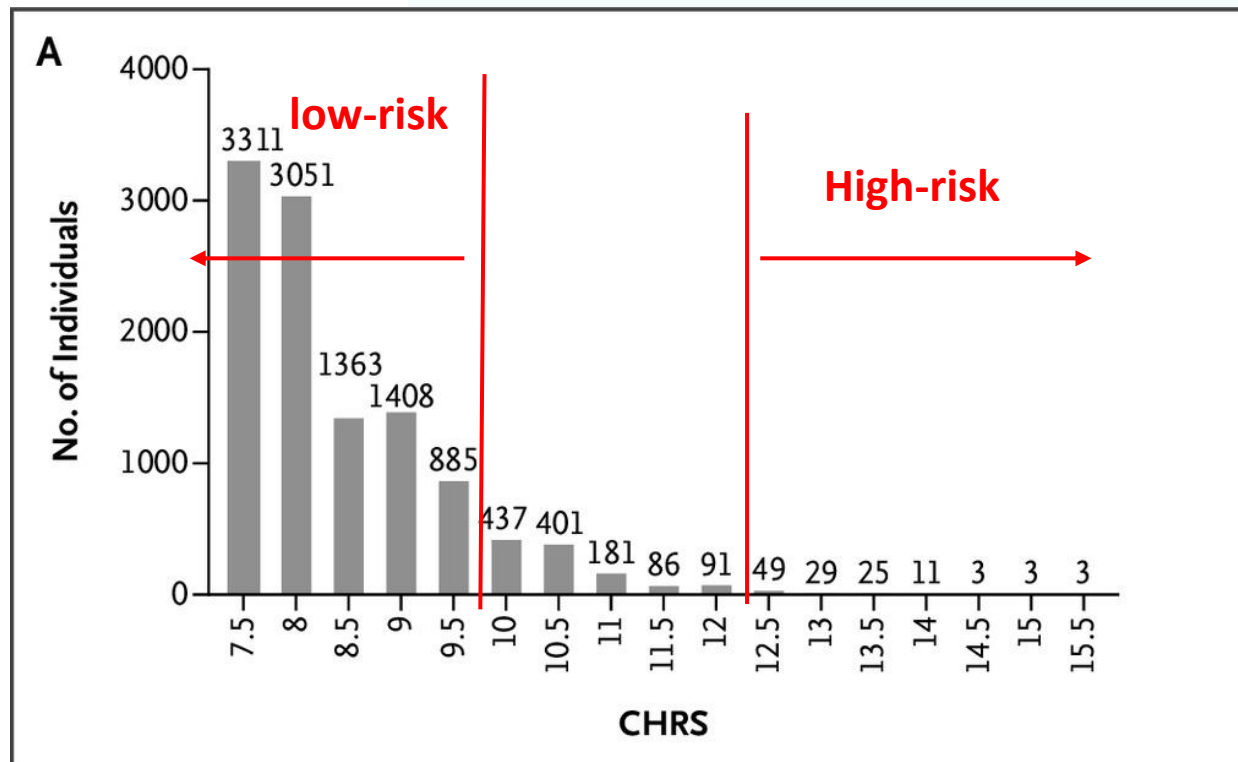


**Number at Risk**

Time (yr)	0	2	4	6	8	10	12
Single DNMTA	6,235	6,200	6,114	6,042	5,948	5,835	2,476
Other CHIP/CCUS	5,102	5,041	4,922	4,809	4,668	4,517	1,945
No CHIP/CCUS	182,407	181,674	180,407	178,734	176,774	174,453	72,254



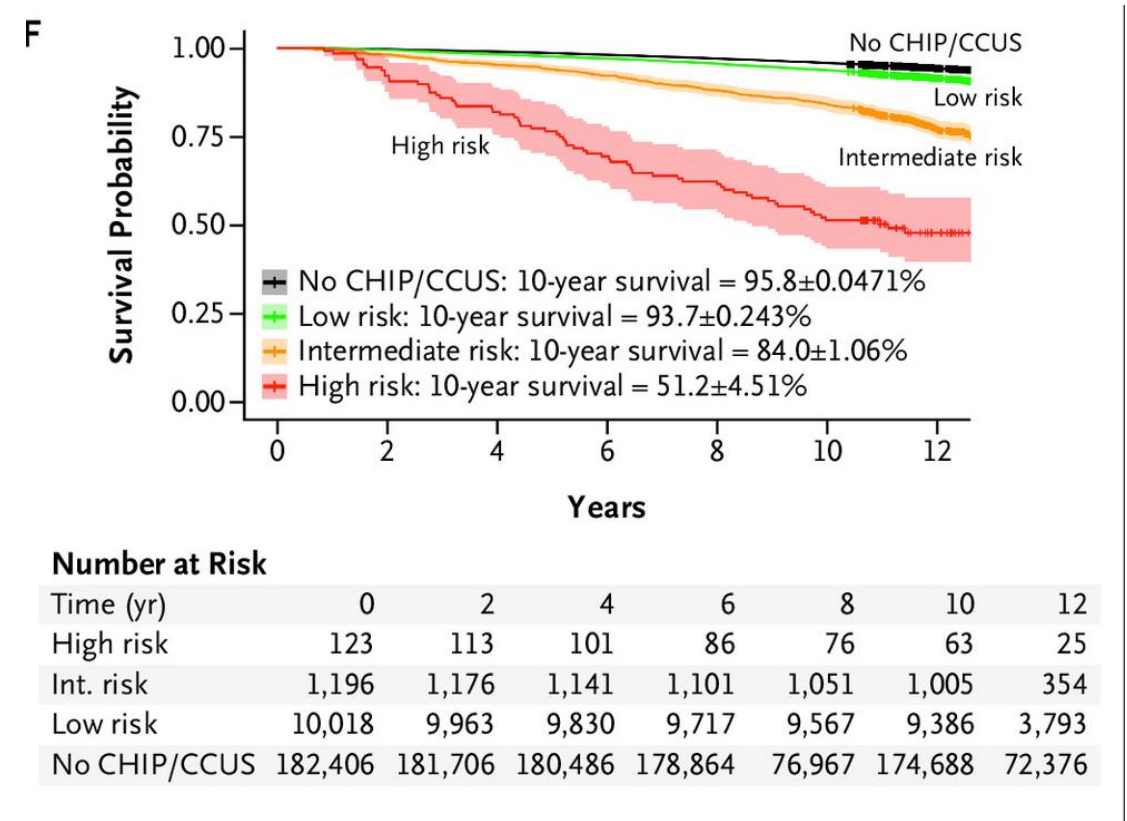
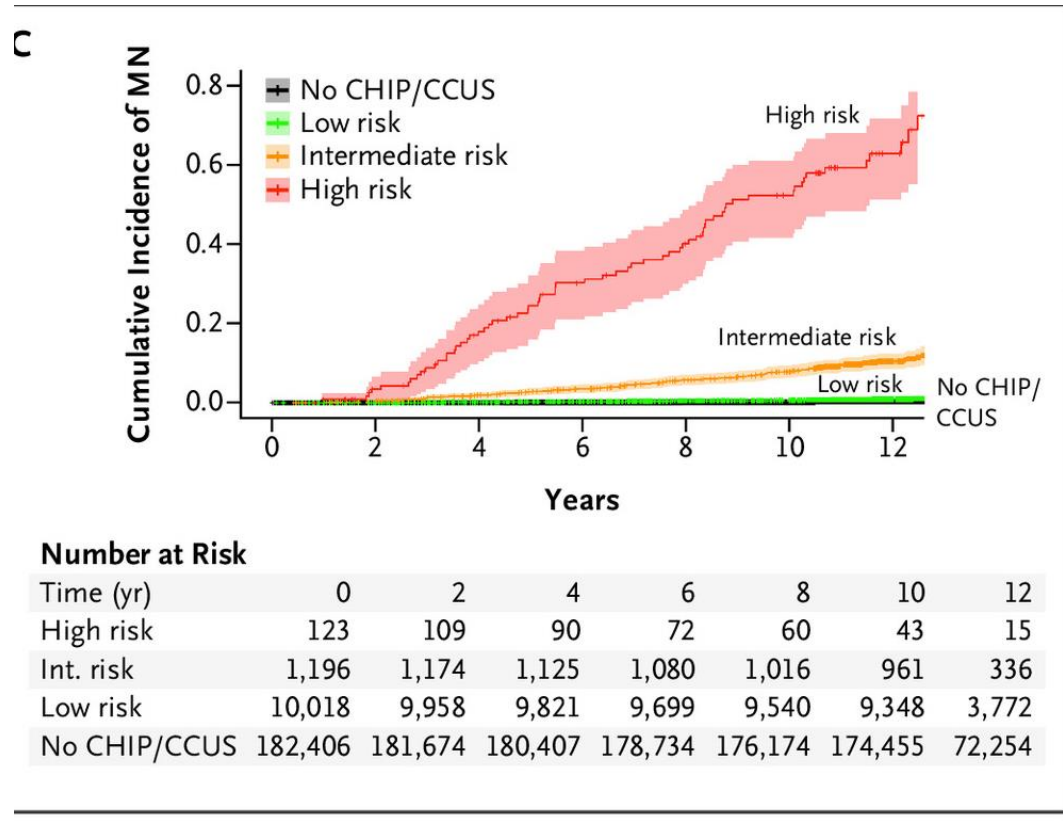
Prognostic Variable	0.5	1	1.5
Single <i>DNMT3A</i>	Present	Absent	
High-risk mutation		Absent	
Mutation number		1	
Variant allele fraction		<0.2	
Red cell distribution width		<15	
Mean corpuscular volume		<100	
	CHIP	CCUS	
	<65	≥65	



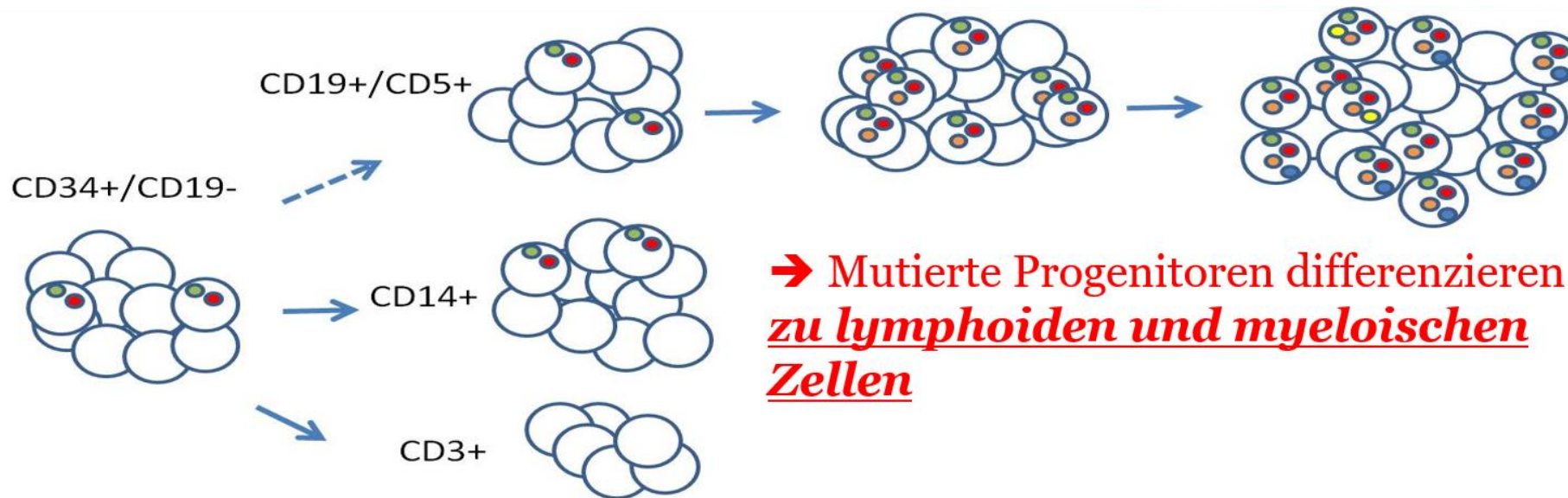
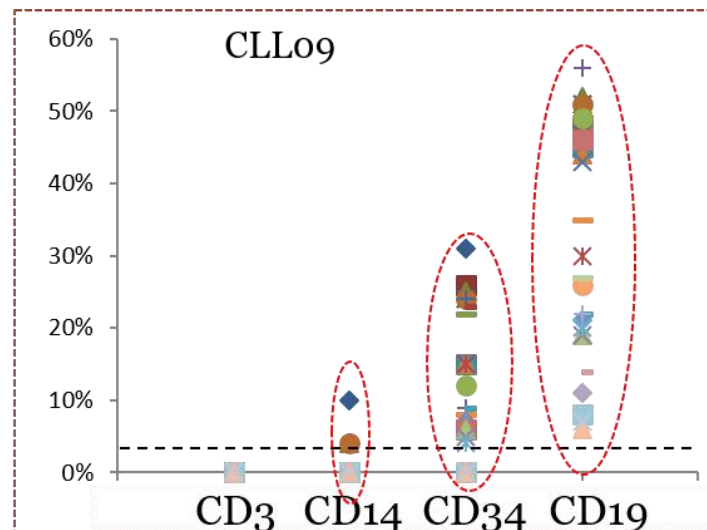
**B**

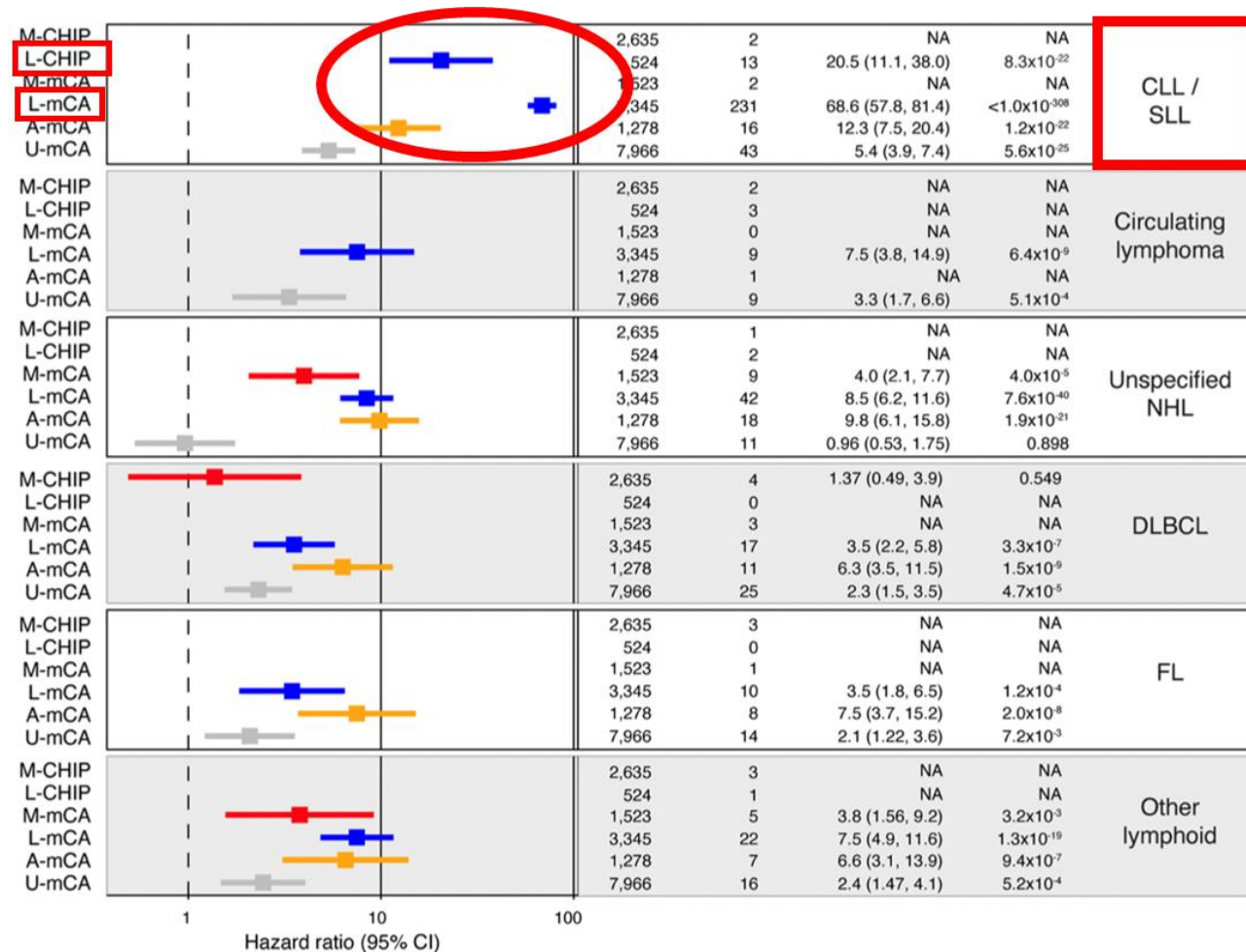
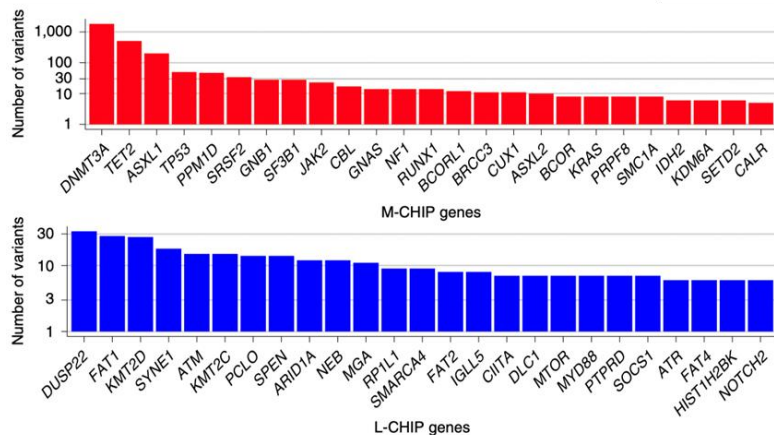
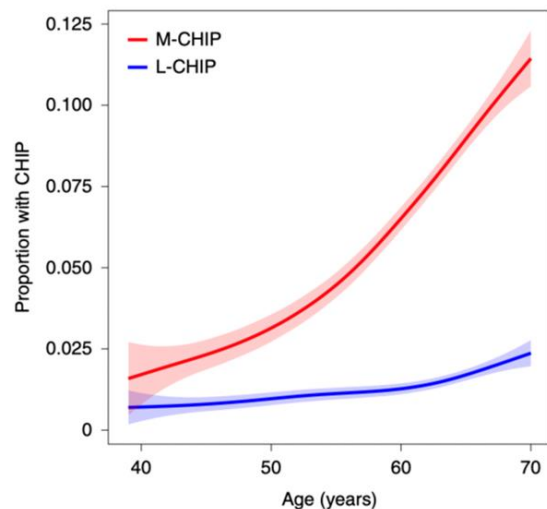
**Risk Categories Defined by CHRS**

Risk Category	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	1,196	112 (9.36%)	2.76±0.482%	7.83±0.807%
Low	≤9.5	10,018	90 (0.90%)	0.232±0.0484%	0.669±0.0827%
No CHIP/CCUS	NA	182,406	495 (0.27%)	0.0740±0.00640%	0.210±0.0108%



14/24 CLL (58%)

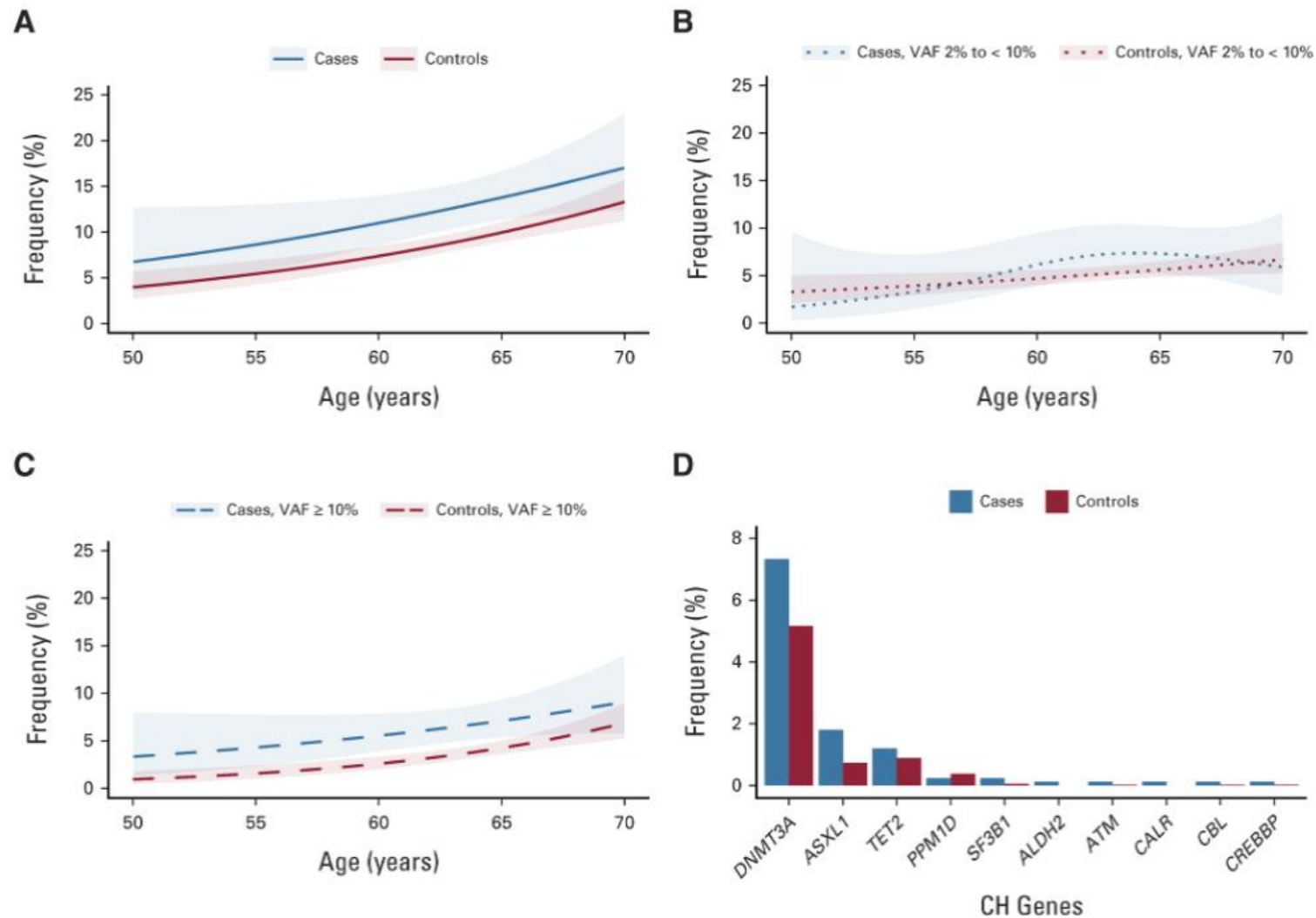




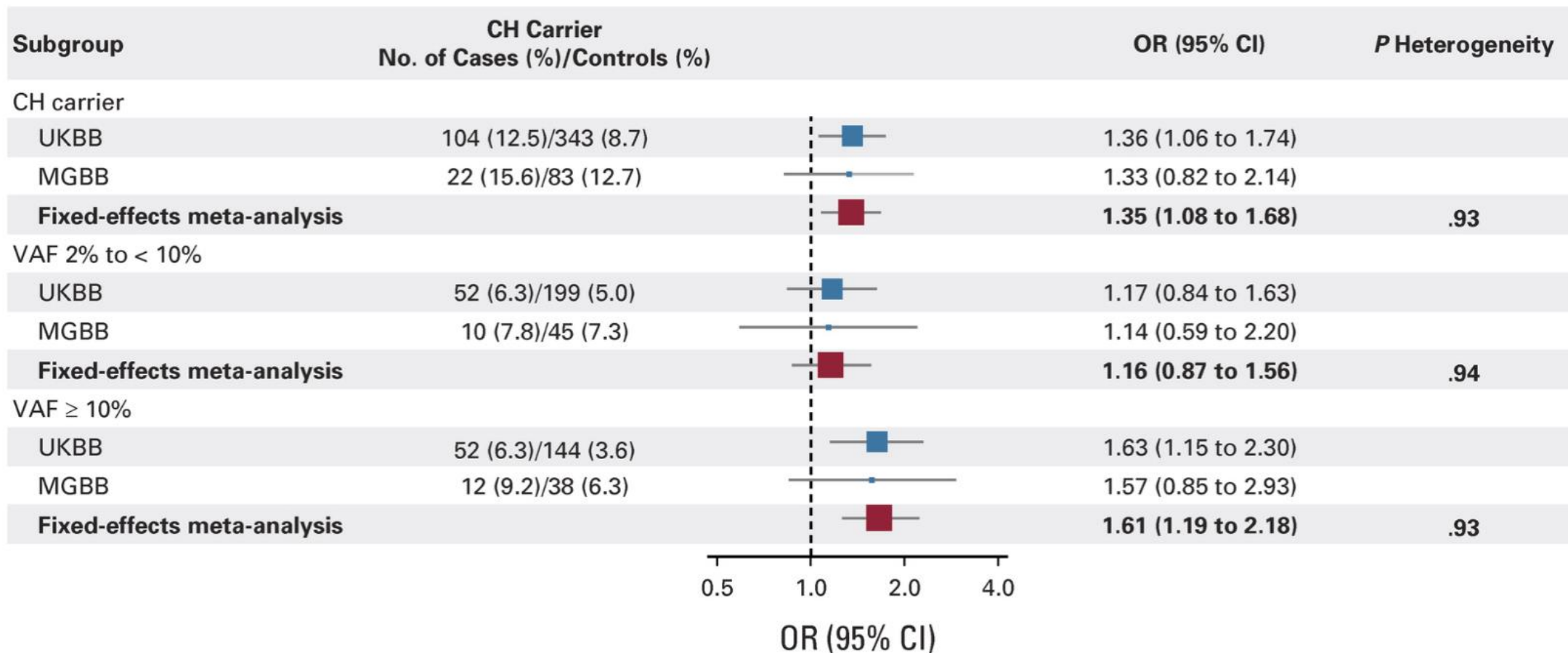
Whole blood DNA **Whole Exome Sequencing** (n = 55,383) and **SNP-array** data (n= 420,969) from healthy individuals in the UK Biobank (UKB) and in the Mass General Brigham Biobank (MGBB).

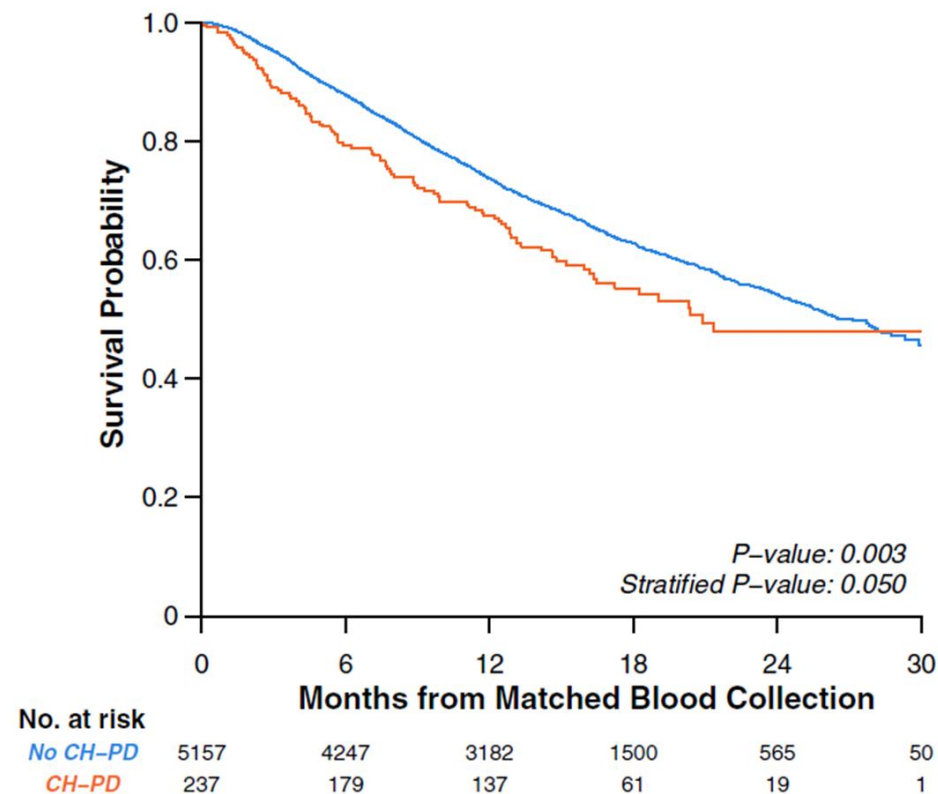
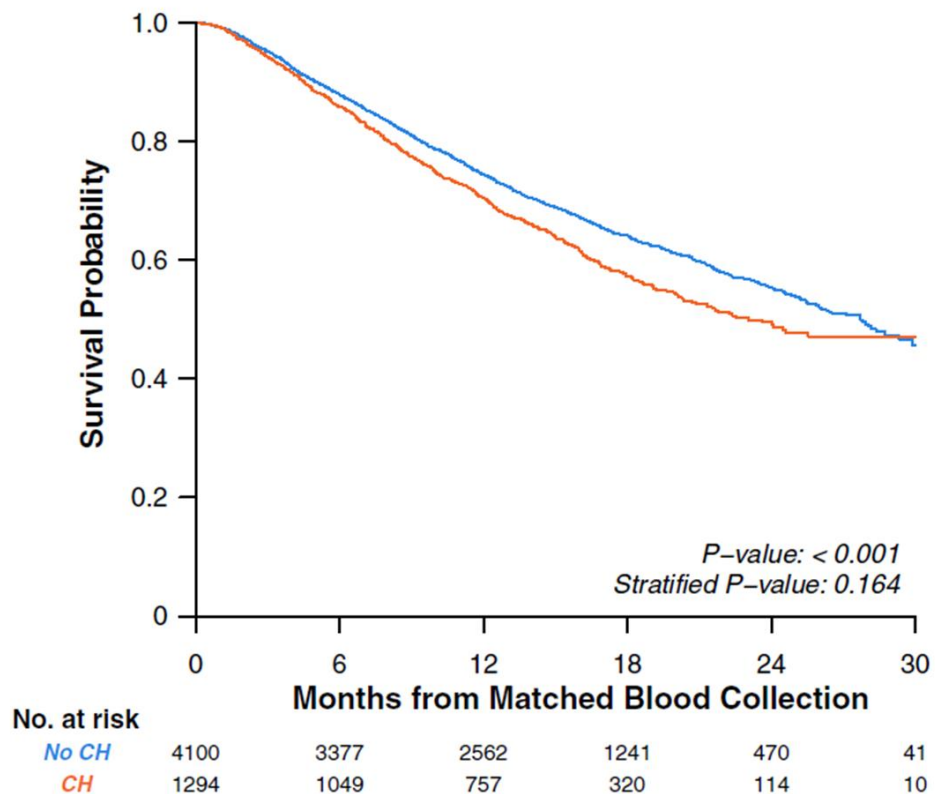


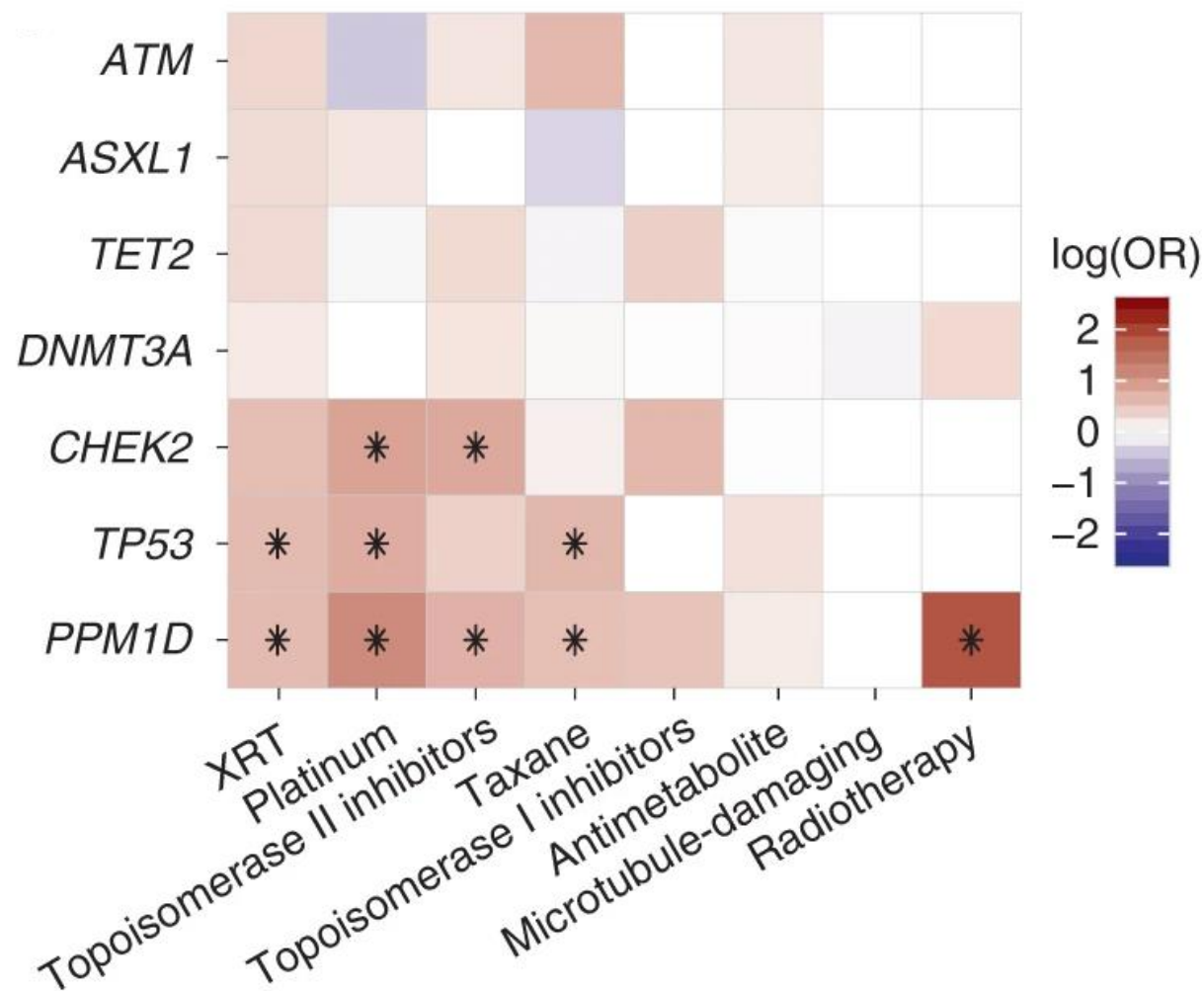
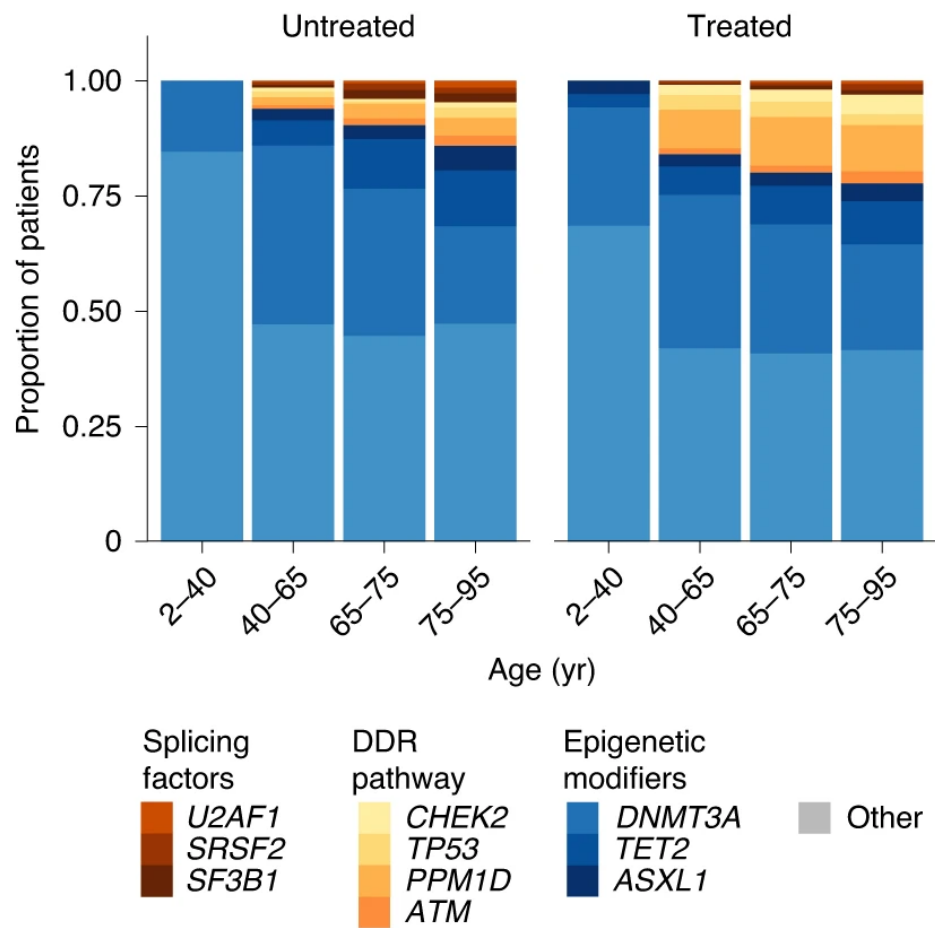
Nested case-control study UK biobank: 832 incident lung cancer cases and 3,951 controls



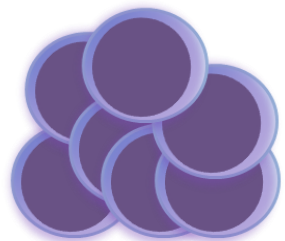
Nested case-control study UK biobank: 832 incident lung cancer cases and 3,951 controls  
Control cohort Mass General Brigham biobank: 141 cases and 652 controls



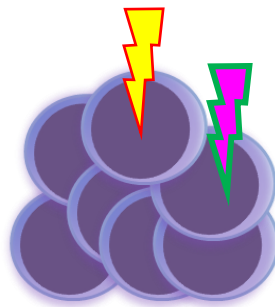
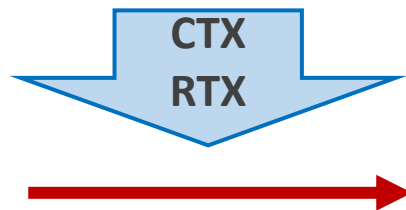




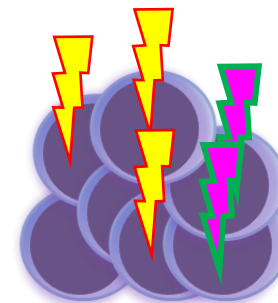
## „Klassisches“ Modell



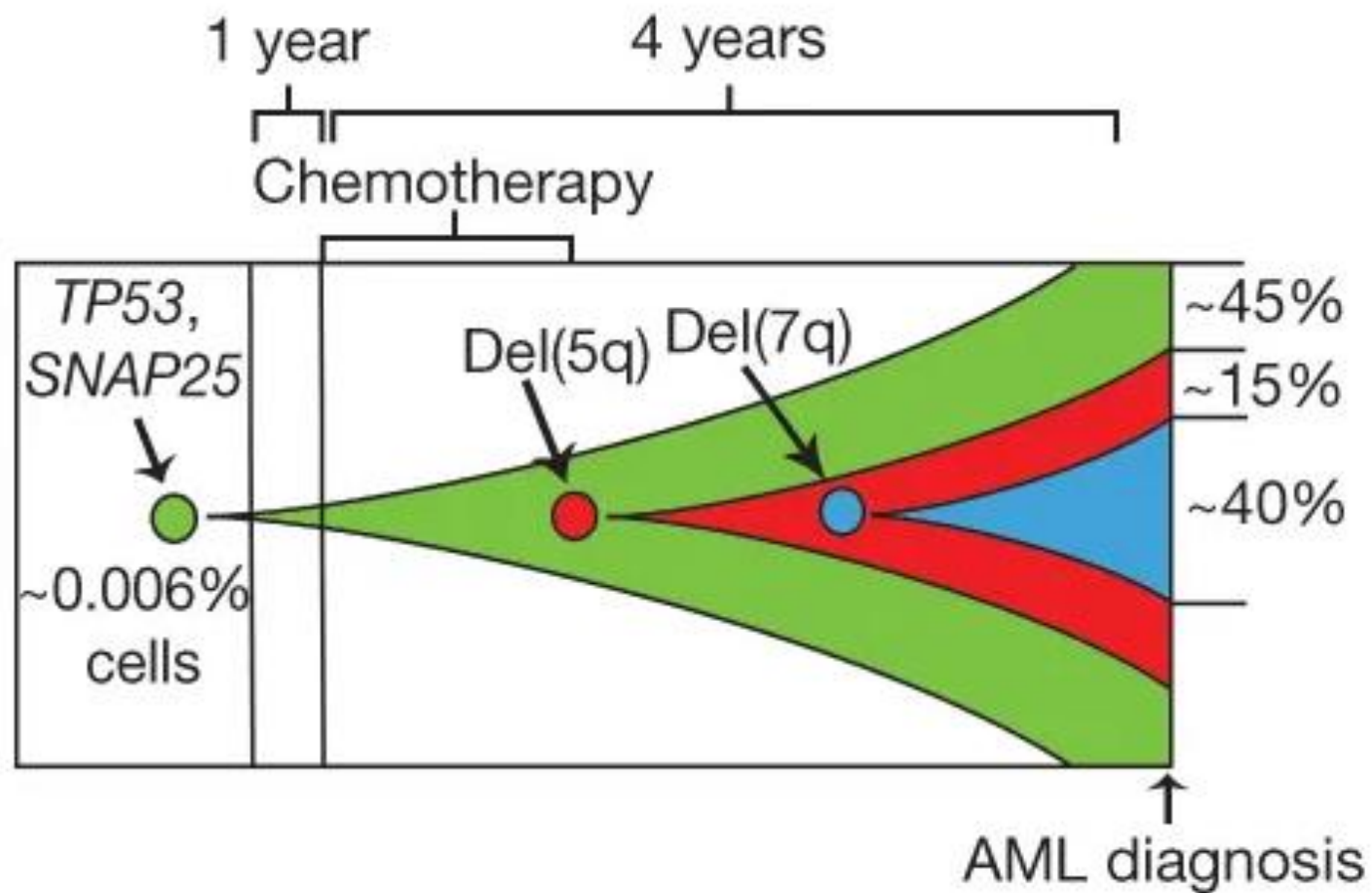
Gesunde HSC



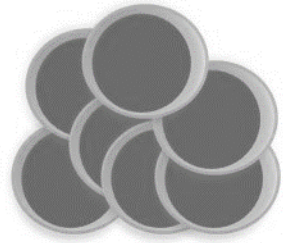
Induktion von Mutationen  
durch Chemo/Radiatio



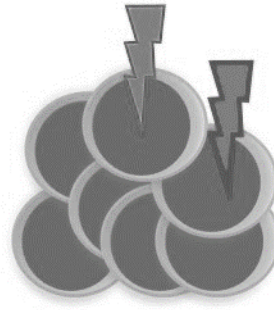
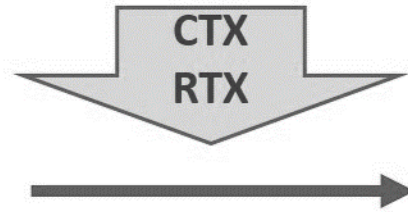
t-MN



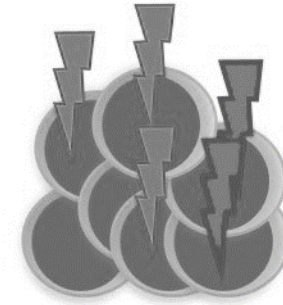
## „Klassisches“ Modell



Gesunde HSC

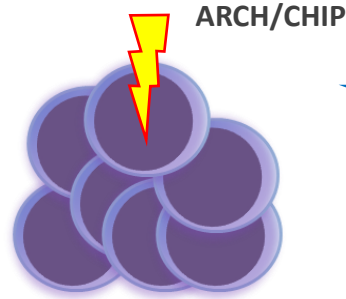


Induktion von Mutationen  
durch Chemo/Radiatio

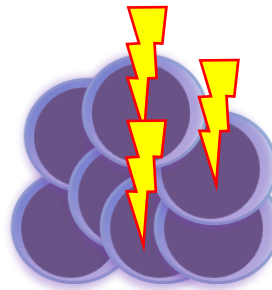
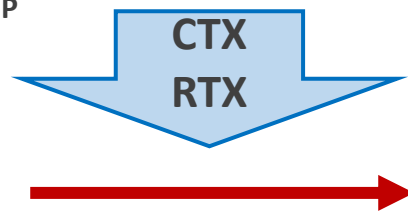


t-MN

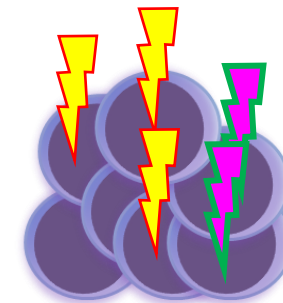
## Neues/alternatives Modell



Prä-therapeutisches CHIP/ARCH



Fitness Vorteil von CHIP/ARCH,  
Klonale Expansion



Weitere Mutationen,  
t-MN

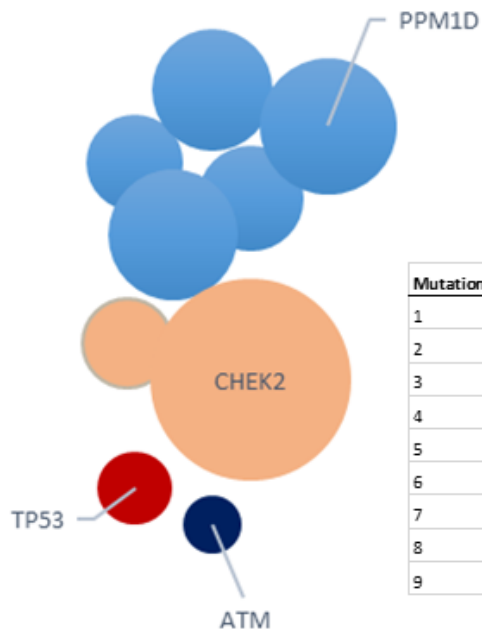
JAMA Oncology | **Original Investigation**

## Preexisting *TP53*-Variant Clonal Hematopoiesis and Risk of Secondary Myeloid Neoplasms in Patients With High-grade Ovarian Cancer Treated With Rucaparib

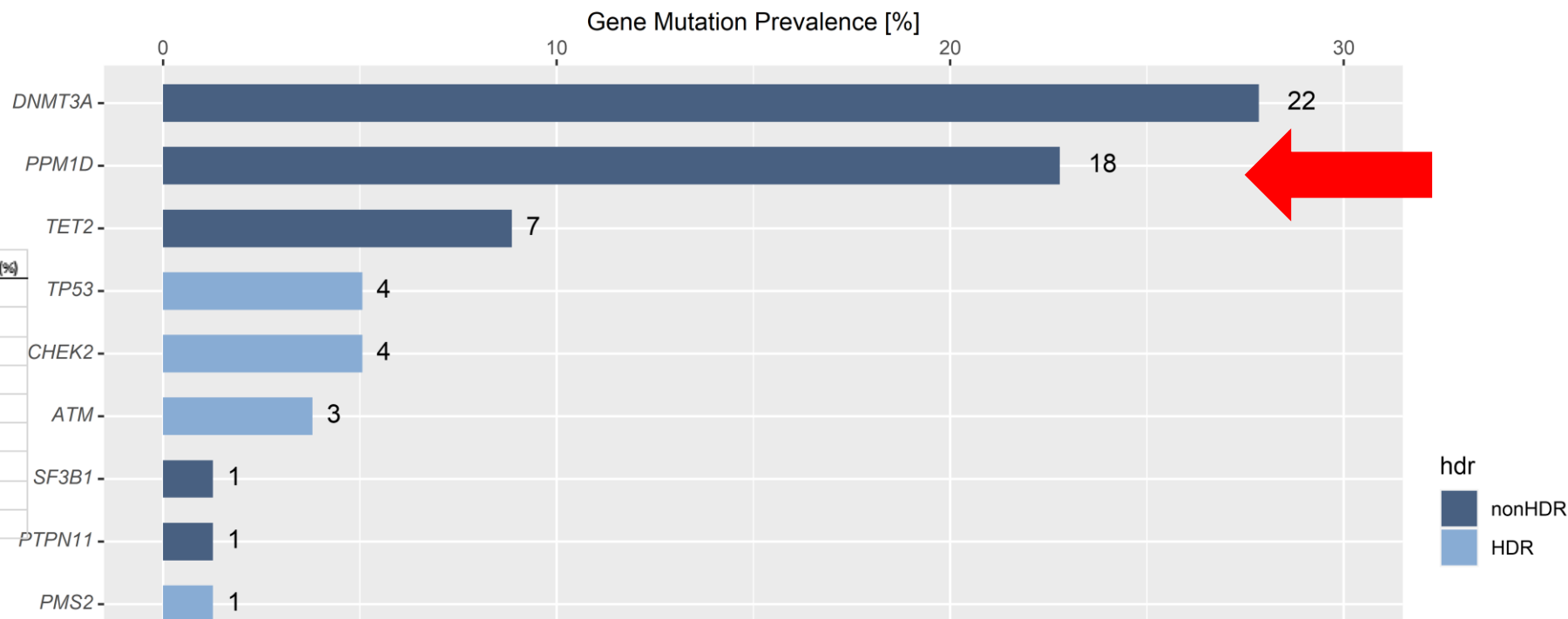
Tanya T. Kwan, PhD; Amit M. Oza, MD; Anna V. Tinker, MD; Isabelle Ray-Coquard, MD, PhD; Ana Oaknin, MD, PhD; Carol Aghajanian, MD, PhD; Domenica Lorusso, MD, PhD; Nicoletta Colombo, MD, PhD; Andrew Dean, MD; Johanne Weberpals, MD; Eric Severson, MD, PhD; Lan-Thanh Vo, BS; Sandra Goble, MS; Lara Maloney, BA; Thomas Harding, PhD; Scott H. Kaufmann, MD, PhD; Jonathan A. Ledermann, MD; Robert L. Coleman, MD; Iain A. McNeish, MD, PhD; Kevin K. Lin, PhD; Elizabeth M. Swisher, MD

- 22/1052 Patientinnen der ARIEL2 und ARIEL3 Studien entwickelten eine t-MN (2.1%).
- Eine längere **Platin-Exposition, das Vorhandensein HRR Mutationen und KH** mit einer TP53-Mutation waren mit der Entwicklung einer t-MN assoziiert

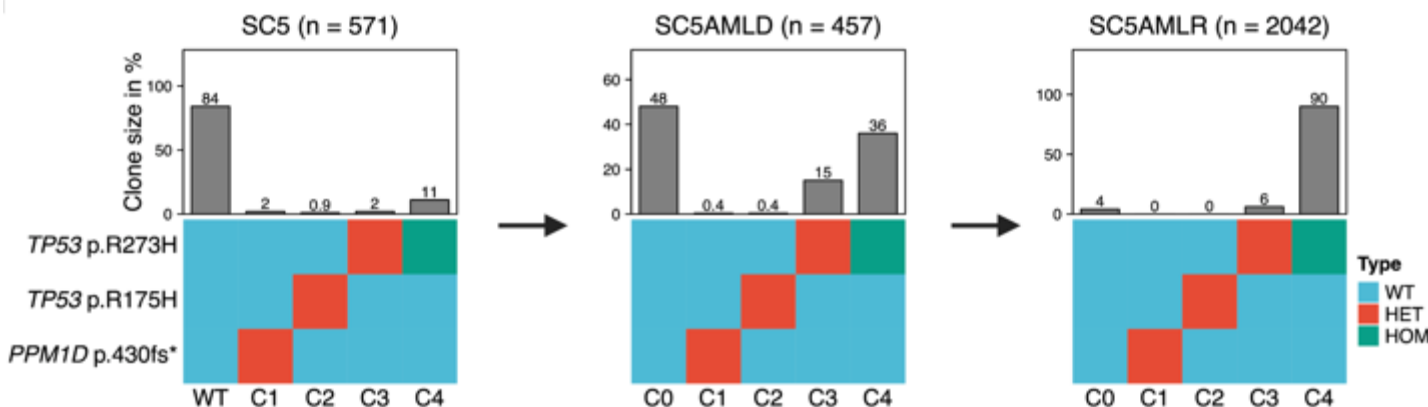




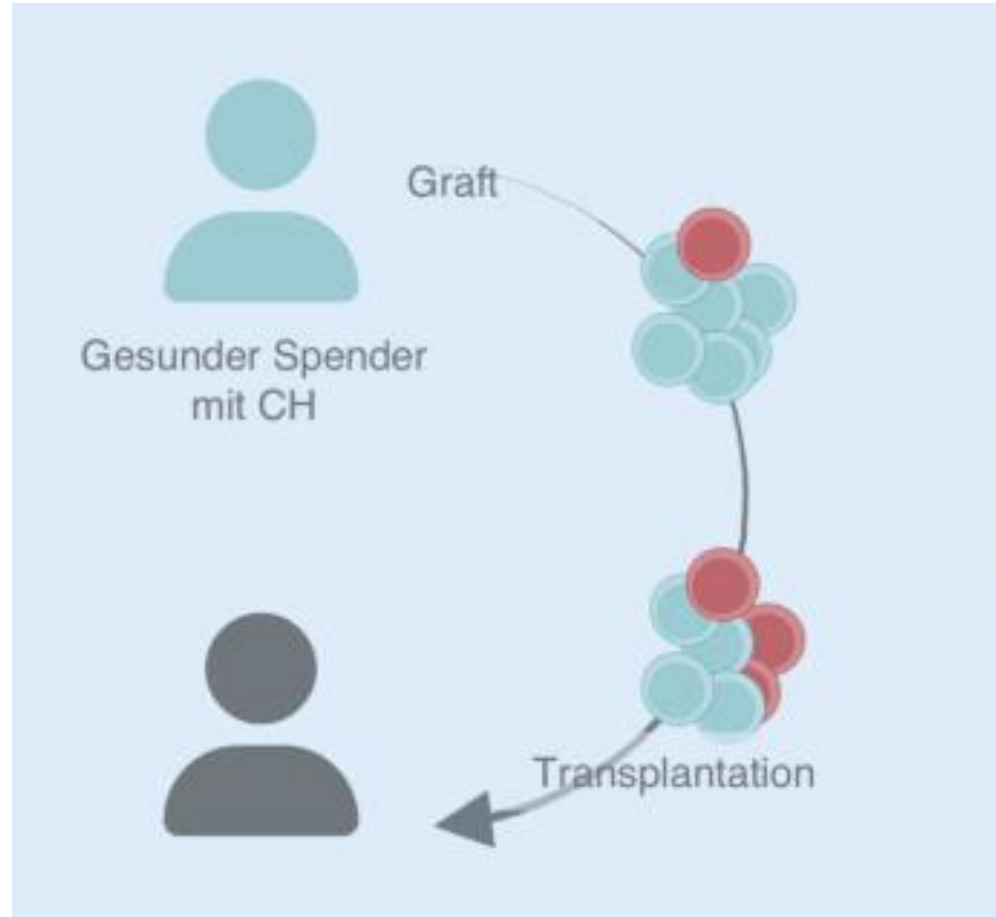
Mutation	Gene	VAF (%)
1	PPM1D	1,36
2	PPM1D	2,18
3	PPM1D	1,66
4	PPM1D	2,49
5	PPM1D	2,76
6	CHEK2	1,16
7	CHEK2	5,97
8	TP53	0,8
9	ATM	0,51



hdr  
 nonHDR  
 HDR



# KH und allogene Stammzelltransplantation

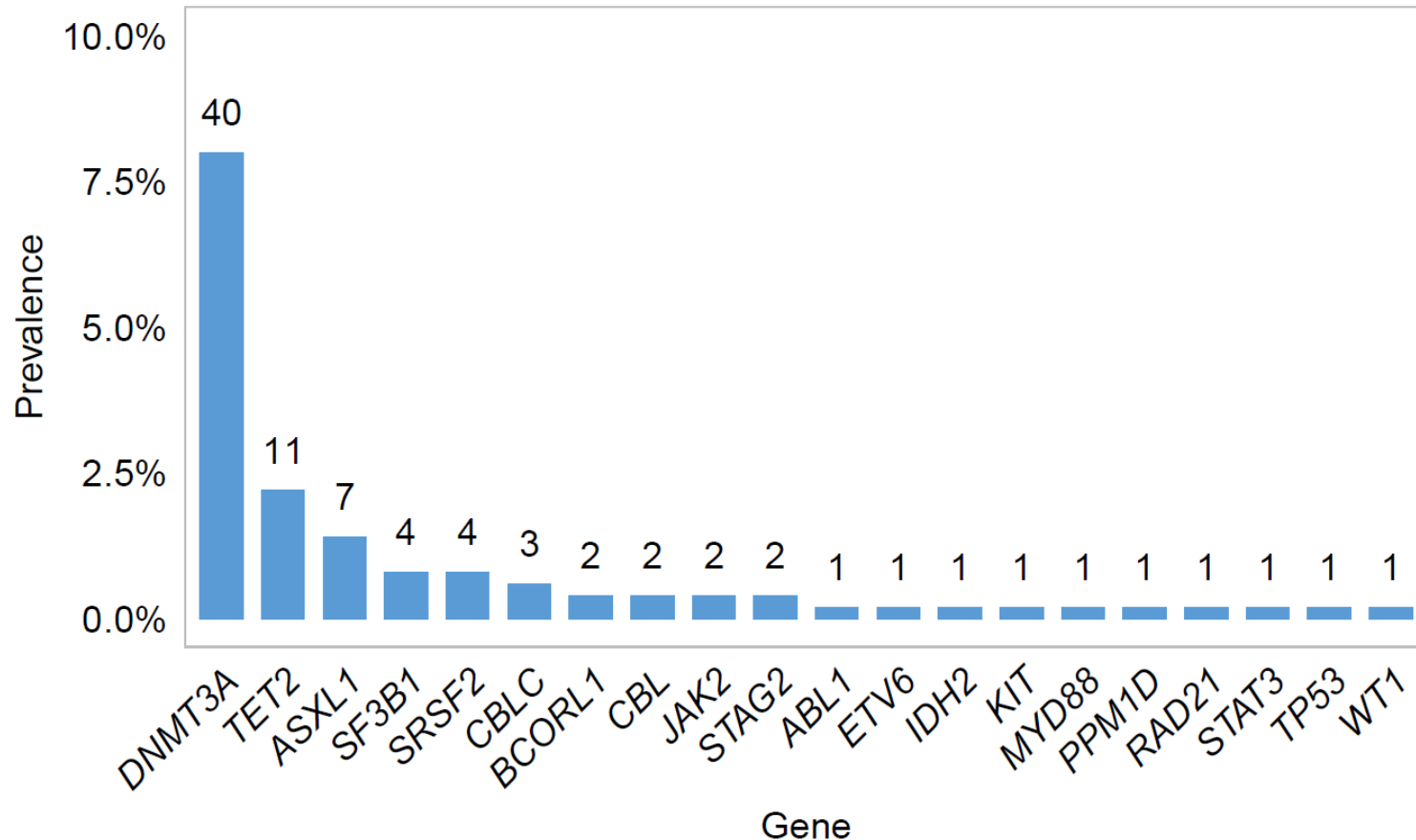


## Allogene SZT

- Therapiebedingte myeloische Neoplasien
- Spender-bedingte Leukämie (DDL)
- Kardiovaskuläre Ereignisse (Myokardinfarkt, Schlaganfall, Thrombose)
- Rezidiv der Grunderkrankung
- **Transplantatversagen**
- **Immunsuppression (Infektionsneigung)**
- **Chronische Graft-versus-Host-Disease (cGvHD)**

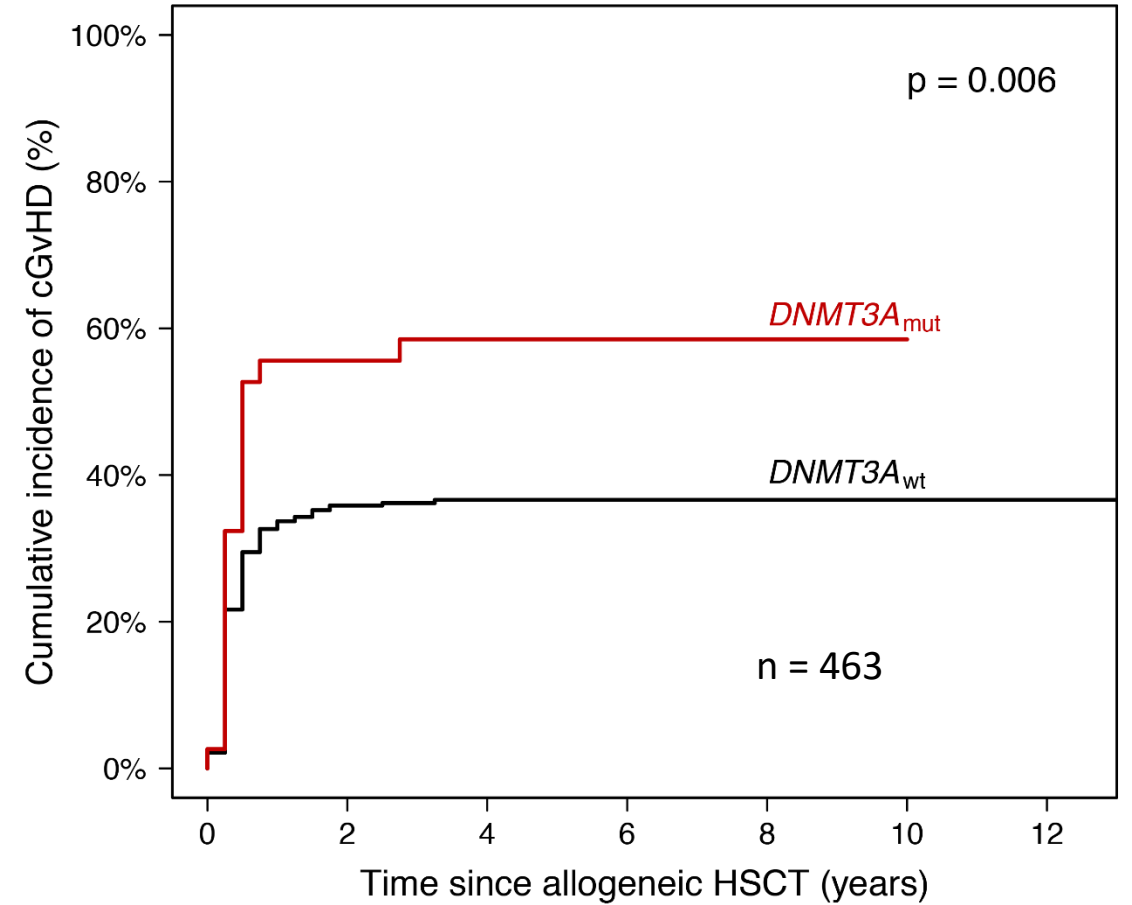
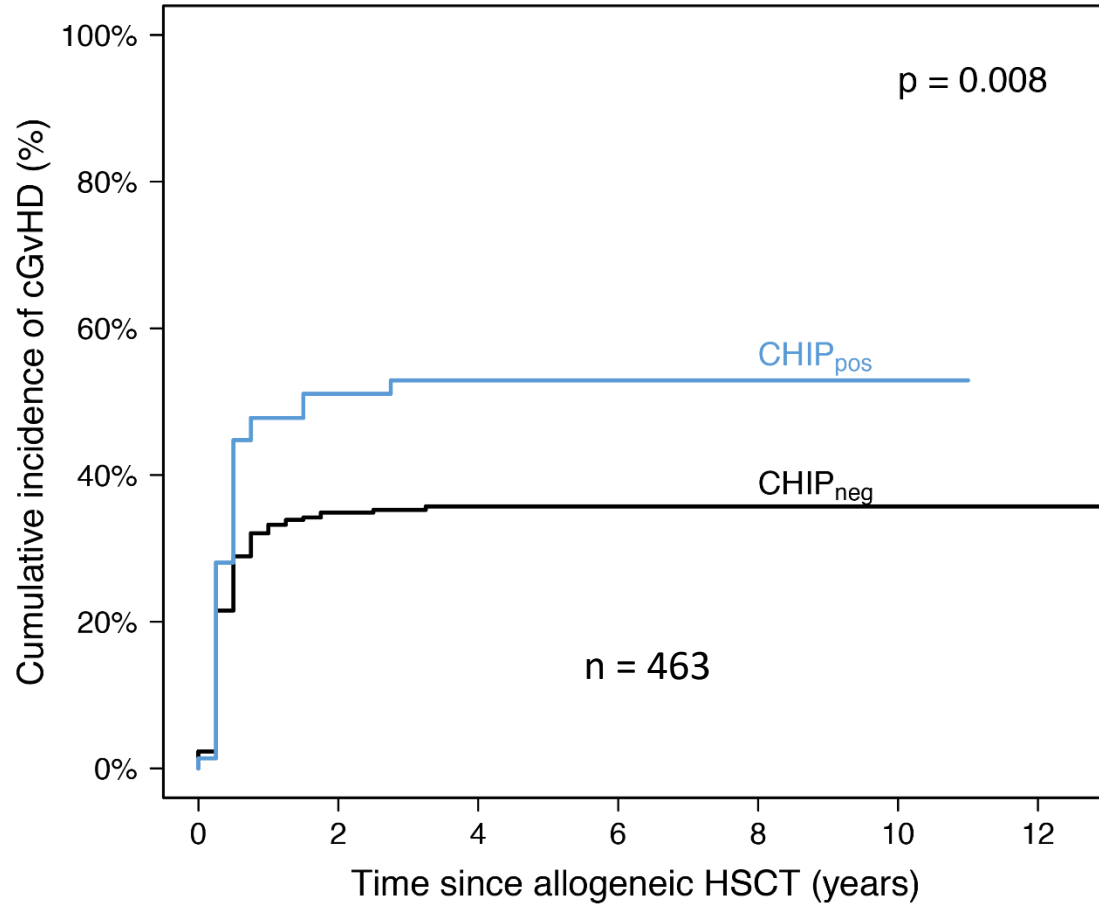
# Sequenziererergebnisse der Spender

92 validierte Mutationen in 500 Spendern (Spender-CHIP Prävalenz = 16.0%)

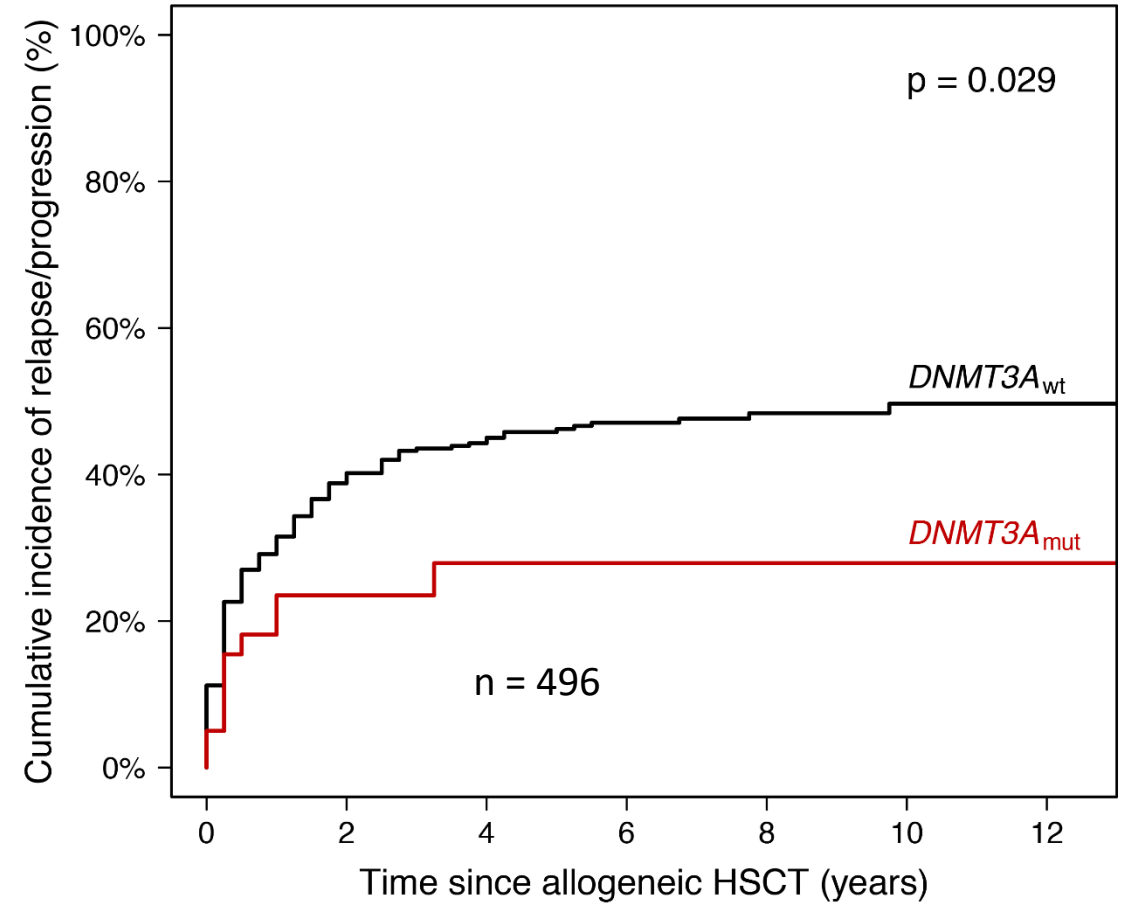
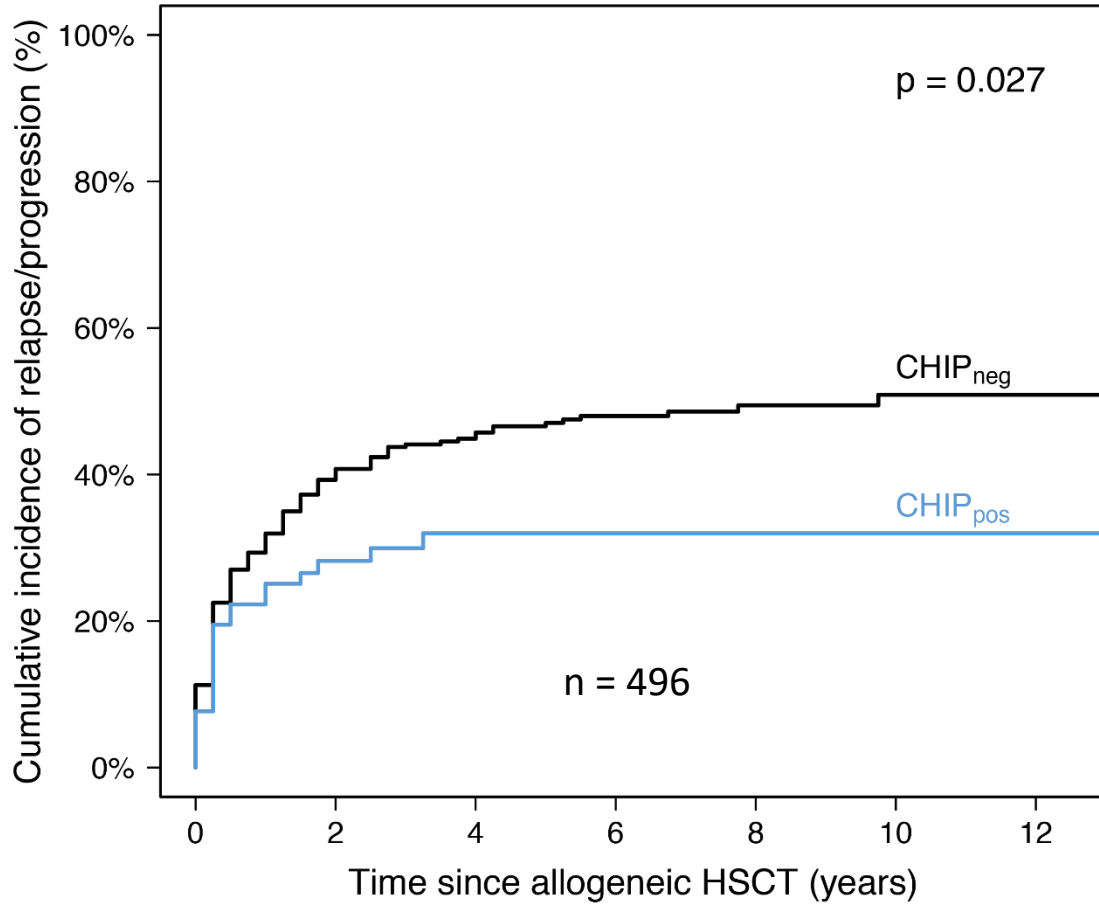


- Mediane VAF 5.9% (Spanne 2 – 43%)
- 25 Mutationen in 20 Patienten mit einer VAF  $\geq 10\%$
- Anzahl der Mutationen pro Spender:
  - Eine Mutation: 70 Spender
  - Zwei Mutationen: 9 Spender
  - Vier Mutationen: 1 Spender
- Häufige Ko-Mutationen:
  - *DNMT3A/DNMT3A* (n=4)
  - *DNMT3A/ASXL1* (n=3)

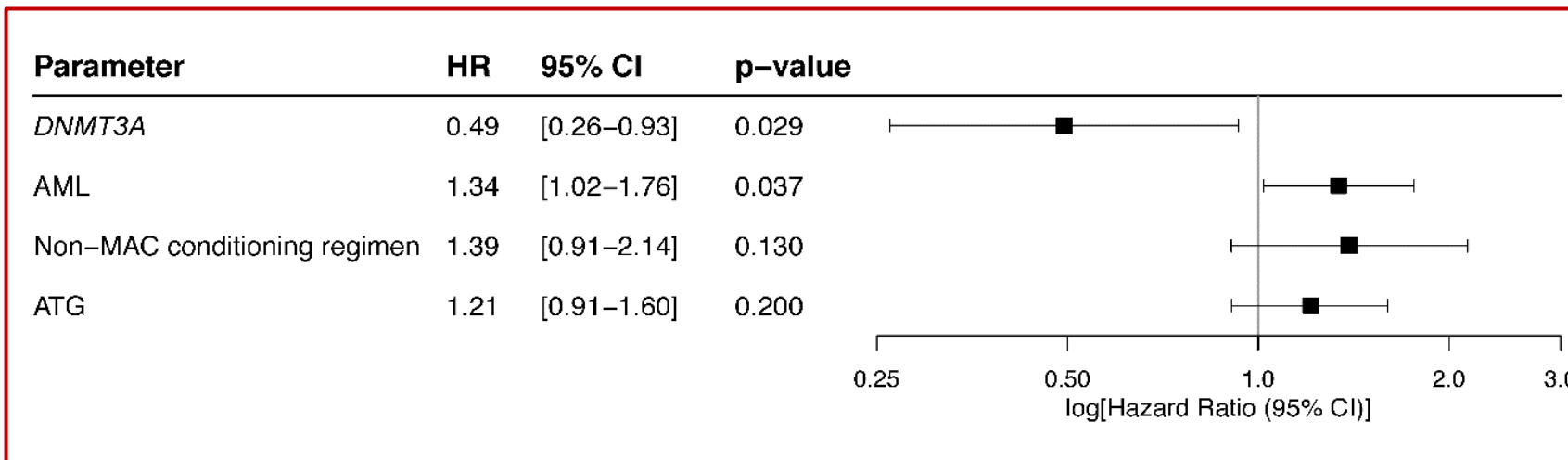
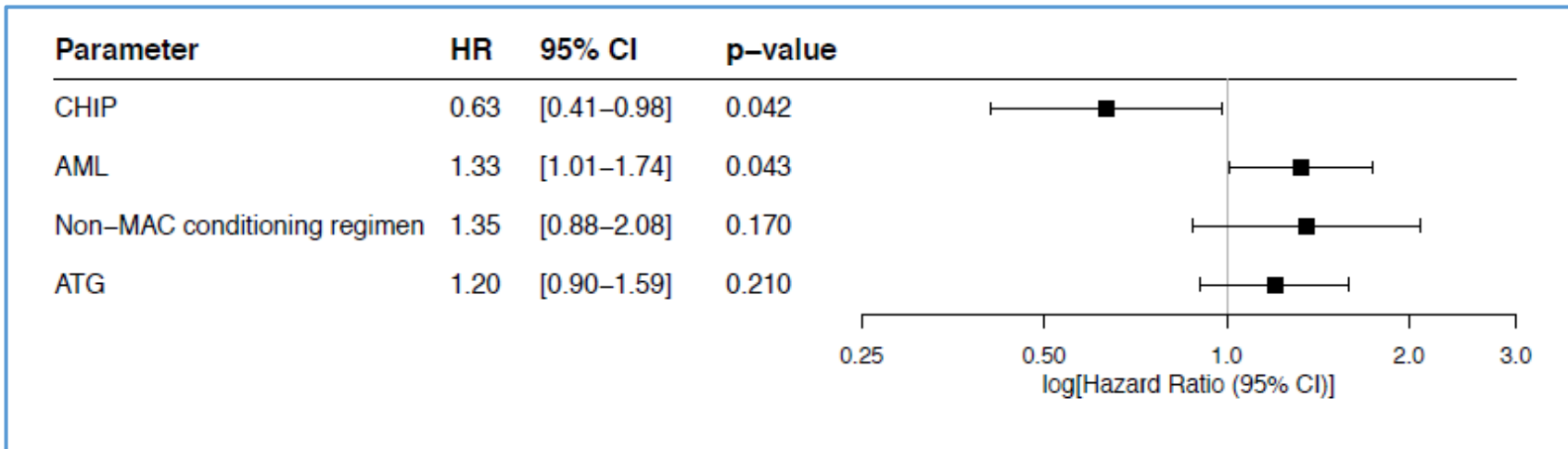
# Transplantations-Outcome: cGvHD



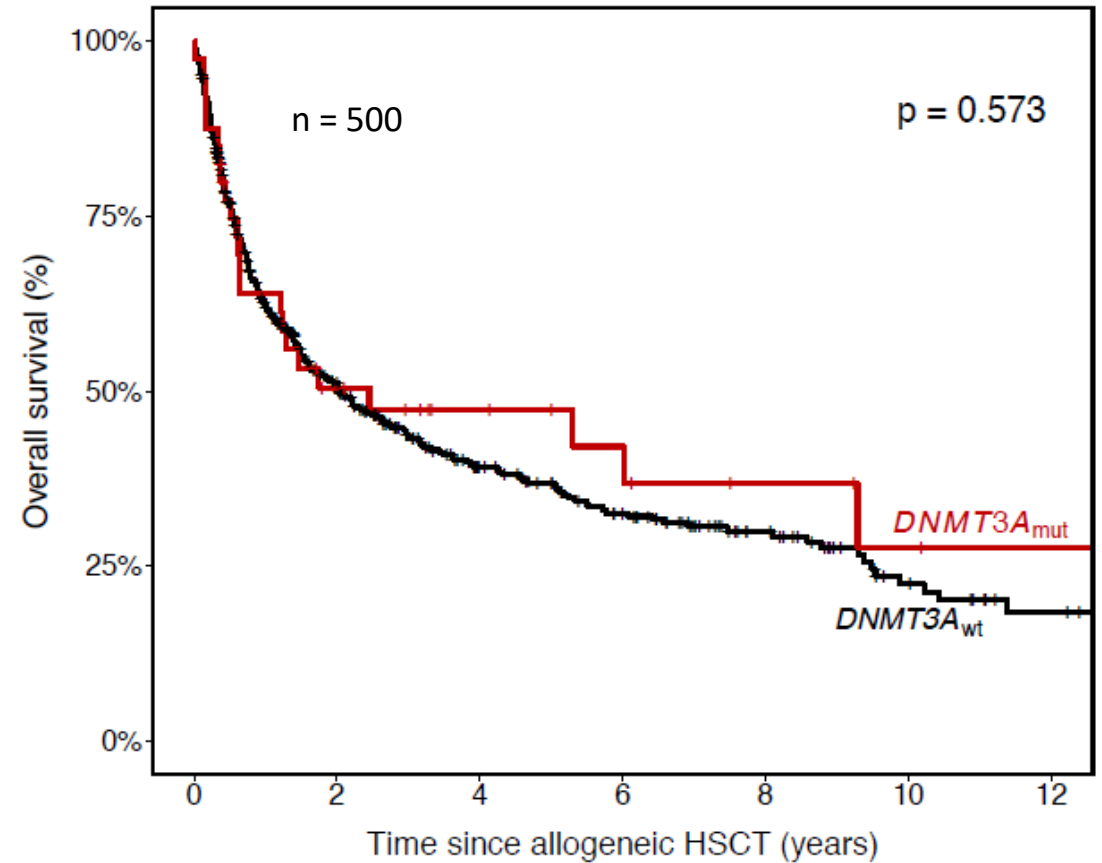
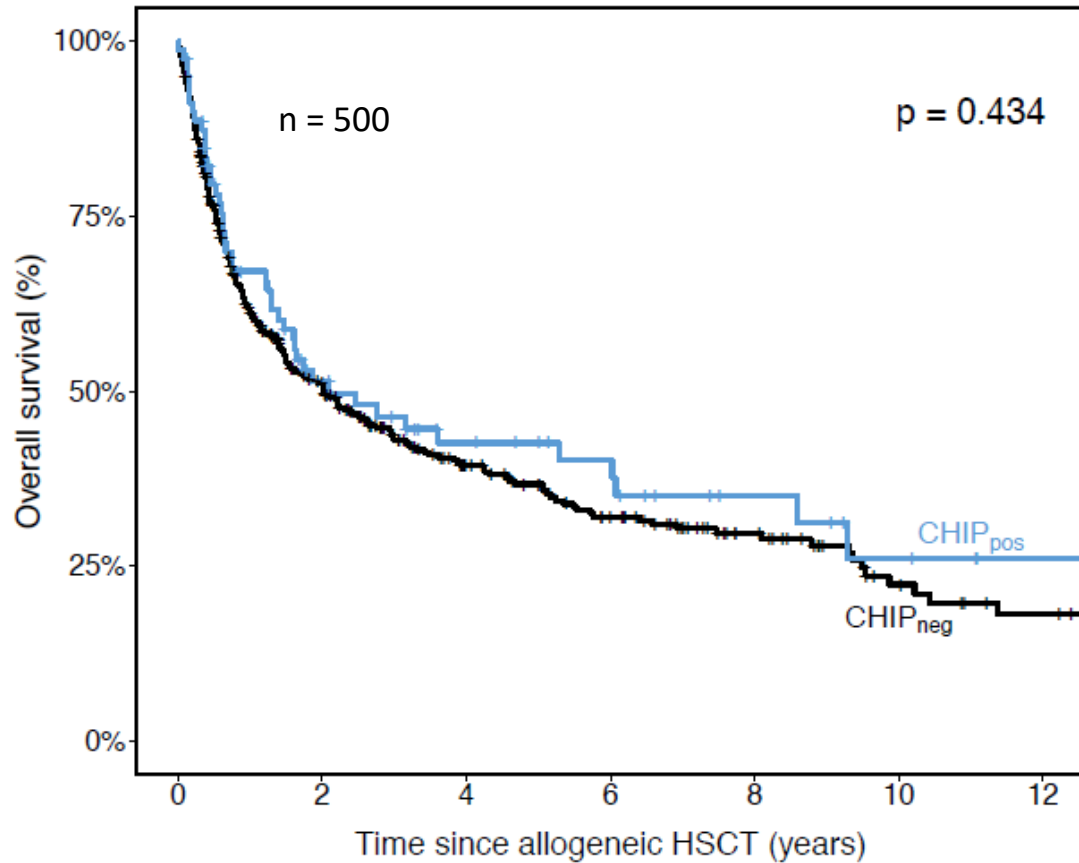
# Transplantations-Outcome: Cumulative Incidence of Relapse/Progression (CIRP)



# Transplantations-Outcome: Cumulative Incidence of Relapse/Progression (CIRP)

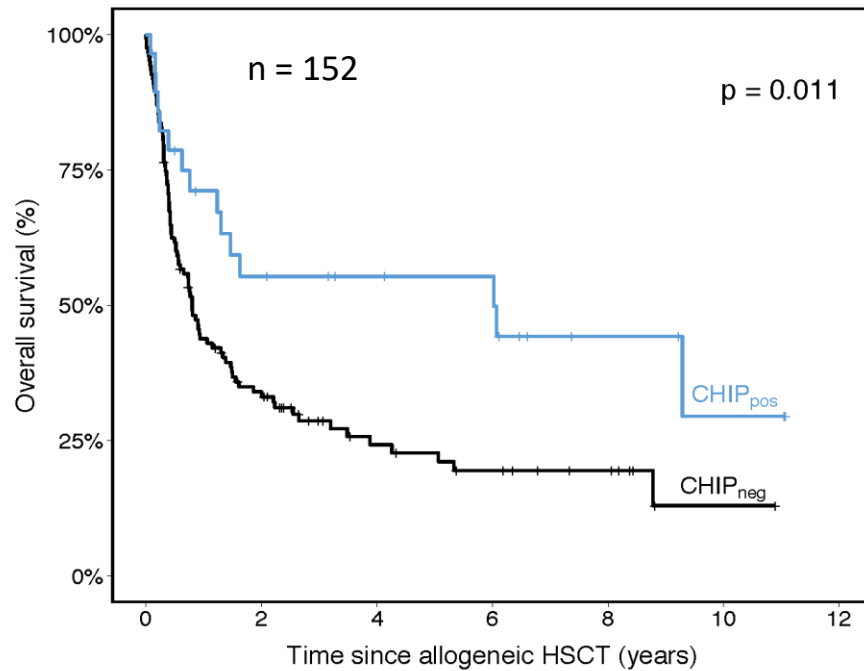


# Transplantations-Outcome: Gesamtüberleben

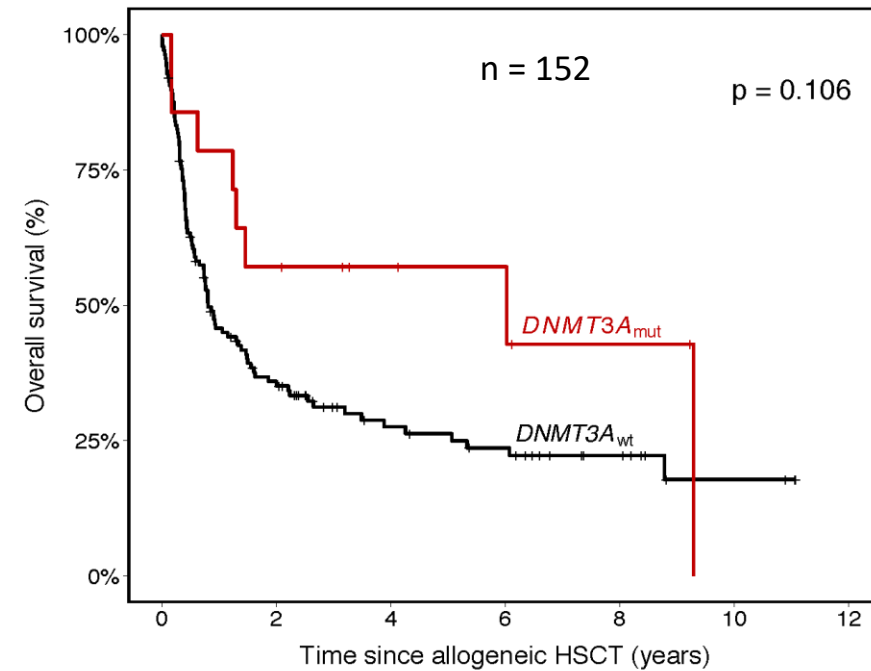


CHIP/*DNMT3A* Mutationsstatus hat keinen negativen Einfluss auf das Überleben

# Transplantations-Outcome: Gesamtüberleben AML/MDS in non-CR



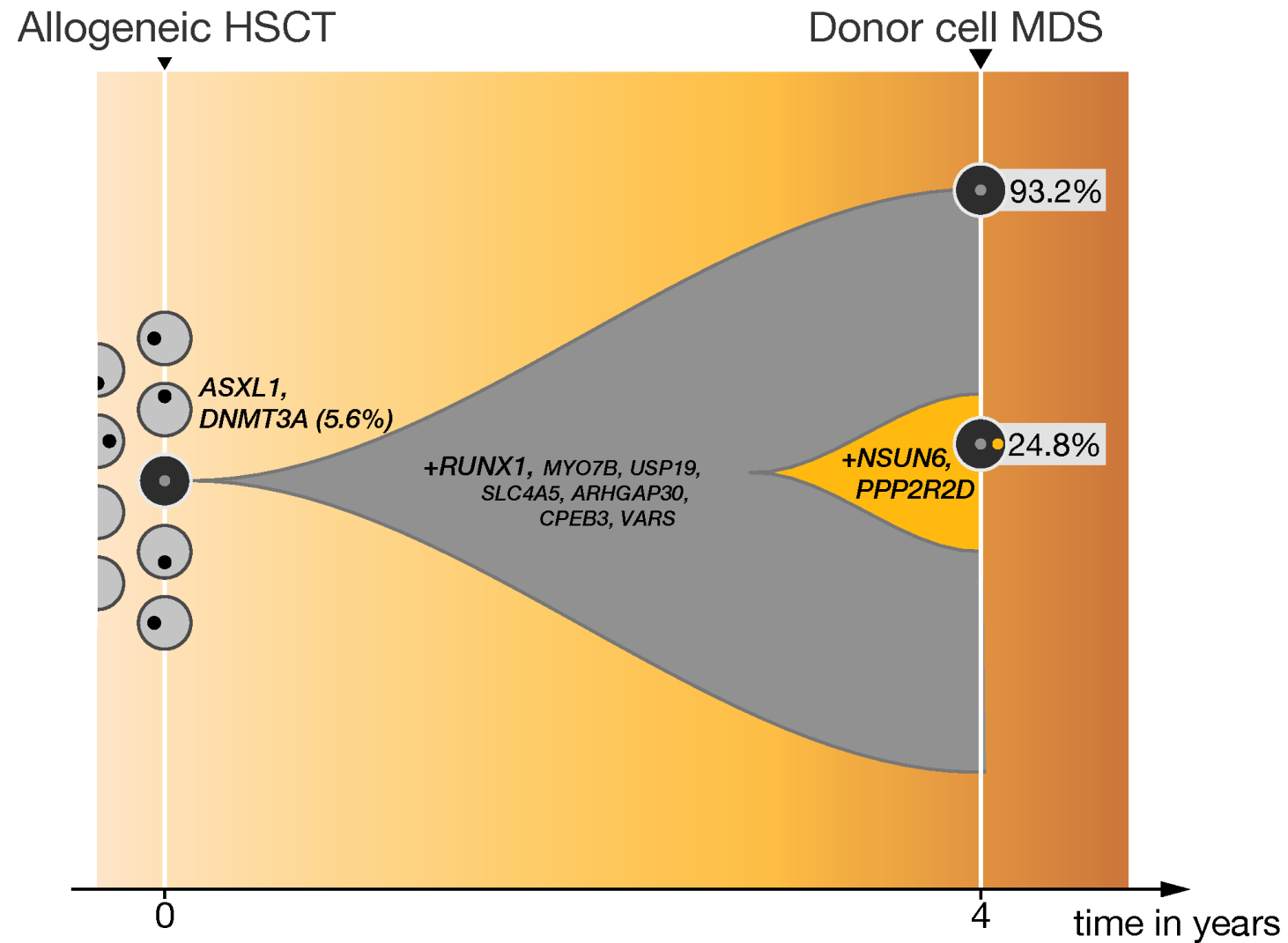
	0	2	4	6	8	10	12
Number at risk (number censored)							
CHIP <sub>neg</sub>	123 (0)	37 (7)	16 (20)	11 (22)	7 (26)	1 (31)	0 (32)
CHIP <sub>pos</sub>	29 (0)	14 (3)	11 (6)	10 (7)	4 (11)	2 (12)	0 (14)



	0	2	4	6	8	10	12
Number at risk (number censored)							
DNMT3A <sub>wt</sub>	138 (0)	43 (10)	22 (23)	17 (25)	9 (32)	3 (37)	0 (40)
DNMT3A <sub>mut</sub>	14 (0)	8 (0)	5 (3)	4 (4)	2 (5)	0 (6)	0 (6)



# KH und Spenderzell-Leukämien

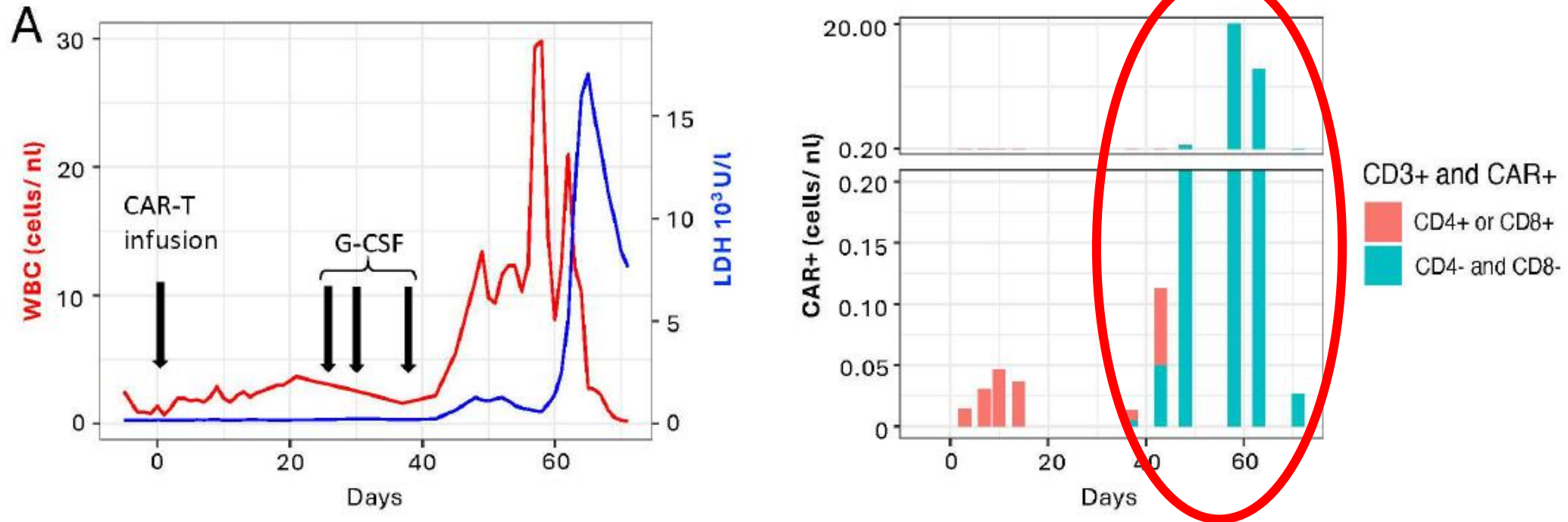


## Donor Clonal Hematopoiesis and Recipient Outcomes After Transplantation

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# KH und CAR T-Zelltherapie

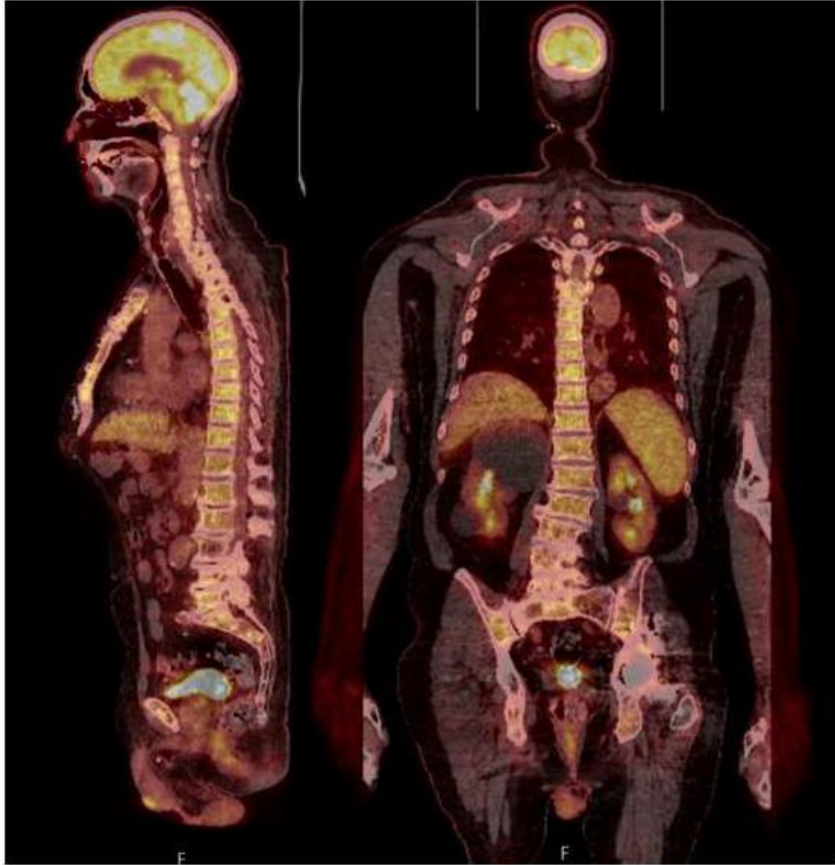
- 11/2023 FDA-Warnung für erhöhtes T-NHL Risiko bei CAR T-Zell Therapien
- 69-jähriger Patient mit r/r PZNSL und Zustand nach autologer Transplantation



Kobbe, ..., Damm\*, Dietrich\*. N Engl J Med 2024  
\*equal contribution

# KH und CAR T-Zelltherapie

- 69-jähriger Patient mit r/r PZNSL und Zustand nach autologer Transplantation



PET-CT an Tag +51

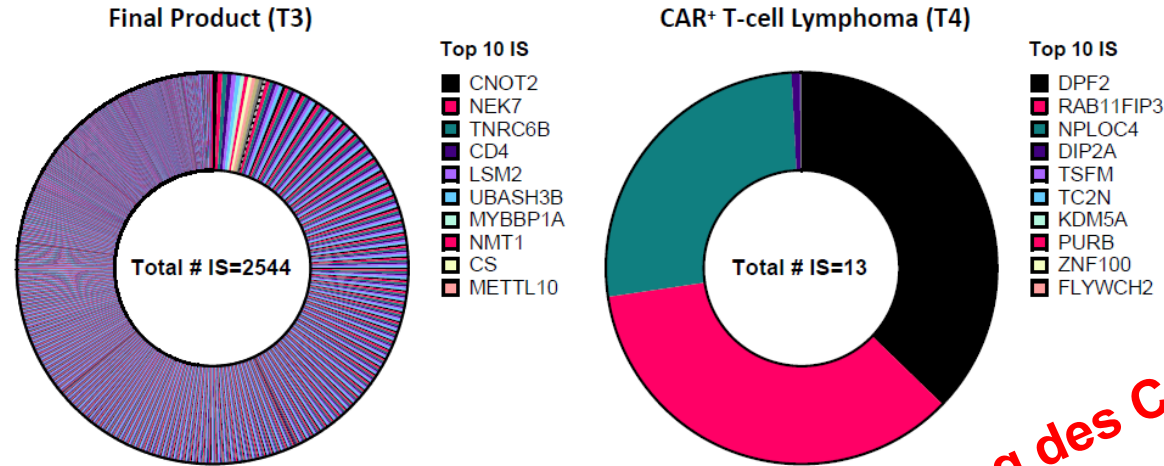
## Knochenmarksbiopsie an Tag +52:

30%-Infiltration durch ein CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup>  
peripheres T-NHL (PCTL-NOS)

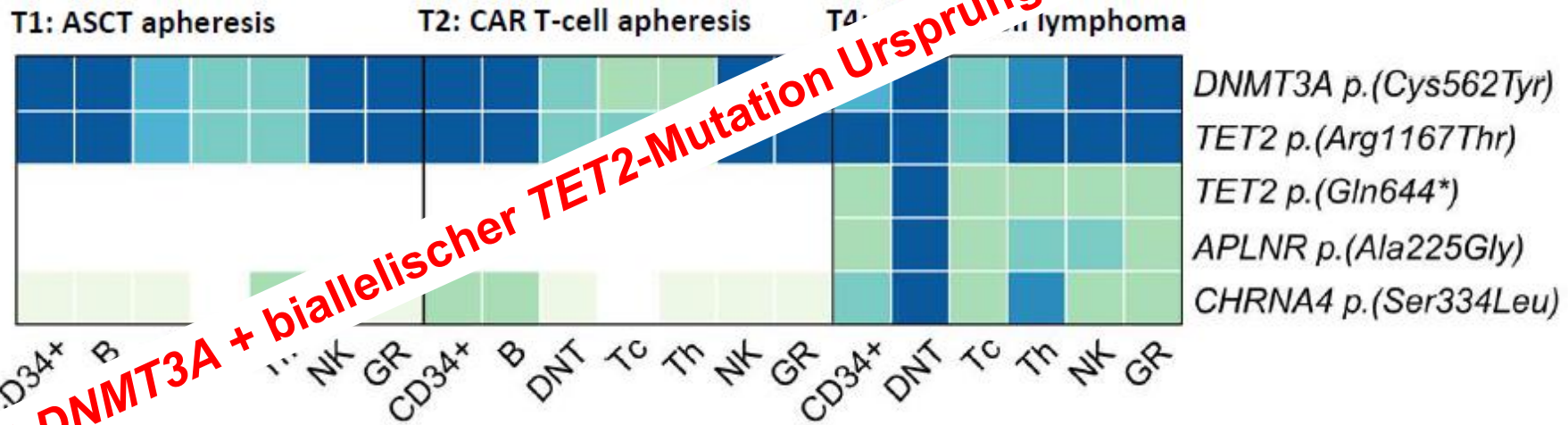
Kobbe, ..., Damm\*, Dietrich\*. N Engl J Med 2024

*\*equal contribution*

# KH und CAR T-Zelltherapie



VCN: 2.4 virale  
Genome/7



**=> CHIP mit DNMT3A + biallelischer TET2-Mutation Ursprung des CAR+ T-Lymphoms**

JAMA Cardiology | **Original Investigation**

## Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure

CLINICAL EPIDEMIOLOGY [www.jasn.org](http://www.jasn.org)

**Association of Clonal Hematopoiesis of Indeterminate Potential with Worse Kidney Function and Anemia in Two Cohorts of Patients with Advanced Chronic Kidney Disease**

 **ESC**  
European Society of Cardiology  
European Heart Journal (2020) 41, 933–939  
doi:10.1093/eurheartj/ehz591

**FASTTRACK CLINICAL RESEARCH**  
Valvular heart disease

**Clonal haematopoiesis in patients with degenerative aortic valve stenosis undergoing transcatheter aortic valve implantation**

**Impact of Clonal Hematopoiesis in Patients With Cardiogenic Shock Complicating Acute Myocardial**

**LETTERS**

<https://doi.org/10.1038/s41591-021-01357-y>

**nature  
medicine**

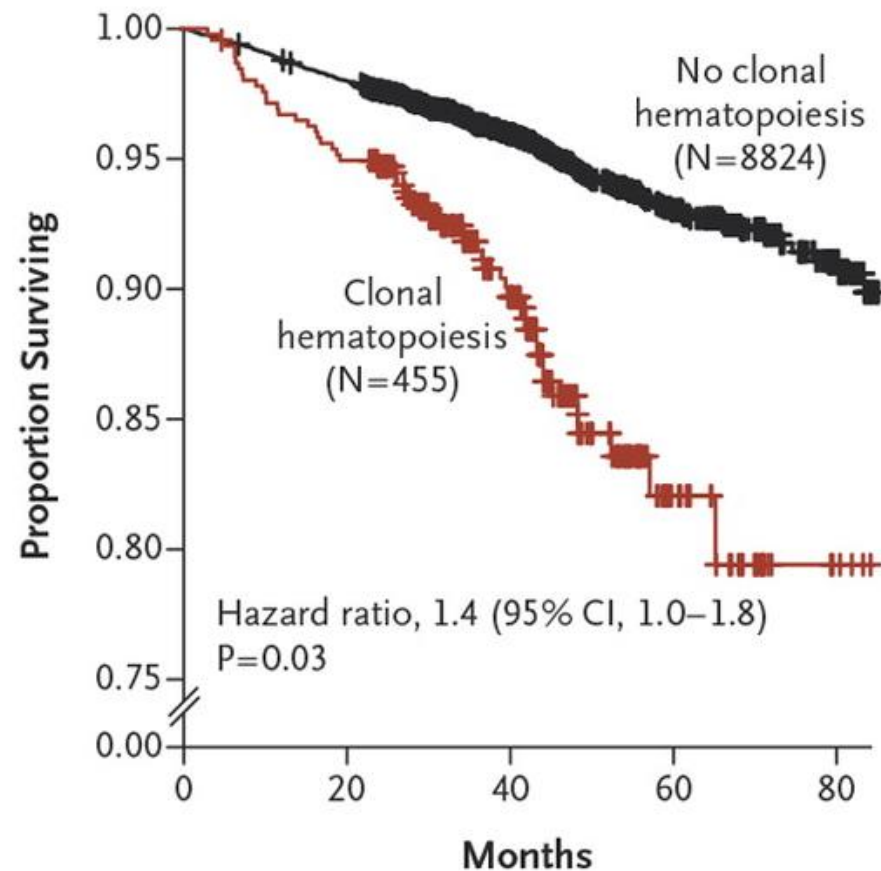
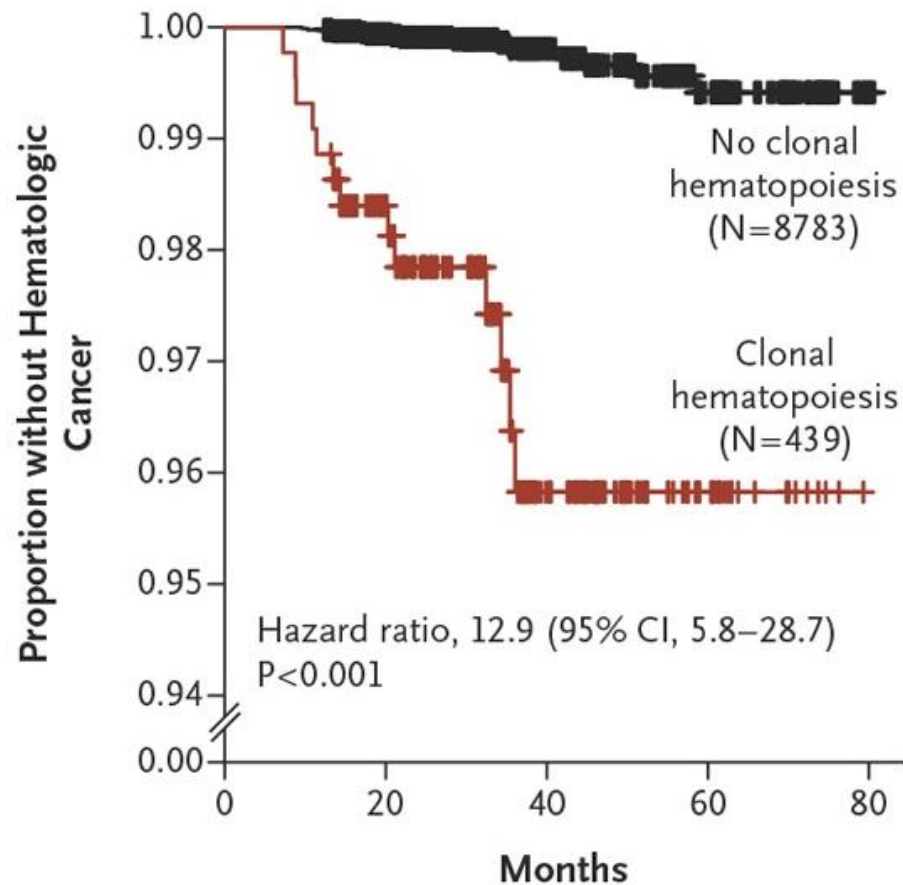
 Check for updates

**HIV is associated with an increased risk of age-related clonal hematopoiesis among older adults**



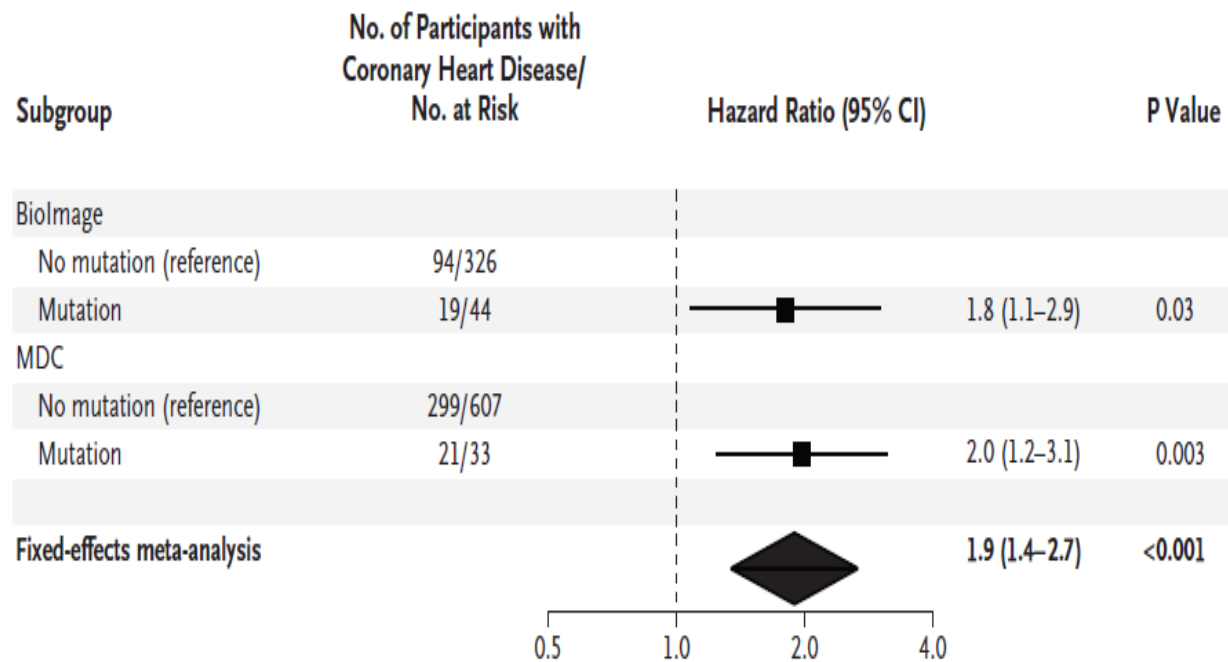
Journal of the American College of  
Cardiology

Volume 80, Issue 16, 18 October 2022, Pages 1545-1556

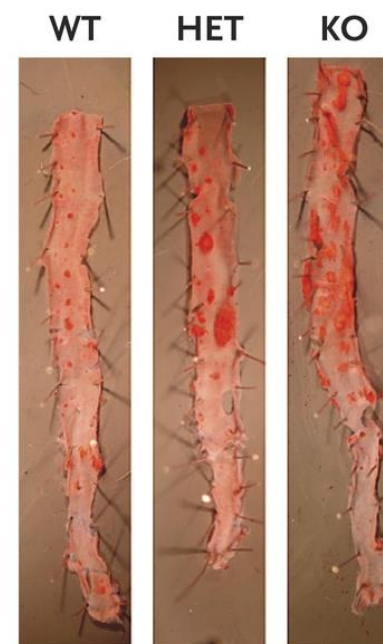


- KH ist mit der Entwicklung von koronarer Herzerkrankung und Atherosklerose assoziiert

## CHIP and Coronary Heart Disease



## Aortic Atherosclerosis (According to Tet2 Status)



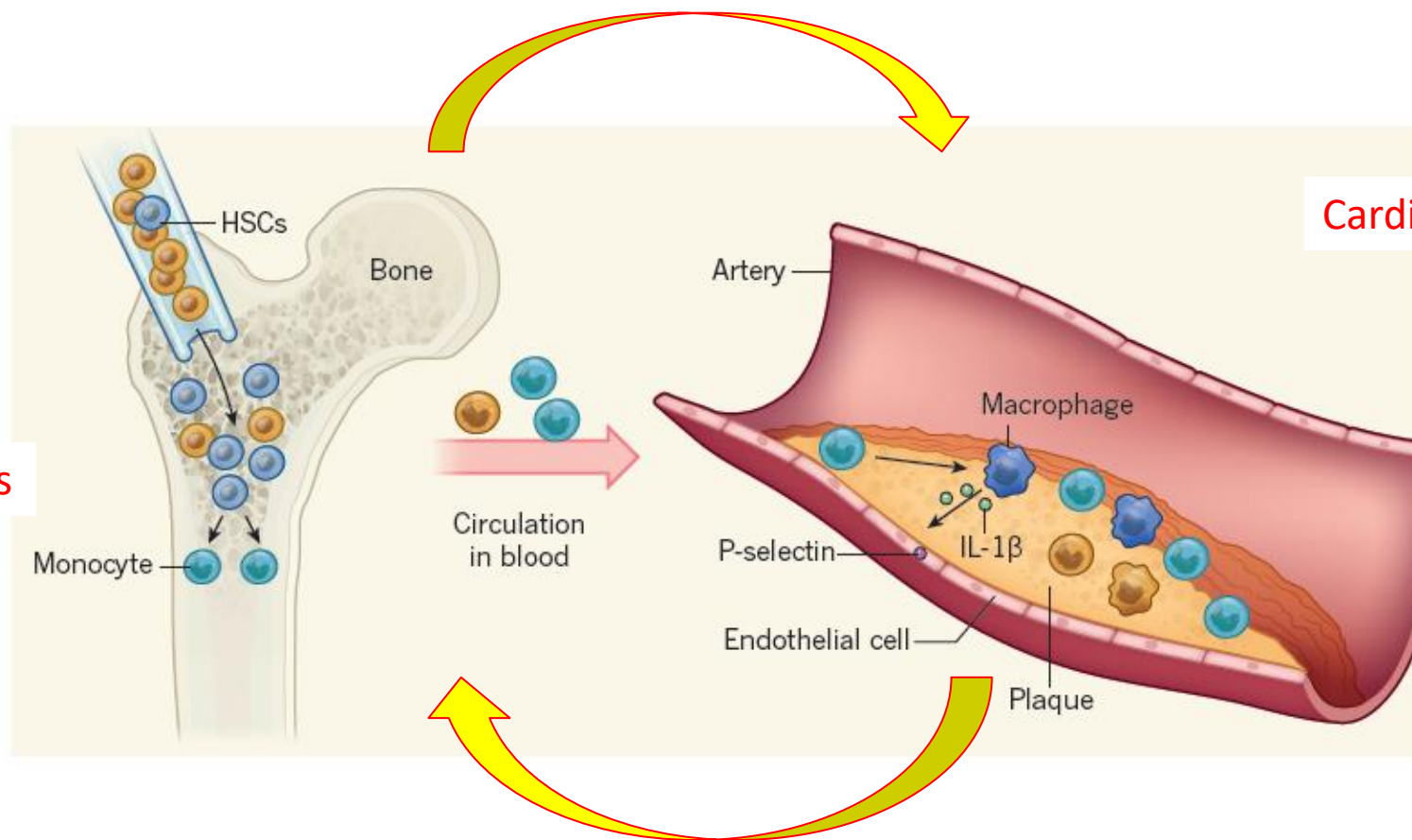
= KH



CHIP => Inflammation

Hematologic neoplasms

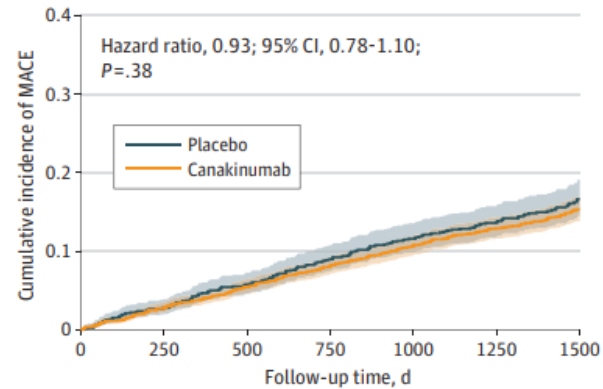
Cardiovascular diseases



CHIP expansion <= Inflammation

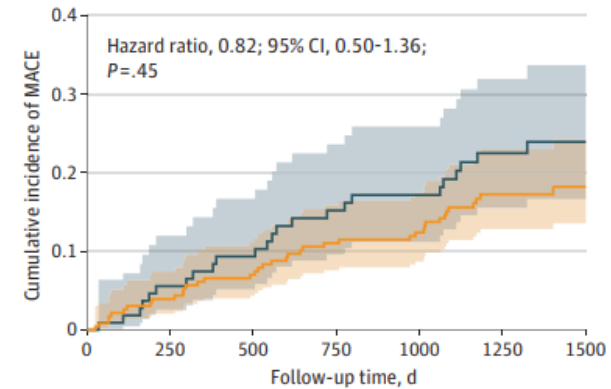
# Canakinumab, KH und kardiovaskuläre Ereignisse

**A** Patients without CHIP



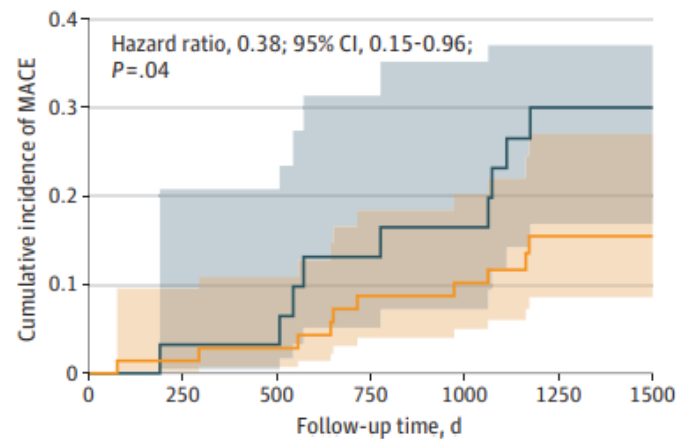
No. at risk	0	250	500	750	1000	1250	1500
Placebo	1181	1137	1090	1040	998	743	453
Canakinumab	2404	2314	2227	2142	2062	1521	933

**B** Patients with CHIP



No. at risk	0	250	500	750	1000	1250	1500
Placebo	108	101	95	86	84	62	32
Canakinumab	230	219	209	198	195	129	72

**C** TET2 patients with CHIP



No. at risk	0	250	500	750	1000	1250	1500
Placebo	31	30	30	26	25	19	11
Canakinumab	71	69	67	62	61	37	14

# Acknowledgements

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S Stintzing

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A Hensen

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E Wagner-Drouet, D Sasca, **Mainz**

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## Internationale Kooperationen

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D Landau, **New York**

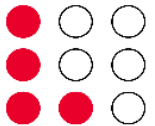
O Bernard, F Nguyen-Khac, G Socié, **Paris**

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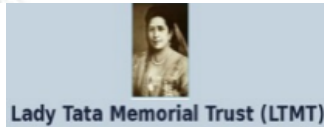
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