Clonal hematopoiesis in hematopoietic stem cell transplantation

Swisstransfusion – September 5, 2024

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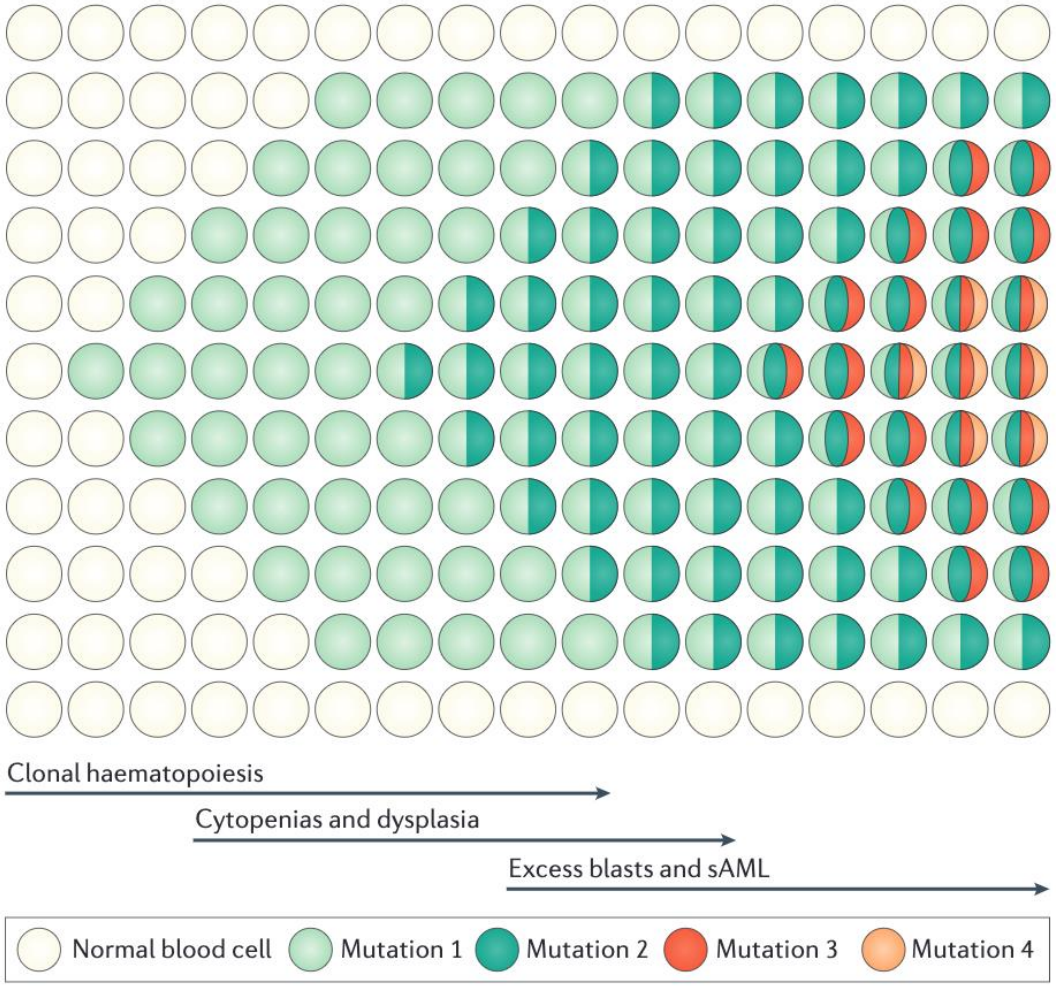
USZ Universitäts Spital Zürich

Universität Zürich[UZH]

Sequential clonal accumulation of somatic mutations in (hematological) cancers



Number of driver mutations:

- CH: 1 (most cases)
- MDS: 3 (median)
- AML: 4-5 (median)

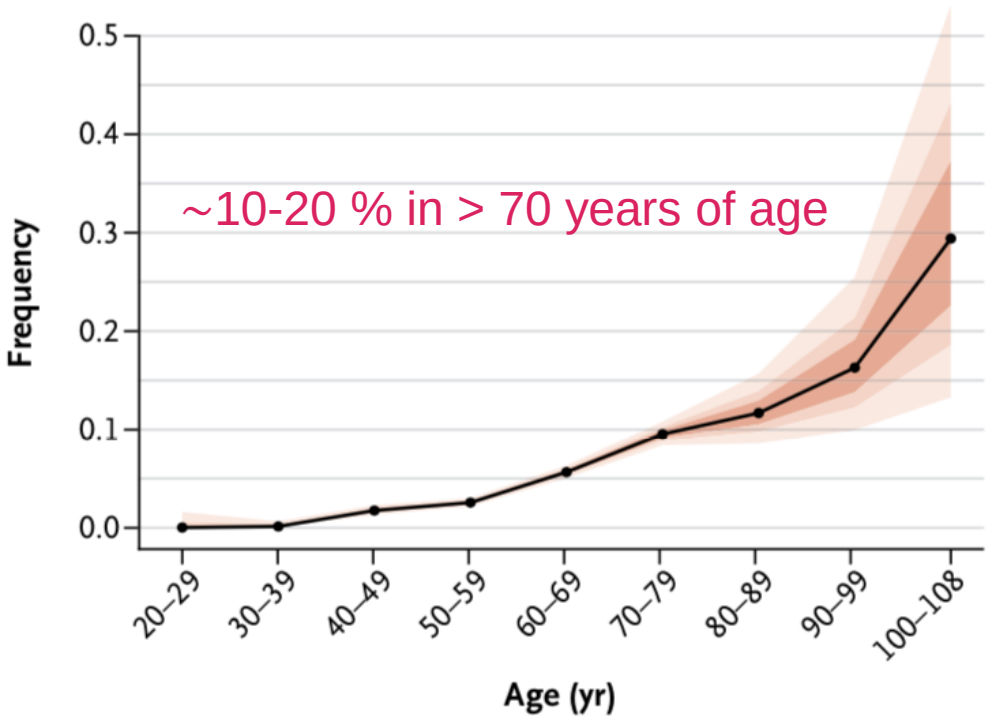
Continuous acquisition of somatic mutations in driver genes promotes development of hematologic malignancies over time

Sperling et al., *Nat Rev Cancer* 2016

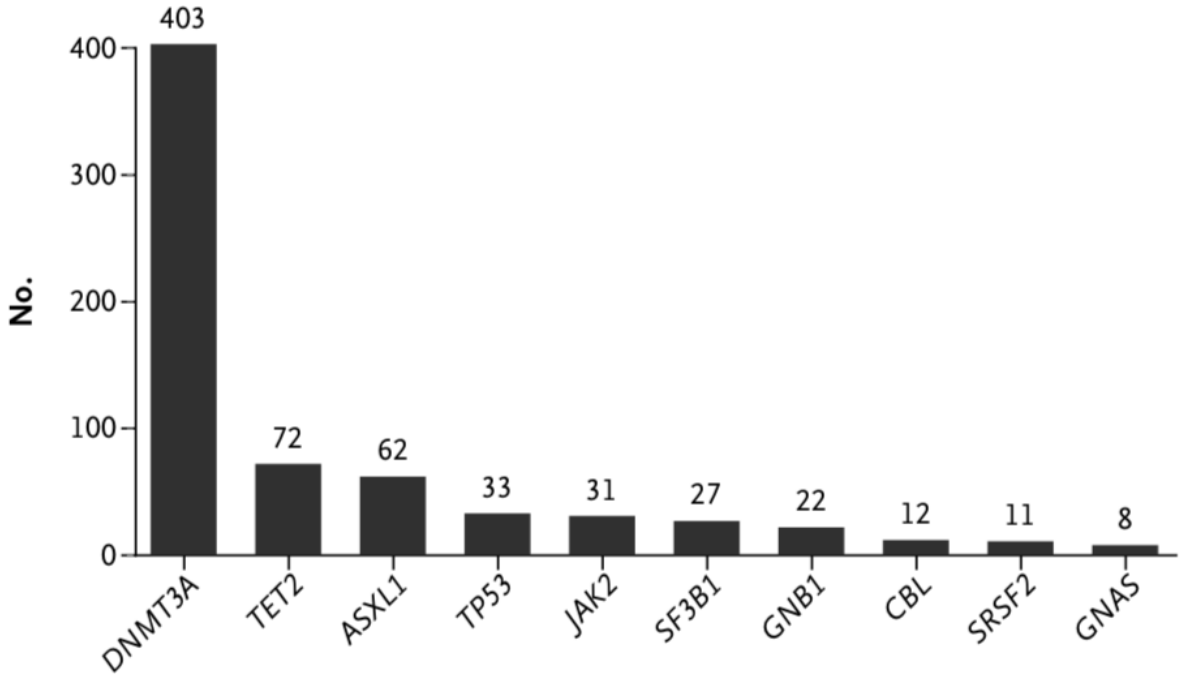
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Definition: Detection of somatic mutations (SNVs) in typical leukemia driver genes leading to expansion of blood cell clones in individuals without hematologic neoplasms.

Age-dependent prevalence



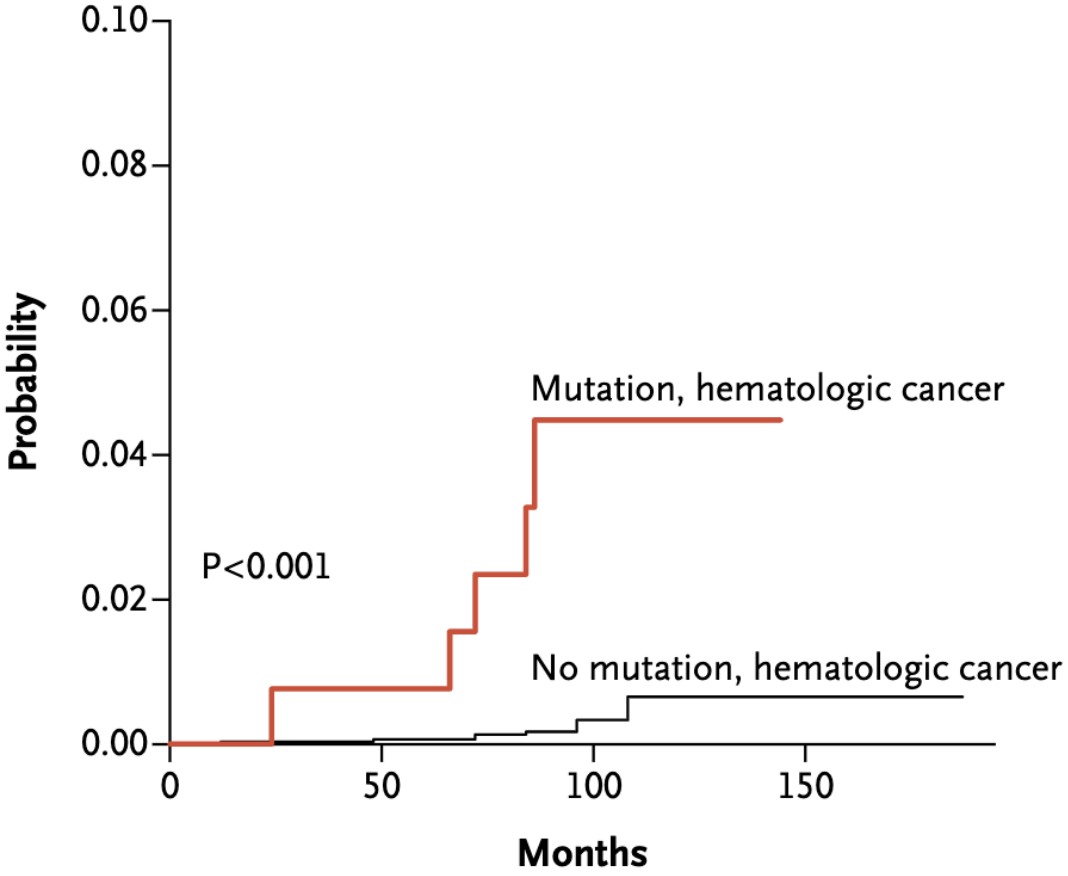
Mutational spectrum

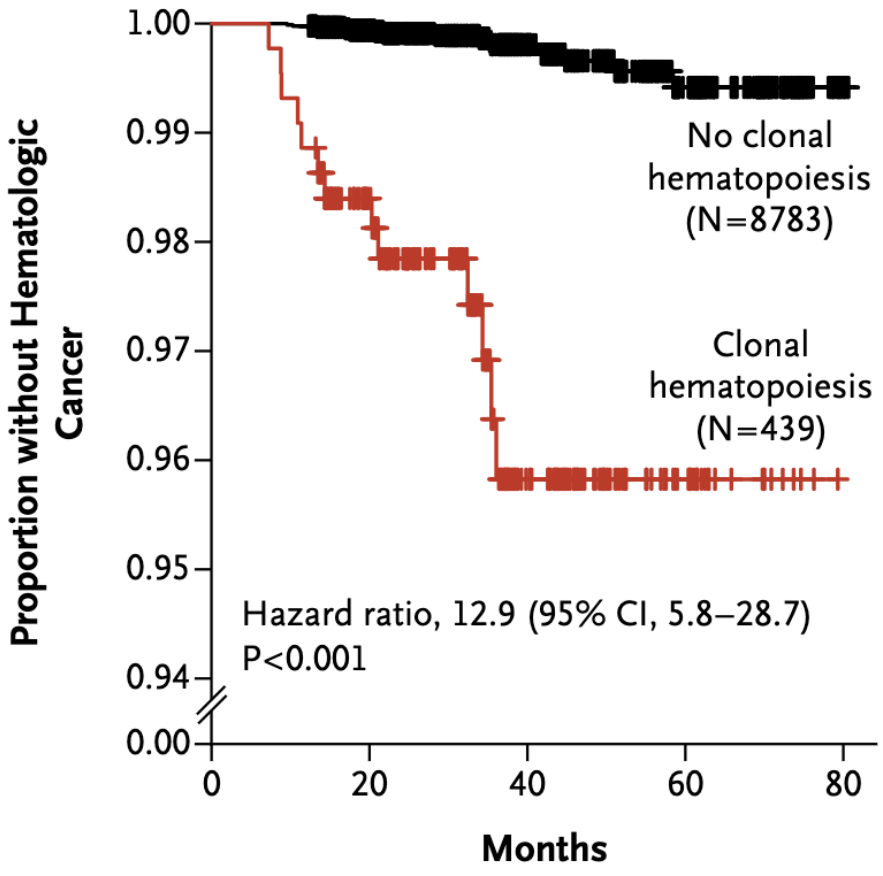


Xie et al., *Nat Med* 2014 Genovese et al., *N Engl J Med* 2014 Jaiswal et al., *N Engl J Med* 2014

CH is a pre-malignant condition for hematologic cancers

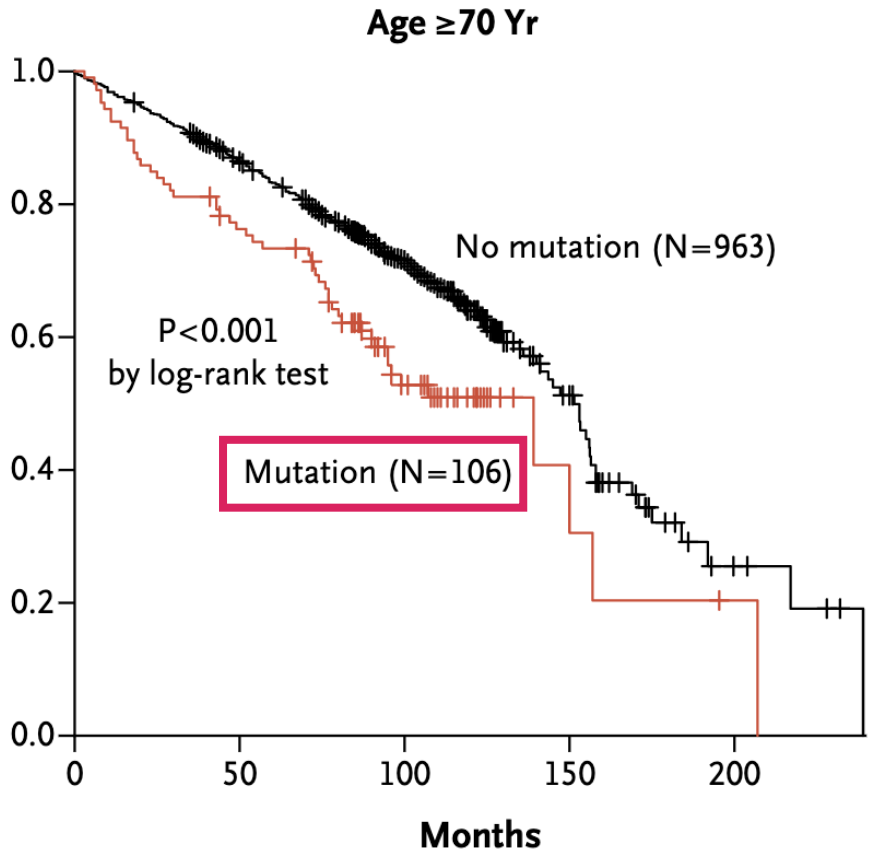
Increased risk for hematologic neoplasms (risk of progression: 1% per year)



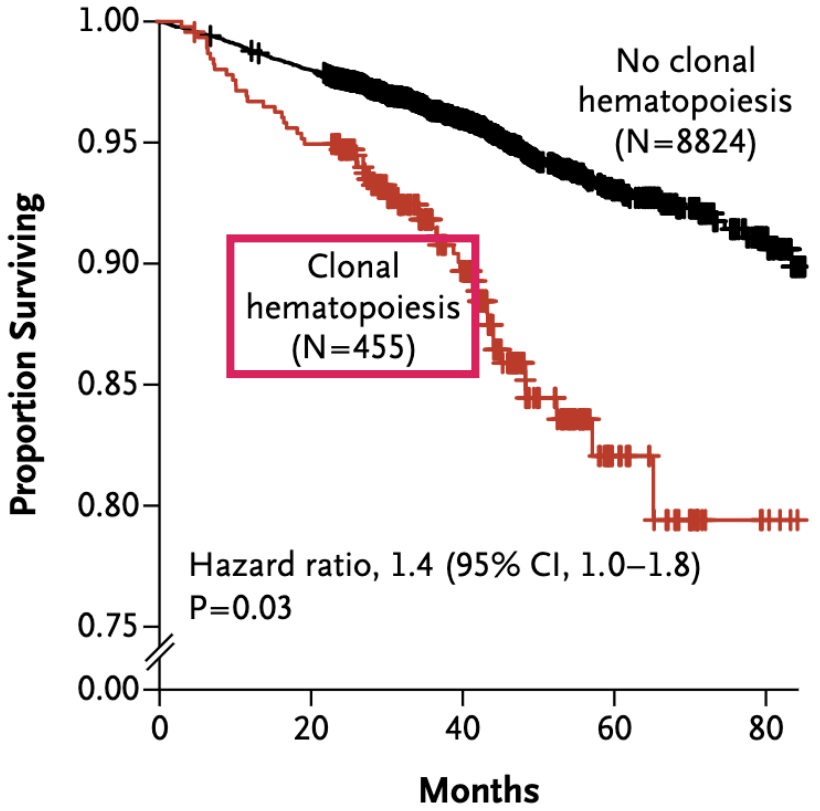


Genovese et al., *N Engl J Med* 2014 Jaiswal et al., *N Engl J Med* 2014

Increased all-cause mortality in individuals with CH



[adjusted for age, sex, and type 2 diabetes]

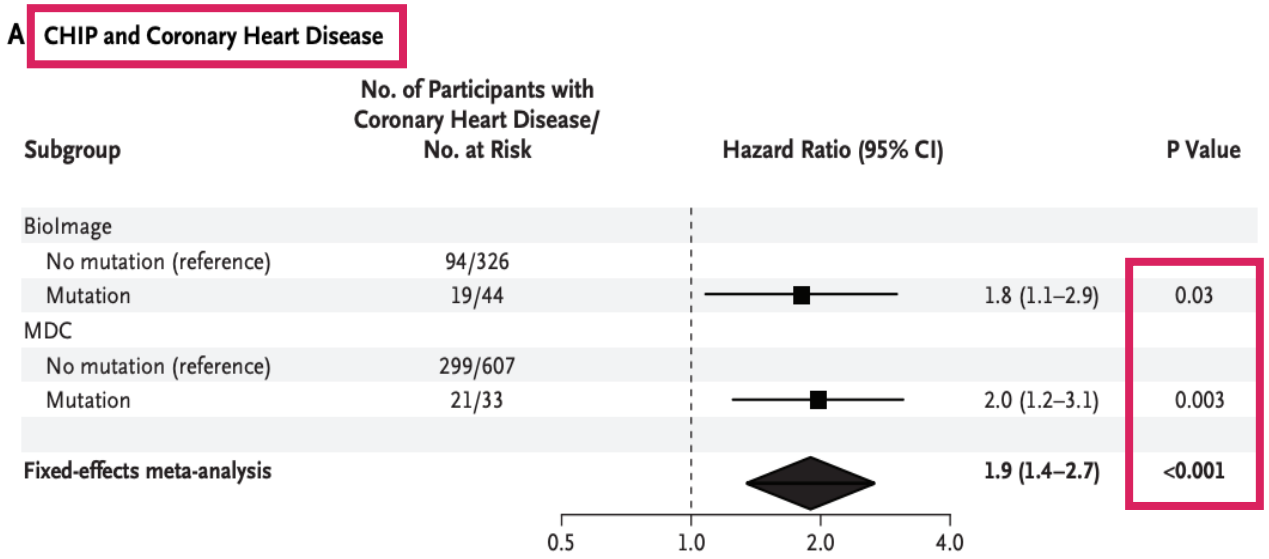


[adjusted for age and sex]

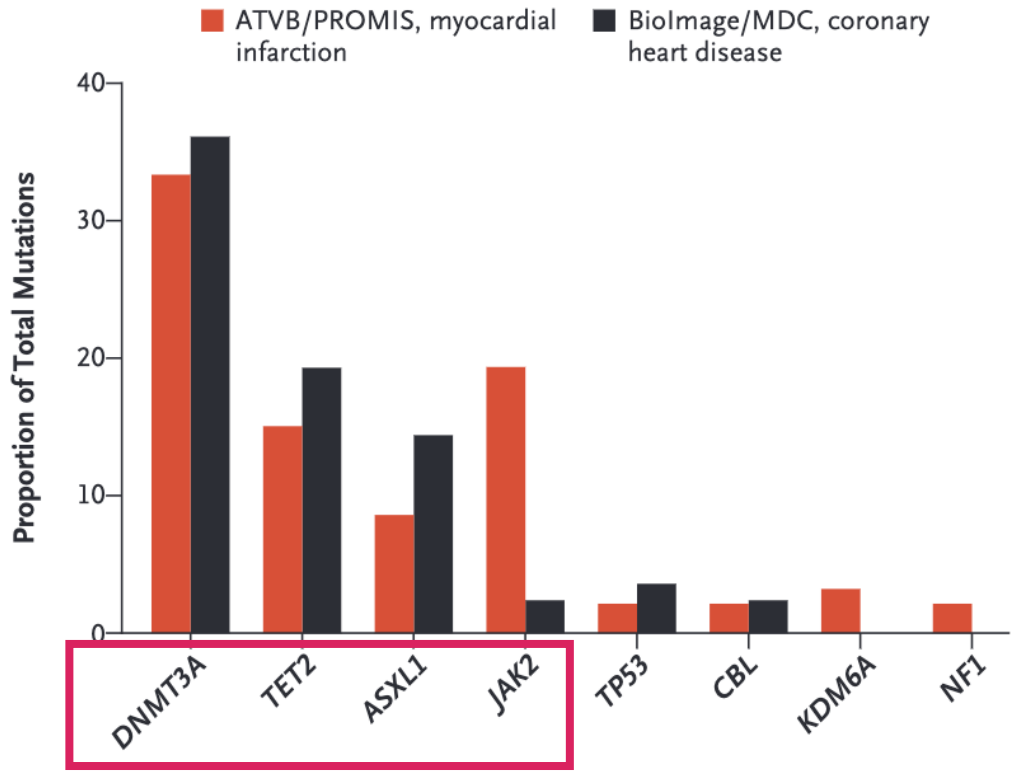
Jaiswal et al., *N Engl J Med* 2014 Genovese et al., *N Engl J Med* 2014

CH and cardiovascular disease (CVD)

Coronary heart disease

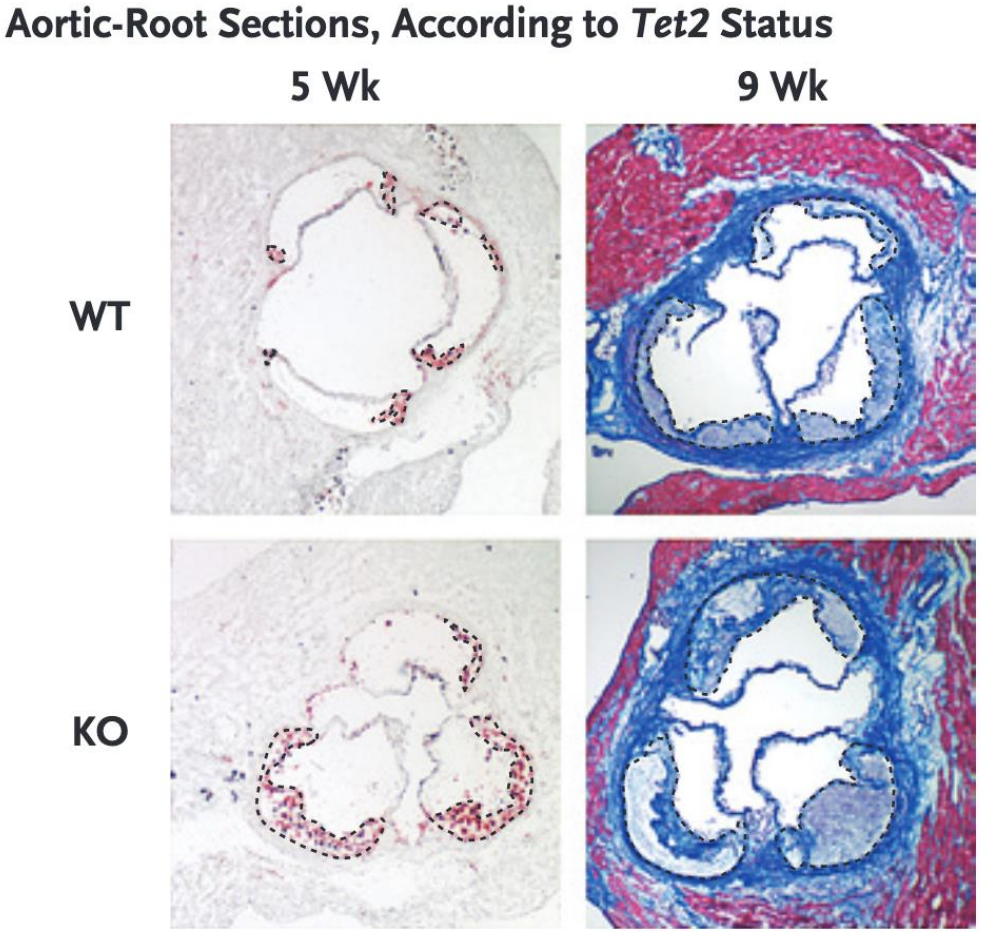


Mutational spectrum

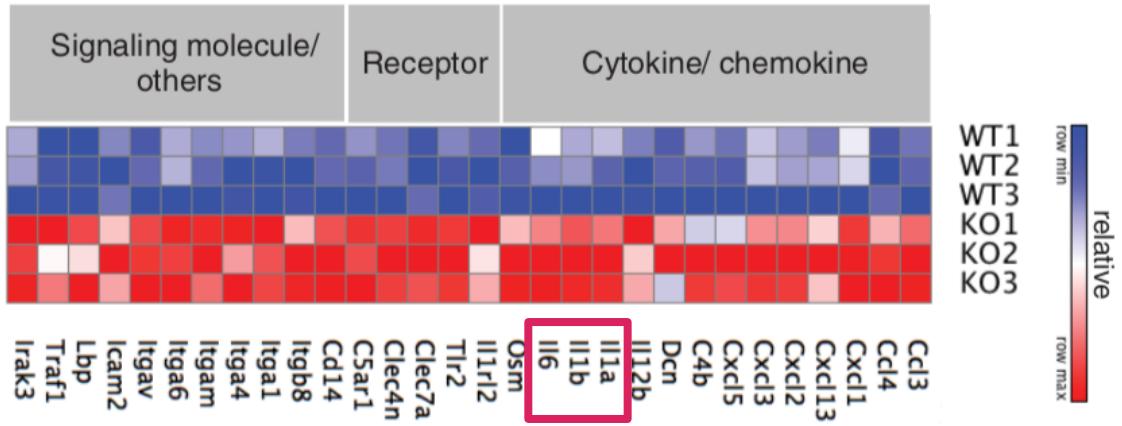


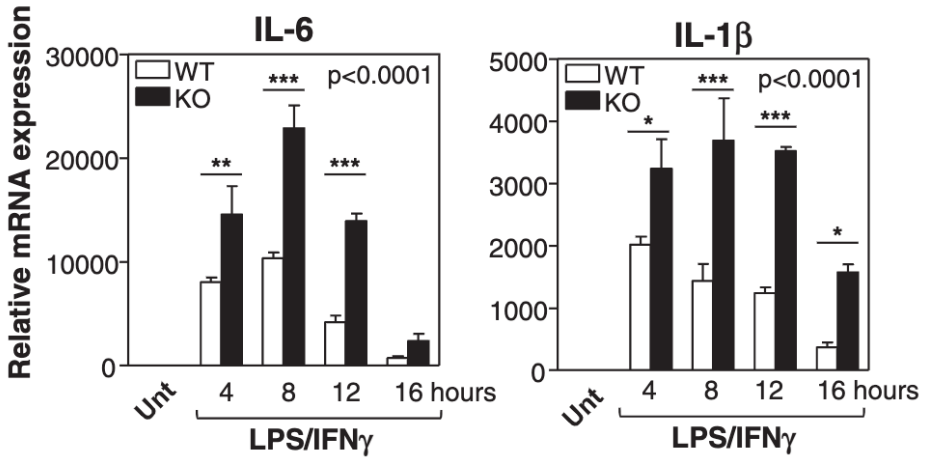
Jaiswal et al., *N Engl J Med* 2017

Mechanistic basis for exacerbated CVD in individuals with CH



Dysregulation of inflammatory molecules in *Tet2*$^{-/-}$ macrophages

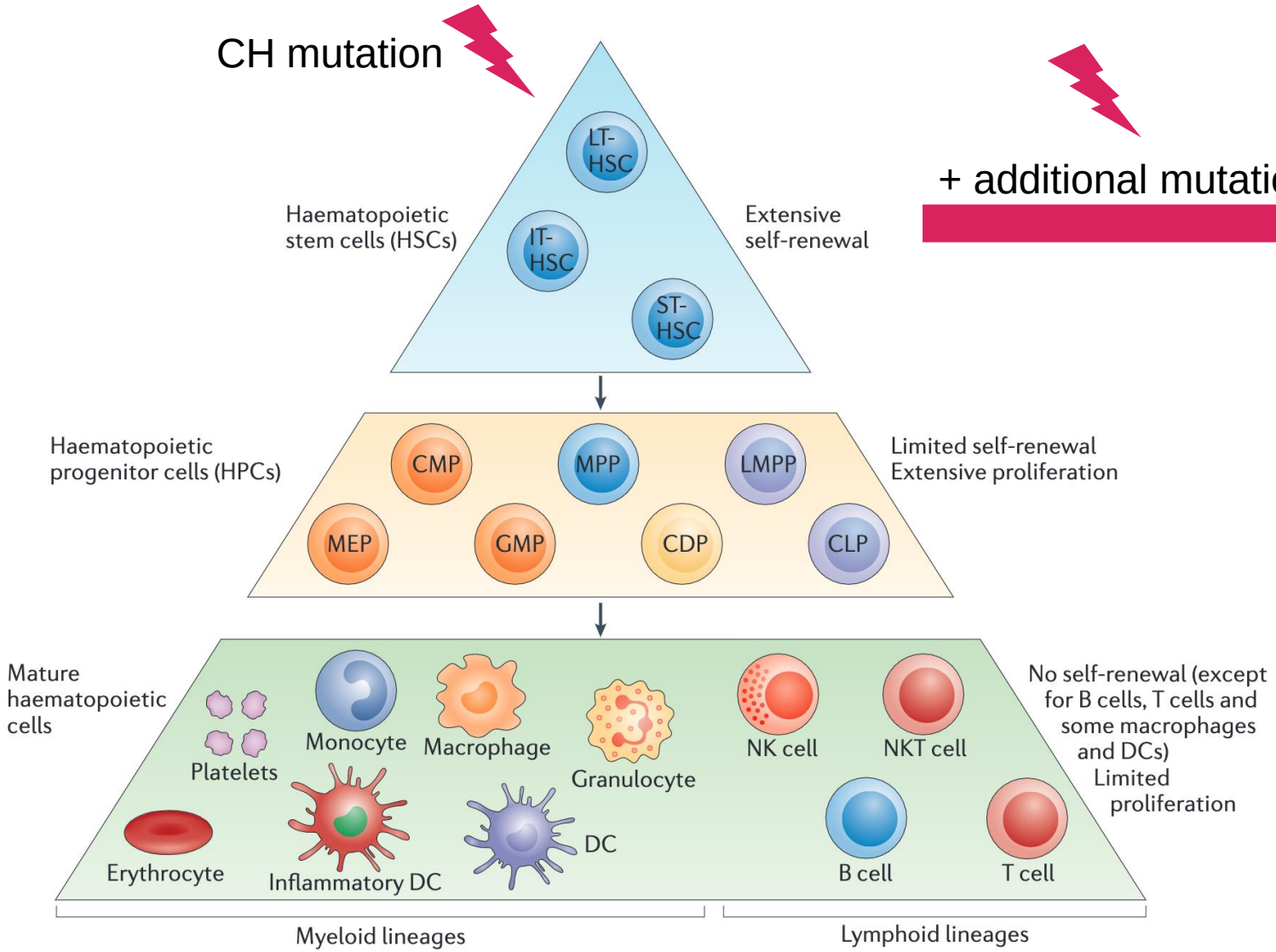




Jaiswal et al., *N Engl J Med* 2017

Fuster et al., *Science* 2017

CH impacts the functionality of HSCs and mature progeny alike



+ additional mutations

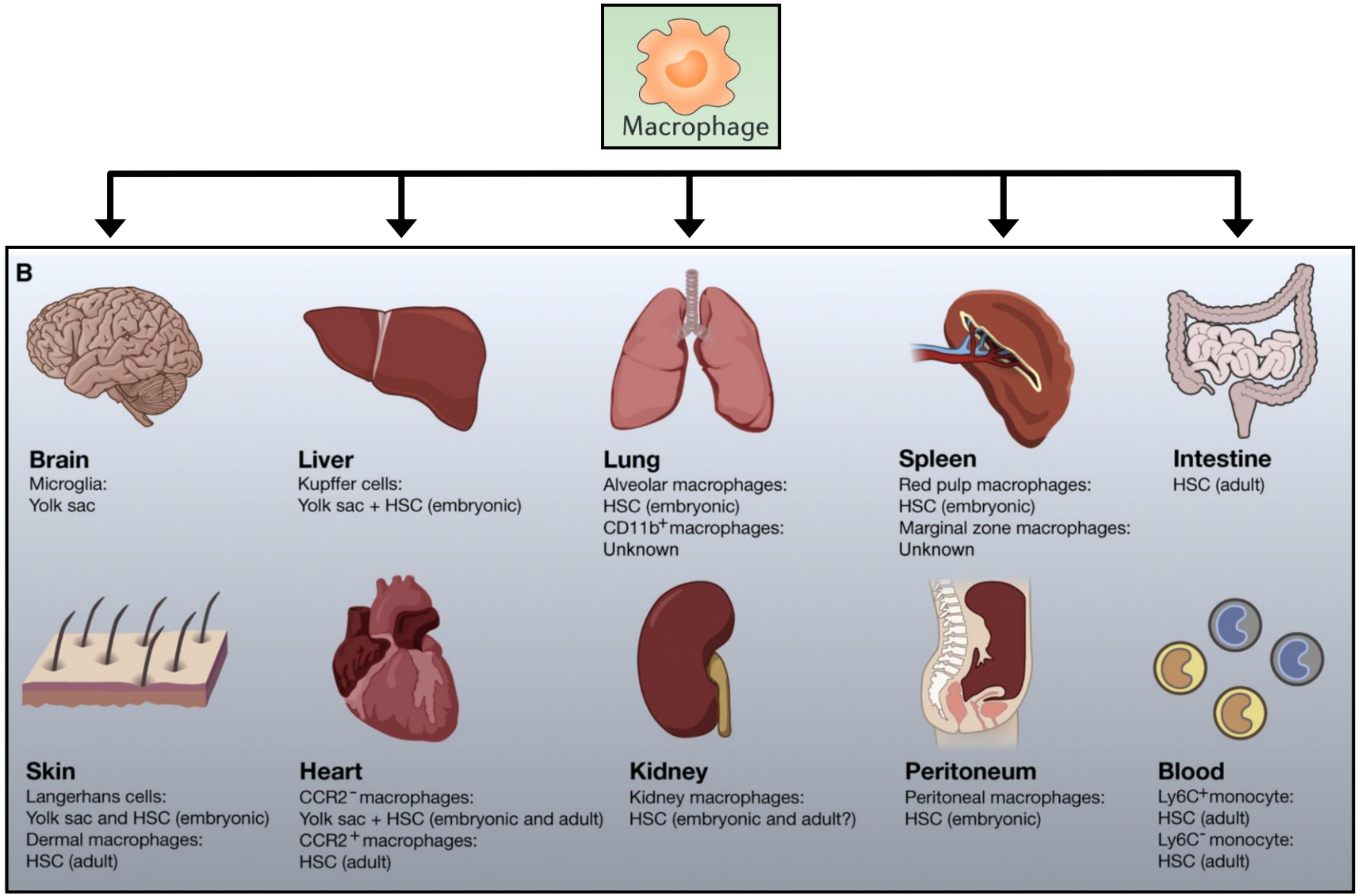
Hematologic Neoplasms (e.g., AML, MDS)

Contribution to the pathogenesis of non-hematological disease (e.g., CVD)

Boettcher and Ebert, *J Clin Oncol* 2018

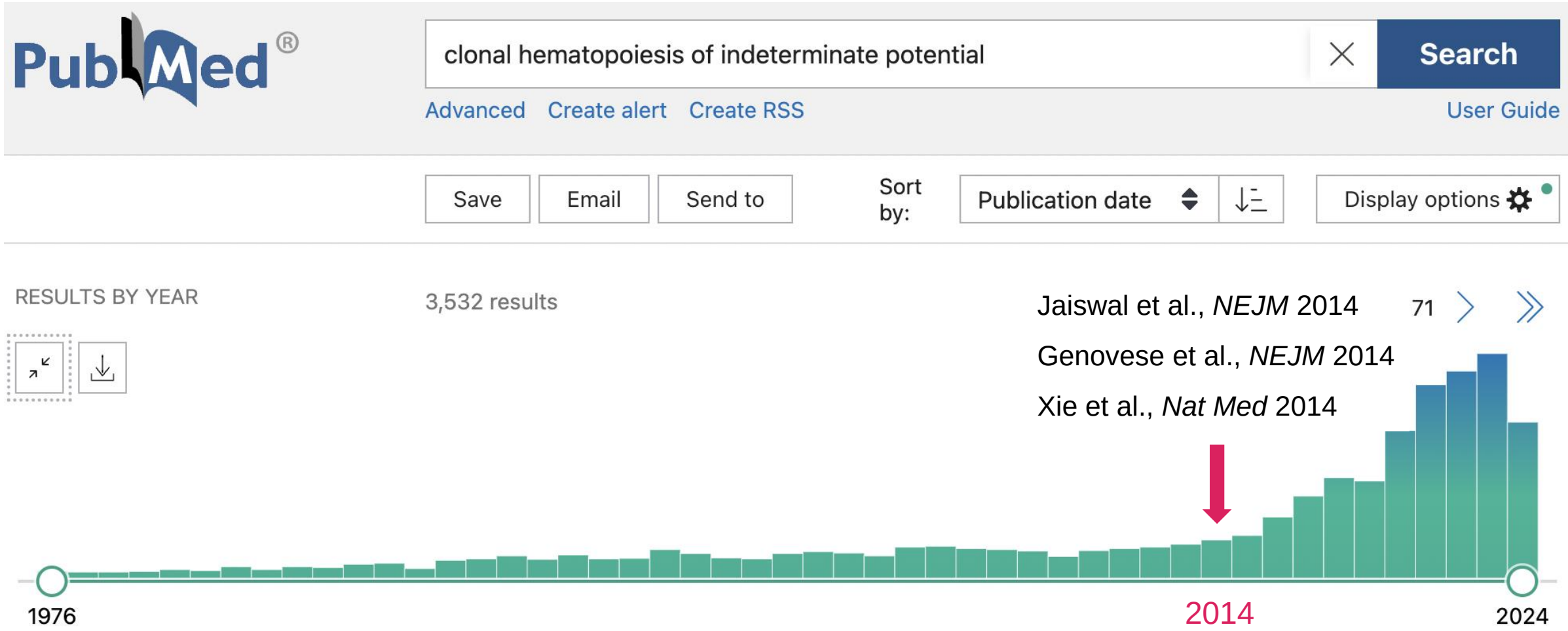
Manz and Boettcher, *Nat Rev Immunol* 2014

Macrophages make up a significant portion of solid organs



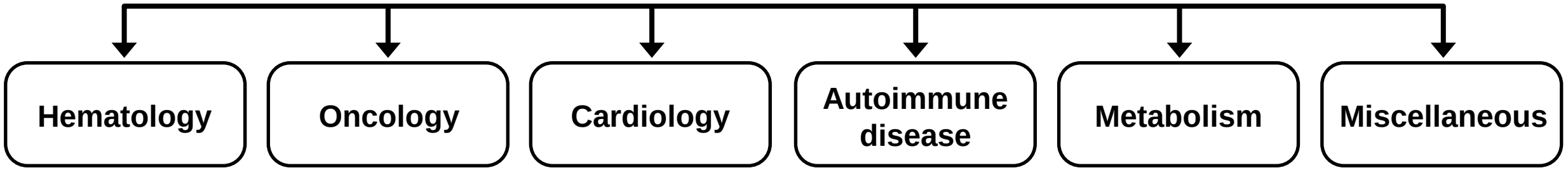
Adapted from Epelman et al., *Immunity* 2014

Massive surge in clonal hematopoiesis research



Retrieved on August 25, 2024

CH is associated with multiple pathologies / disease states



Hematology

- AML / MDS[1,2,3,4,5]
- Aplastic anemia[6]
- Dyskeratosis congenita[7]
- Pure red cell aplasia[8]
- Erdheim-Chester Dis.[9]
- HLH[10]
- Lymphoma[11]
- Plasma cell myeloma[12]
- Thrombosis[13]
- Stem cell transplant[14,15,16]

Oncology

- Solid tumors[17]

Cardiology

- CAD[18,19]
- Heart failure[20]
- Aortic stenosis[21]

Autoimmune disease

- Rheumat. arthritis[22]
- ANCA+ vasculitis[23]
- Systemic sclerosis[24]
- Ulcerative colitis[25]

Metabolism

- Diabetes[26]

Miscellaneous

- HIV[27]
- CVID[28]
- COVID-19[29,30,31]
- Space flight[32]

[1]Jaiswal et al., *NEJM* 2014
[2]Genovese et al., *NEJM* 2014
[3]Xie et al., *Nat Med* 2014
[4]Abelson et al., *Nature* 2018
[5]Desai et al., *Nature* 2018
[6]Yoshizato et al, NEJM 2015
[7]Perdigones et al., *AJH* 2016
[8]Fujishima et al., *Sci Rep* 2021
[9]Aubart et al., *Blood* 2020
[10]Miller et al., *Blood* 2020
[11]Eskelund et al., *Blood* 2020
[12]Chitre et al., *Leukemia* 2018
[13]Dunbar et al., Blood 2021
[14]Gibson et al., JCO 2017
[15]Frick et al., JCO 2019
[16]Boettcher et al., *Blood* 2020
[17]Coombs et al., *Cell Stem Cell* 2017
[18]Jaiswal et al., *NEJM* 2017
[19]Fuster et al., *Science* 2017
[20]Dorsheimer et al., *JAMA Cardiol* 2019
[21]Abplanalp et al., *JAMA Cardiol* 2020
[22]Savola et al., *Blood Cancer J* 2018
[23]Arends et al., *Haematologica* 2019
[24]Ricard et al., *Rheumatology* 2019
[25]Zhang et al., *Exp Hematol* 2019
[26]Fuster et al., *Cell Rep* 2020
[27]Bick et al., *medRxiv* 2020
[28]Wong et al., *JCI Insight* 2019
[29]Hameister et al., *HemaSphere* 2020
[30]Duployez et al., *Cancers* 2020
[31]Bolton et al., *medRxiv* 2020
[32]Trinchant et al., *Cell Rep* 2020

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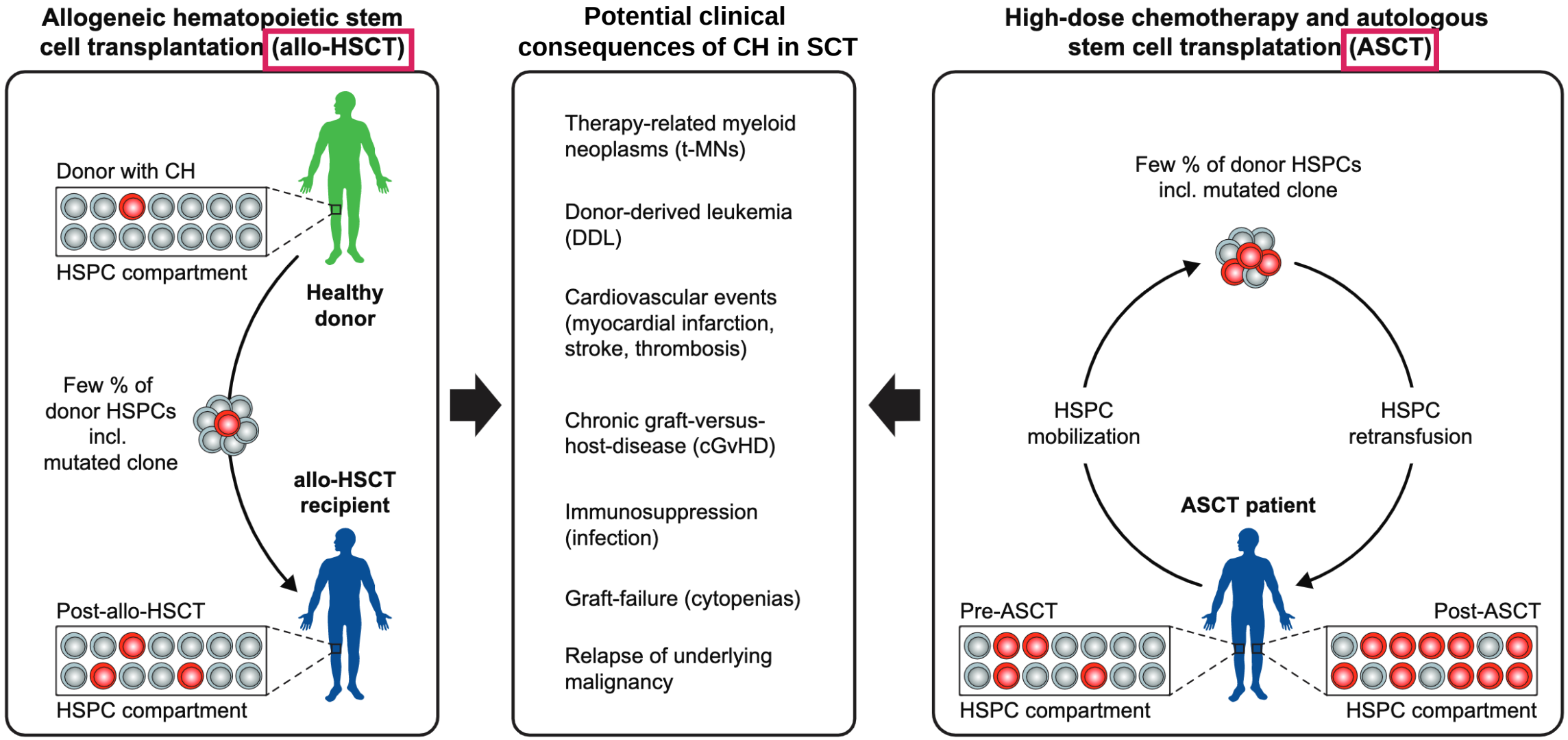
CH in hematopoietic stem cell transplantation



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Wilk, Manz, and Boettcher *Curr Opin Hematol* 2020

Allo-HSCT – Unexplained cytopenias

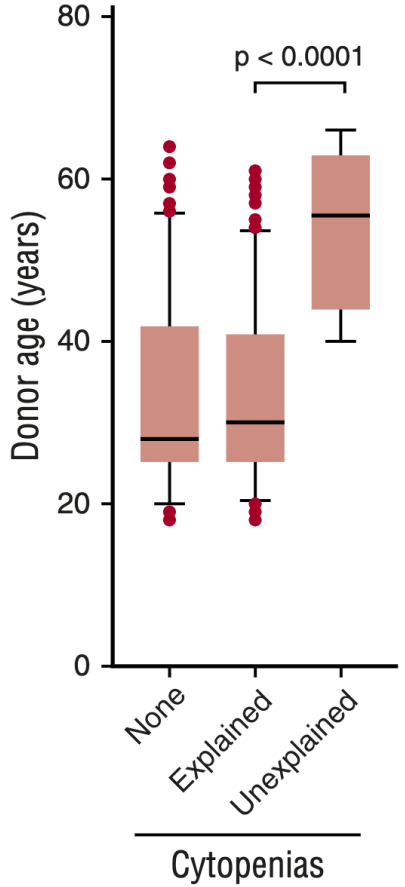
89 / 552 (16%) allo-HSCT recipients had **cytopenias**

83 / 89 (93%) had an **identifiable cause**

5 / 6 (83%) <u>without</u> an identifiable cause had detectable **CH**

Table 1. Characteristics of patients with donor-engrafted HSC clones

Recipient	Donor source	Age at HSCT, y	Donor age, y*	Donor-engrafted mutation	Time of detection, mo	Donor VAF, %†	VAF at detection, %‡	Clonal evolution	Additional mutation(s)
1	MUD	57	40	*DNMT3A* T862N	18	5.9	4.4	Yes	*ASXL1*, *TP53*
2	MRD	67	59	*DNMT3A* Q356X	13	1.6	4.0	No	None
3	MRD	51	53	*DNMT3A* R882H	4	2.6	2.6	No	None
4	MRD	68	66	*DNMT3A* S786X	6	1.5	3.7	No	None
5	MRD	63	62	*DNMT3A* R729Q	30	6.4	11.1	No	None



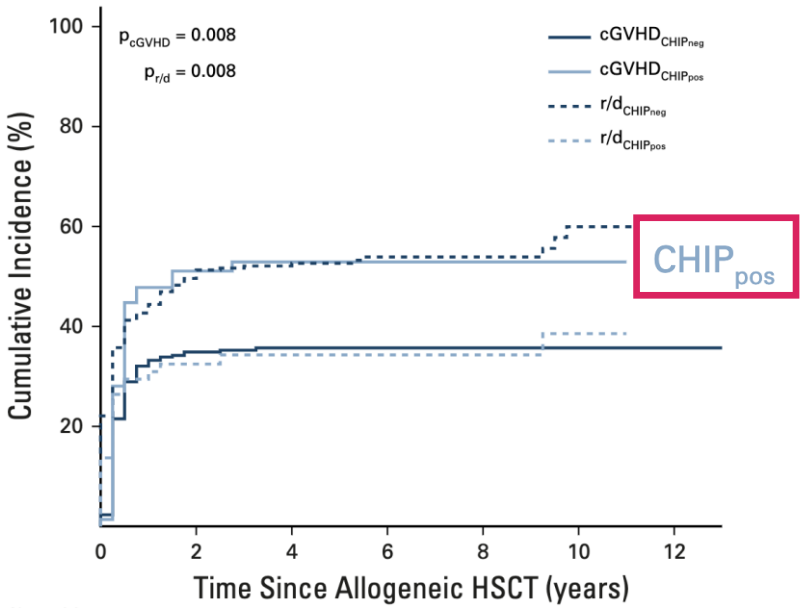
→ **CH is common among allo-HSCT recipients with unexplained cytopenias**

Gibson et al., *Blood* 2017

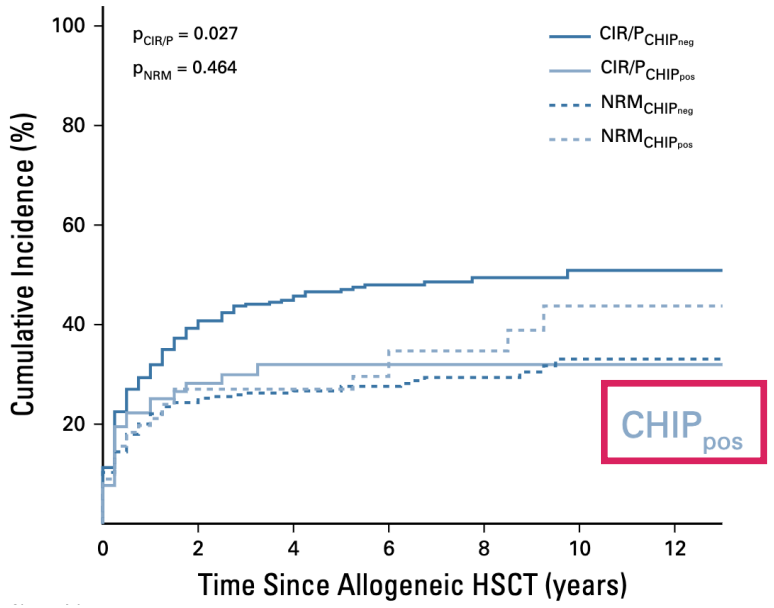
Allo-HSCT – Clinical outcomes

- Related donors (≥55 years), PB or BM from time of donation, median FU time 3.3 years
- n = 80 / 500 (16%) allo-HSCT donors had at least one CHIP mutation

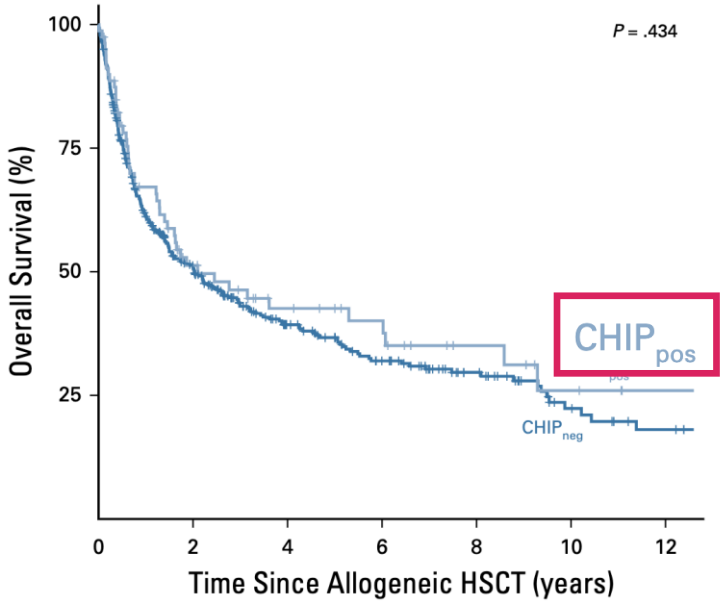
Cumulative incidence cGvHD



Cumulative incidence relapse / progression



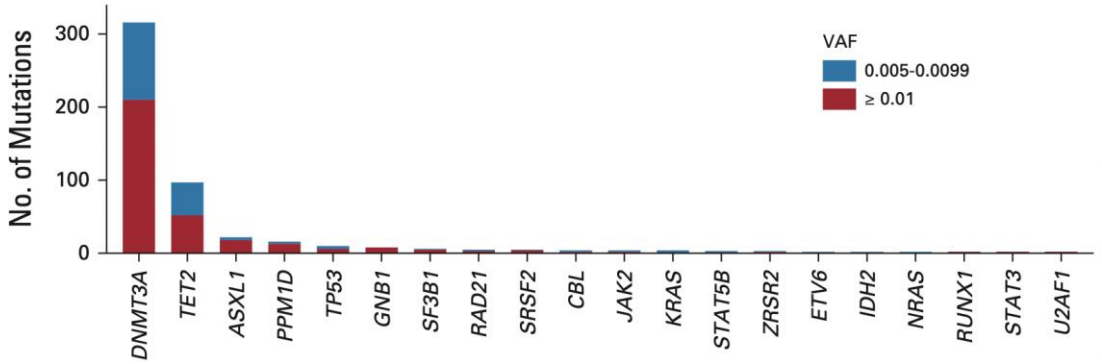
Overall survival

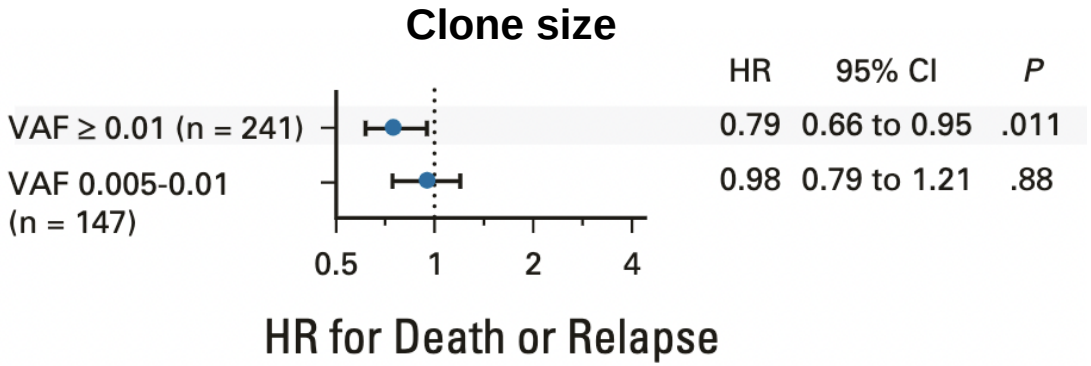


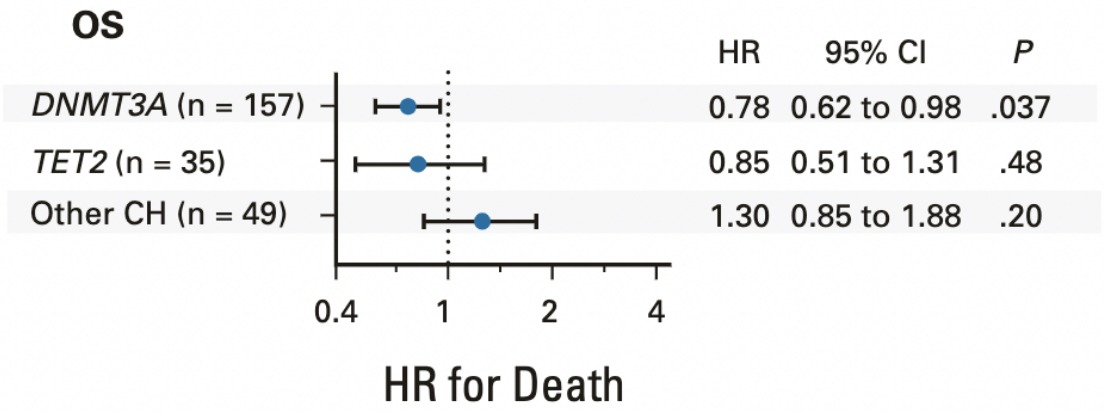
Frick et al., *J Clin Oncol* 2018

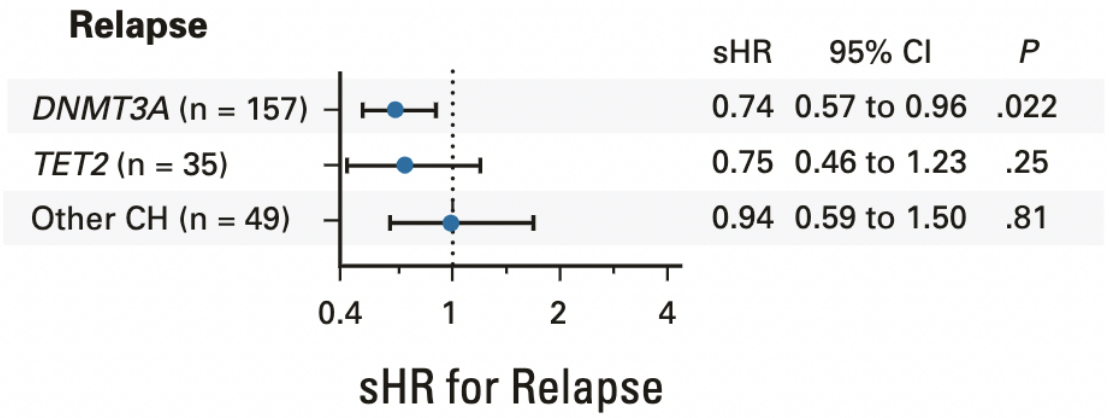
Allo-HSCT – Clinical outcomes

- Related or unrelated donors (≥40 years), PB or BM from time of donation
- n = 388 / 1,727 (22.5%) allo-HSCT donors had at least one CHIP mutation (VAF cut-off 0.005)









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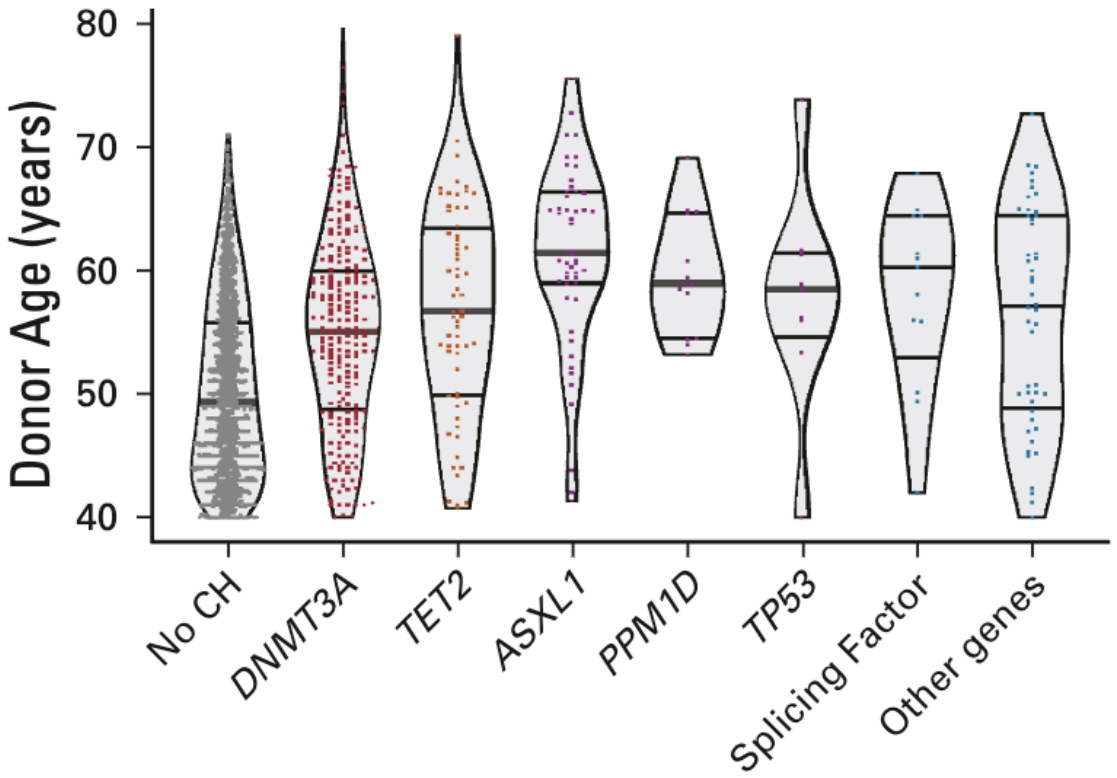
Gibson et al., *J Clin Oncol* 2021

Donor CH is associated with donor age

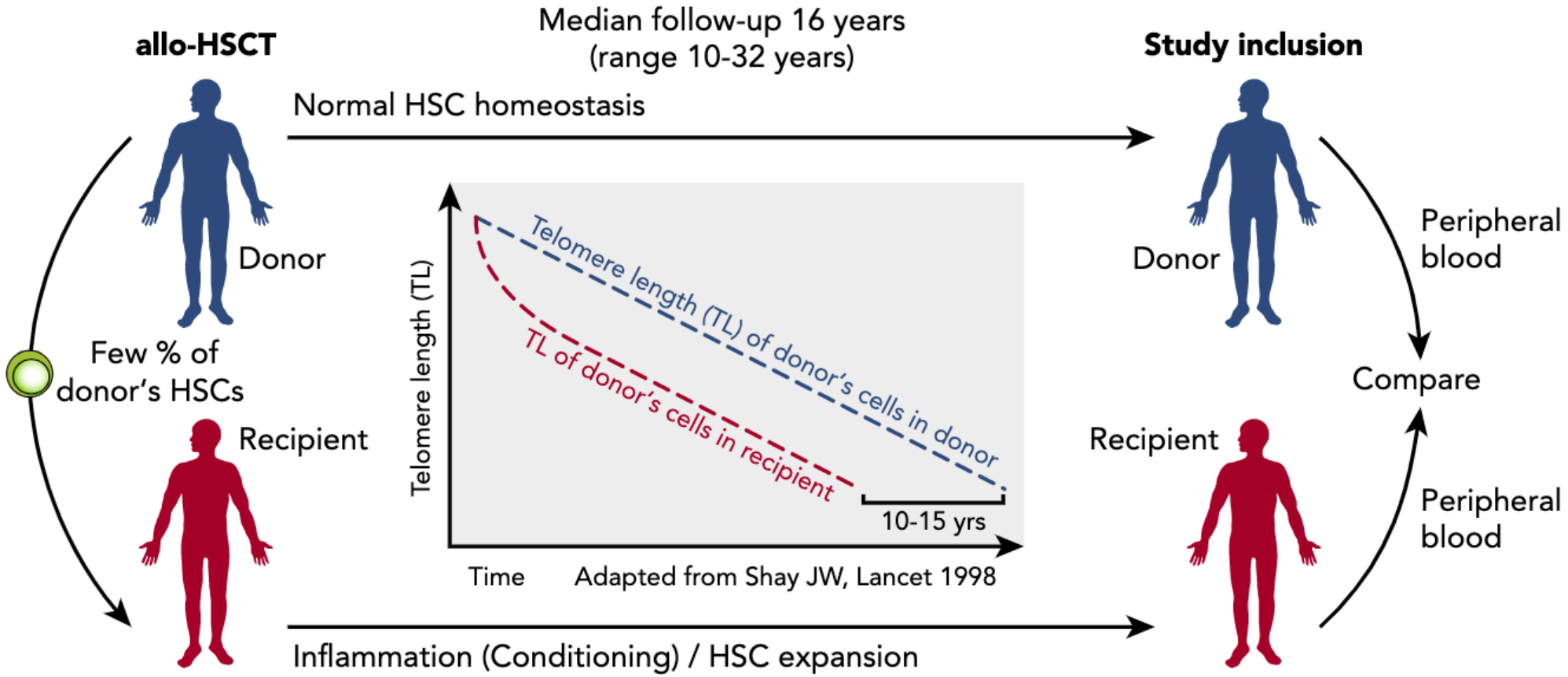


Gibson et al., *J Clin Oncol* 2021

Allo-HSCT – Clonal dynamics in the long-term

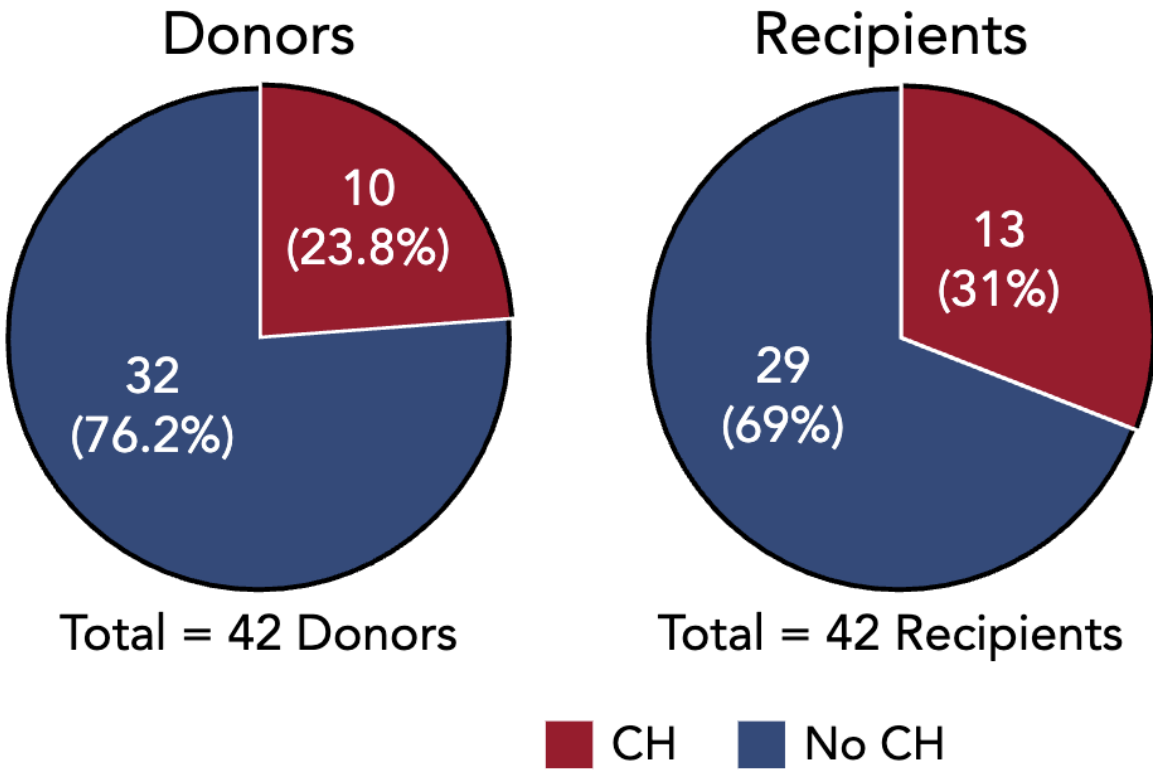
The median age at transplantation:
- Donors: 37 years
- Recipients: 39 years

The median age at study inclusion / sequencing:
- Donors: 57 years
- Recipients: 61 years



Boettcher et al., *Blood* 2020

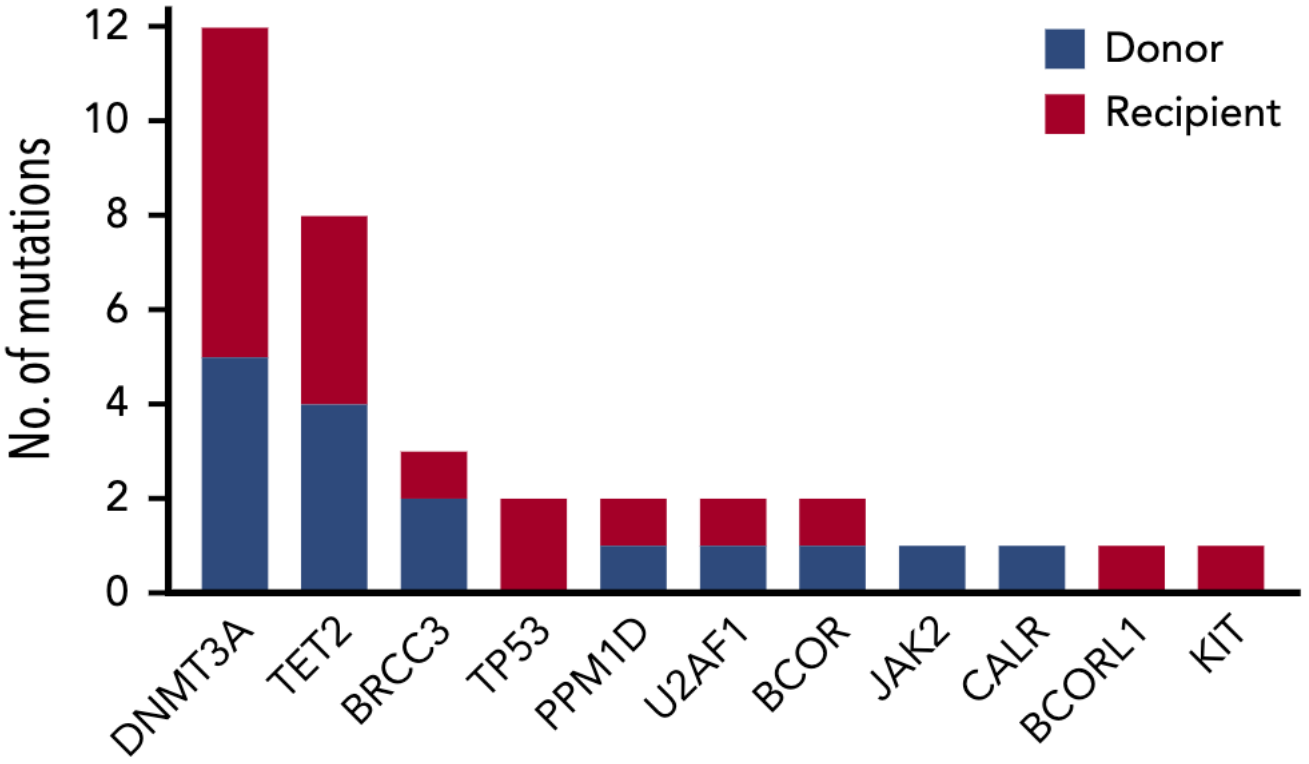
Allo-HSCT – Clonal dynamics in the long-term



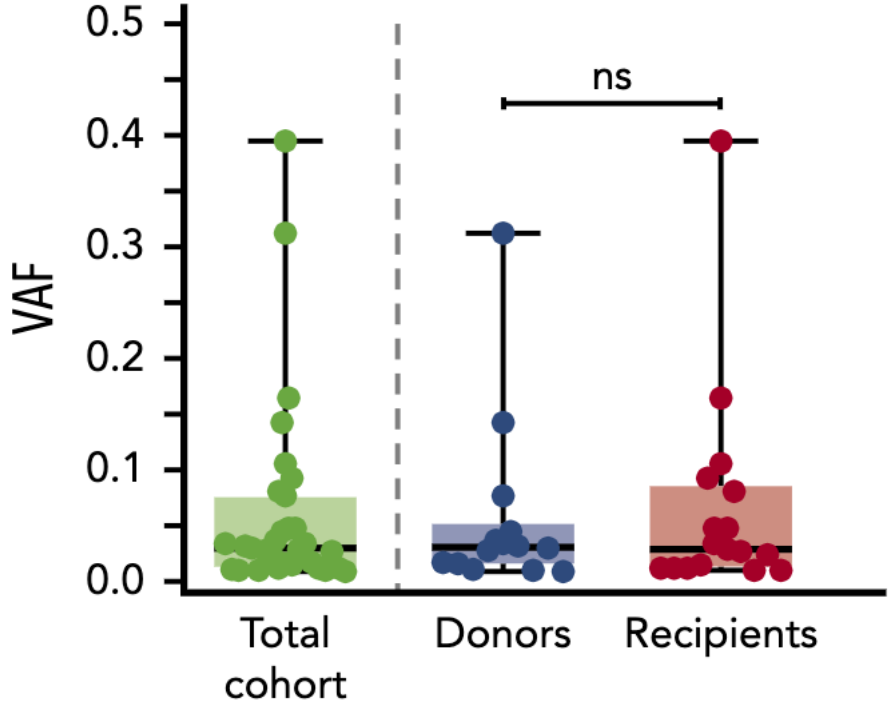
Boettcher et al., *Blood* 2020

Allo-HSCT – Clonal dynamics in the long-term

Mutational spectrum



Clone size

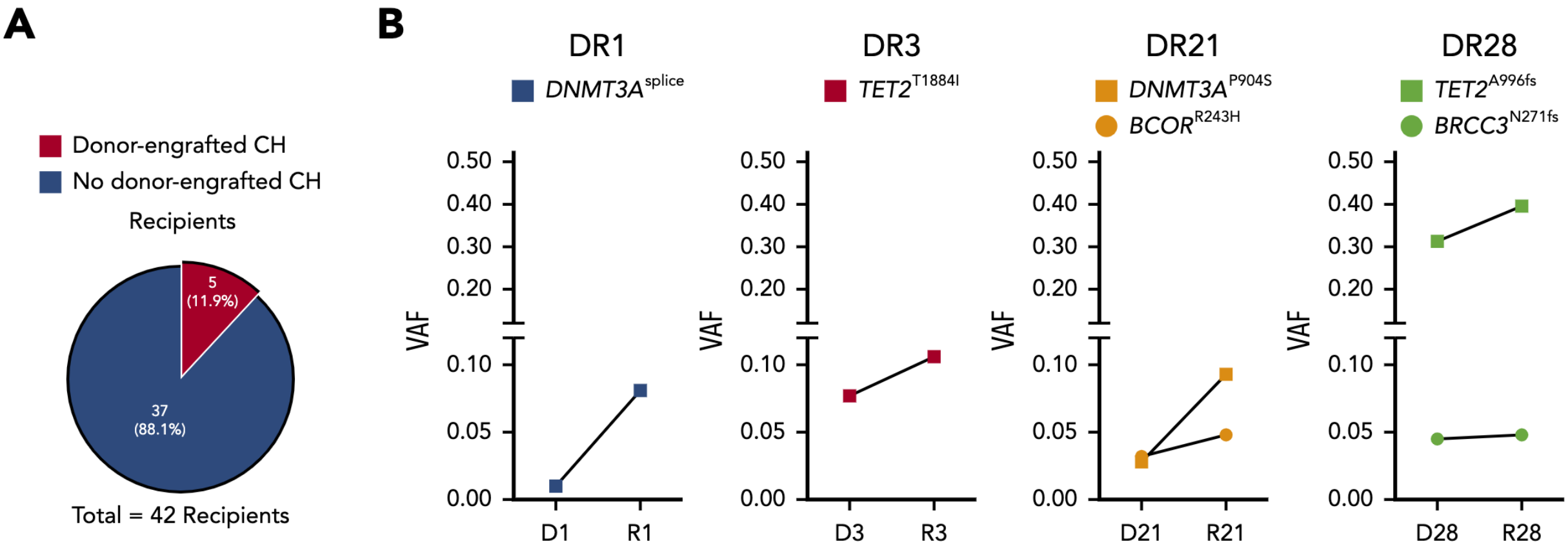


mean VAF	0.062	0.057	0.066
median VAF	0.030	0.031	0.029

Boettcher et al., *Blood* 2020

Allo-HSCT – Clonal dynamics in the long-term

Donor-engrafted CH clones expand in allo-transplant recipients



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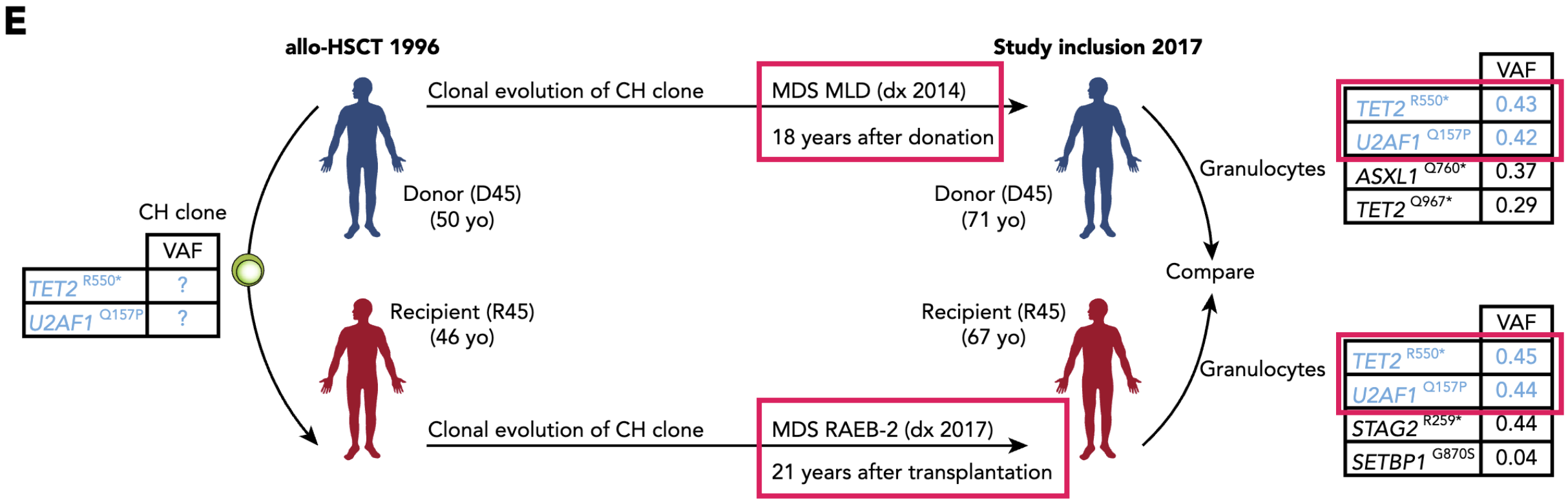
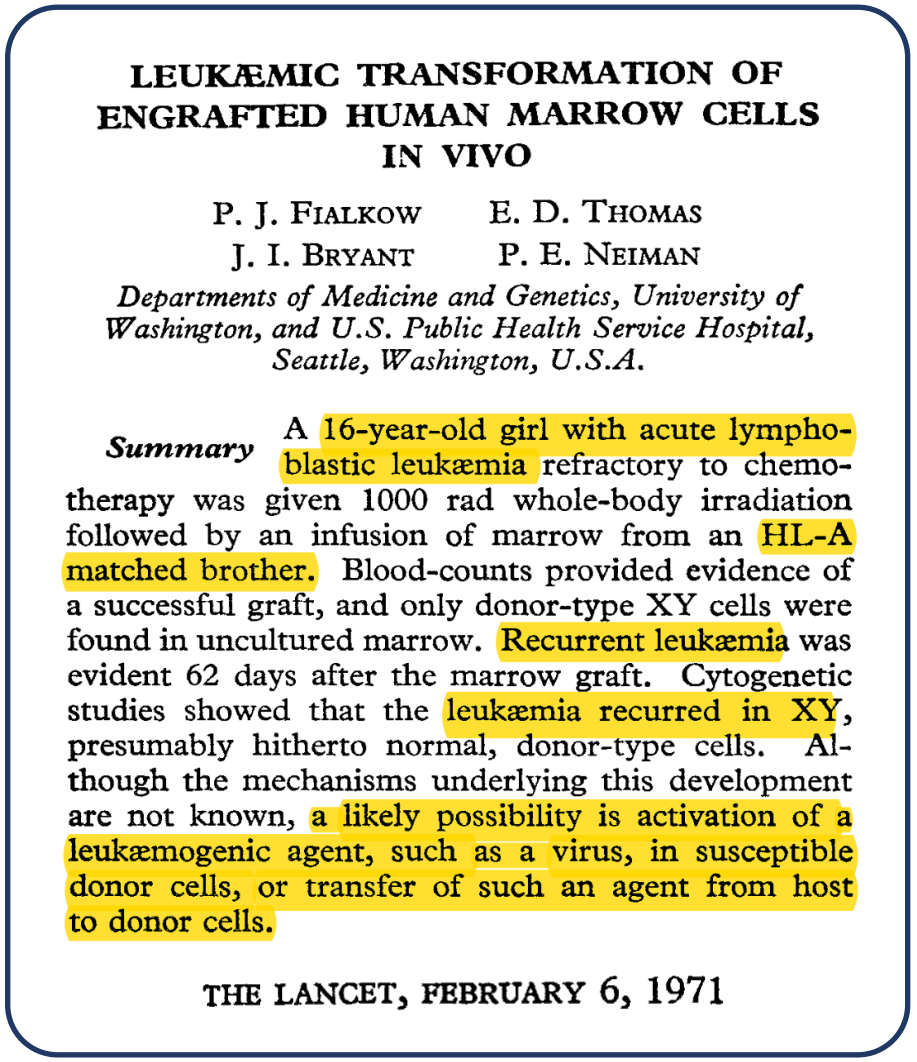
Boettcher et al., *Blood* 2020

Allo-HSCT – Donor-derived AML / MDS



Boettcher et al., *Blood* 2020

Allo-HSCT – Donor cell leukemia (DCL)



LEUKÆMIC TRANSFORMATION OF ENGRAFTED HUMAN MARROW CELLS IN VIVO

P. J. FIALKOW E. D. THOMAS
J. I. BRYANT P. E. NEIMAN

Departments of Medicine and Genetics, University of Washington, and U.S. Public Health Service Hospital, Seattle, Washington, U.S.A.

Summary A 16-year-old girl with acute lymphoblastic leukæmia refractory to chemotherapy was given 1000 rad whole-body irradiation followed by an infusion of marrow from an HL-A matched brother. Blood-counts provided evidence of a successful graft, and only donor-type XY cells were found in uncultured marrow. Recurrent leukæmia was evident 62 days after the marrow graft. Cytogenetic studies showed that the leukæmia recurred in XY, presumably hitherto normal, donor-type cells. Although the mechanisms underlying this development are not known, a likely possibility is activation of a leukæmogenic agent, such as a virus, in susceptible donor cells, or transfer of such an agent from host to donor cells.

THE LANCET, FEBRUARY 6, 1971

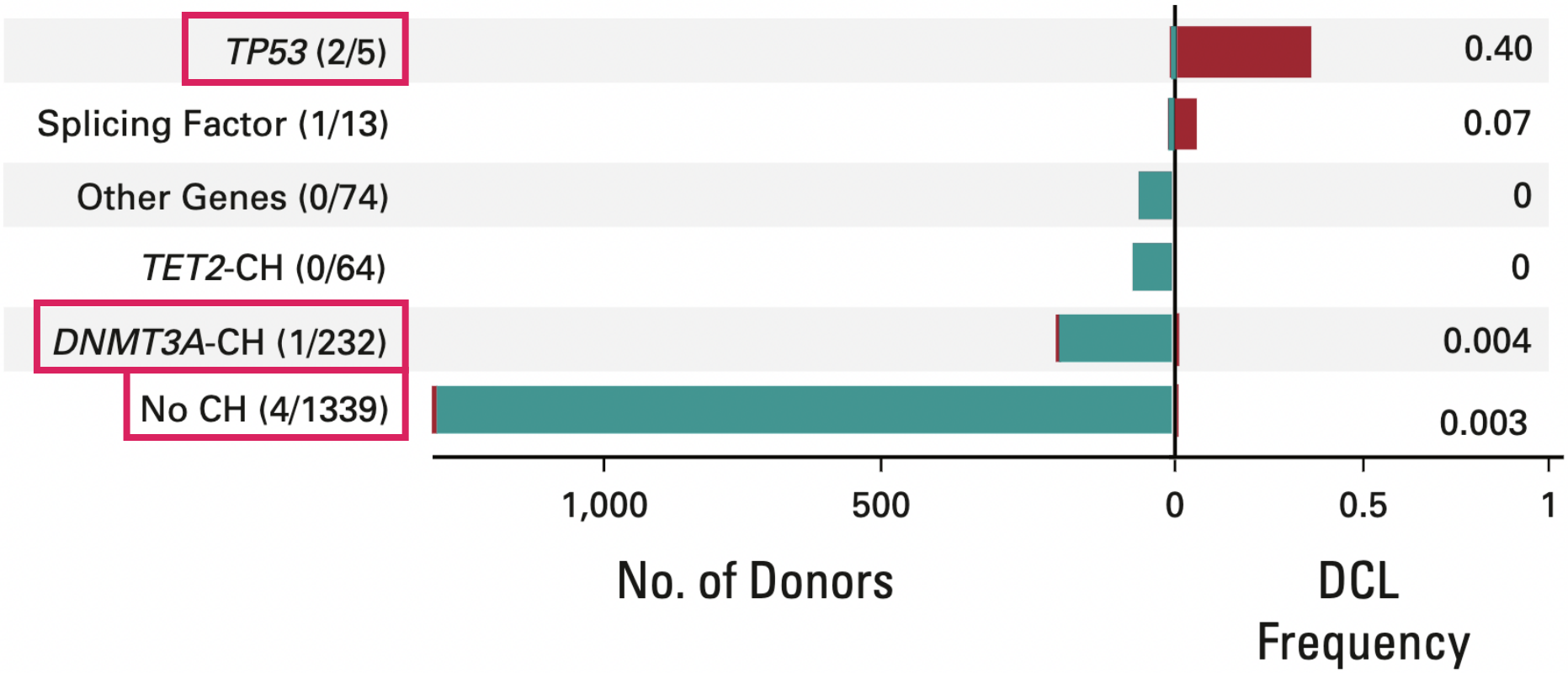
- **14** DCL cases in **10,498** transplant recipients (**0.13 %**) between 1982 and 2003 [1]
- **8** DCL cases in **2,390** transplant recipients (**0.33 %**) between 1992 and 2010 [2]
- **44** DCL cases in **32,898** transplant recipients (**0.13 %**) between 1974 and 2012 [3]

→ **Risk for DCL 0.1 - 0.3%**

[1] Hertenstein et al., *Haematologica* 2005 [2] Dietz et al., *Br J Haematol* 2014 [3] Kato et al., *Leukemia* 2016

TP53 mutations in donor cell leukemia in allo-HSCT

8 DCL cases in **1,727** transplant recipients (**0.7 % 10-year cumulative incidence**)

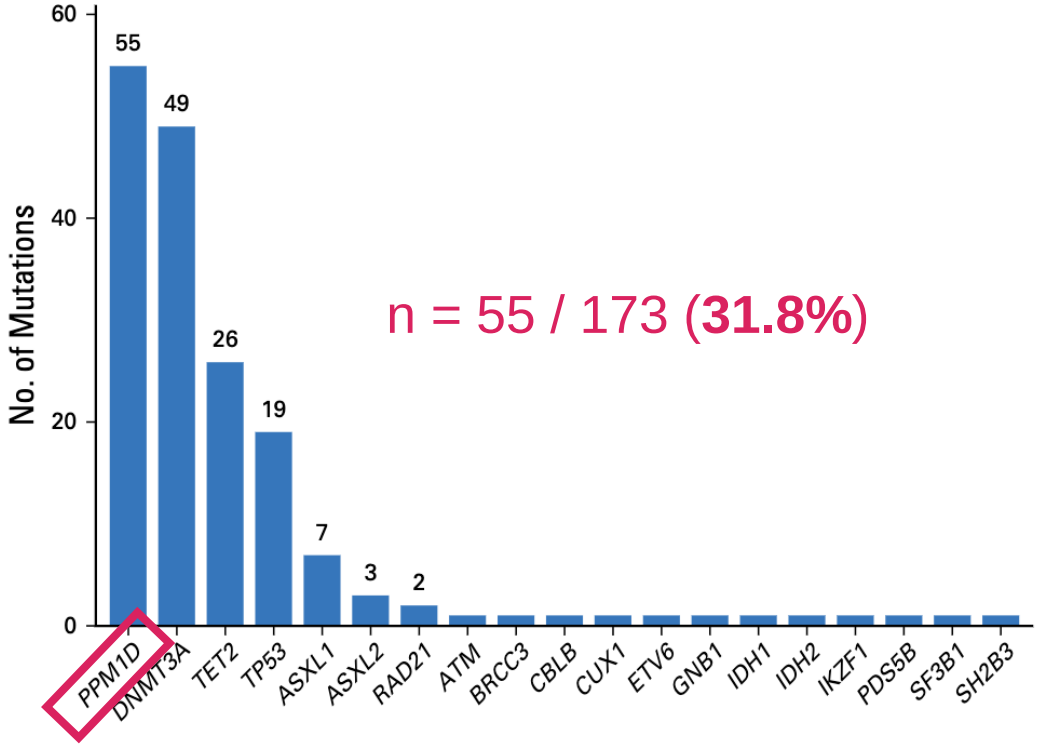


Gibson et al., *J Clin Oncol* 2021

Autologous stem cell transplantation

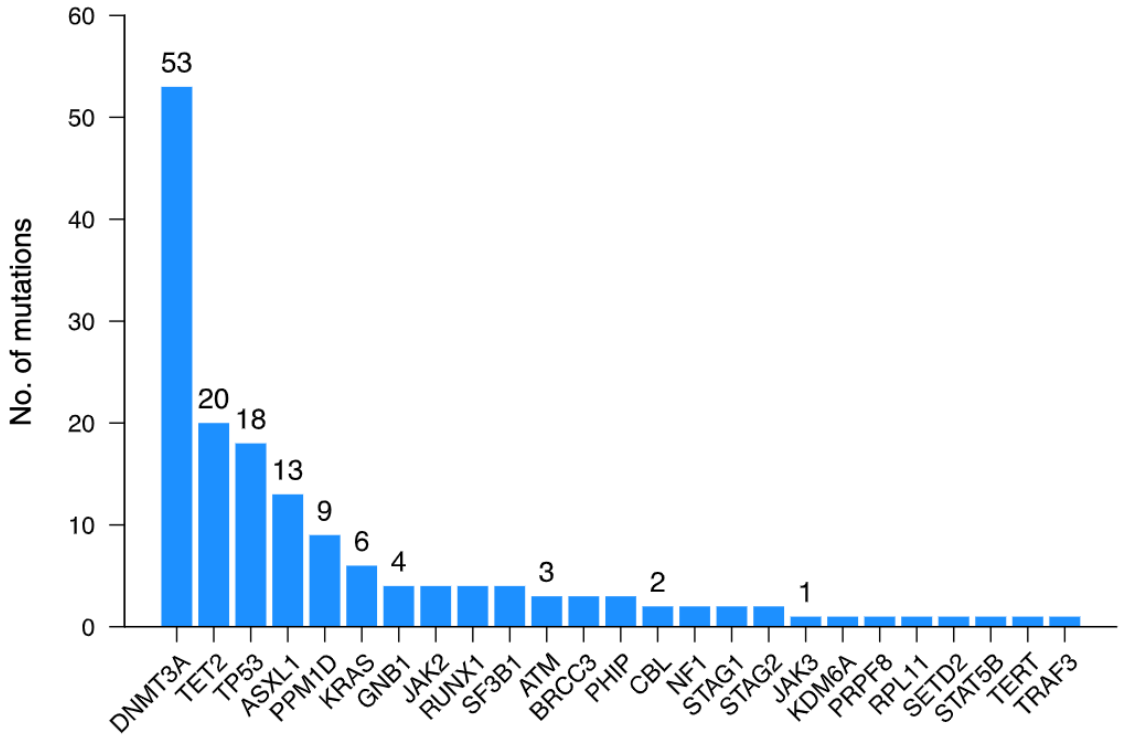
Autologous stem cell transplantation (ASCT) – mutational spectrum

Lymphoma patients [1]



n = 55 / 173 (**31.8%**)

Plasma cell myeloma patients [2]



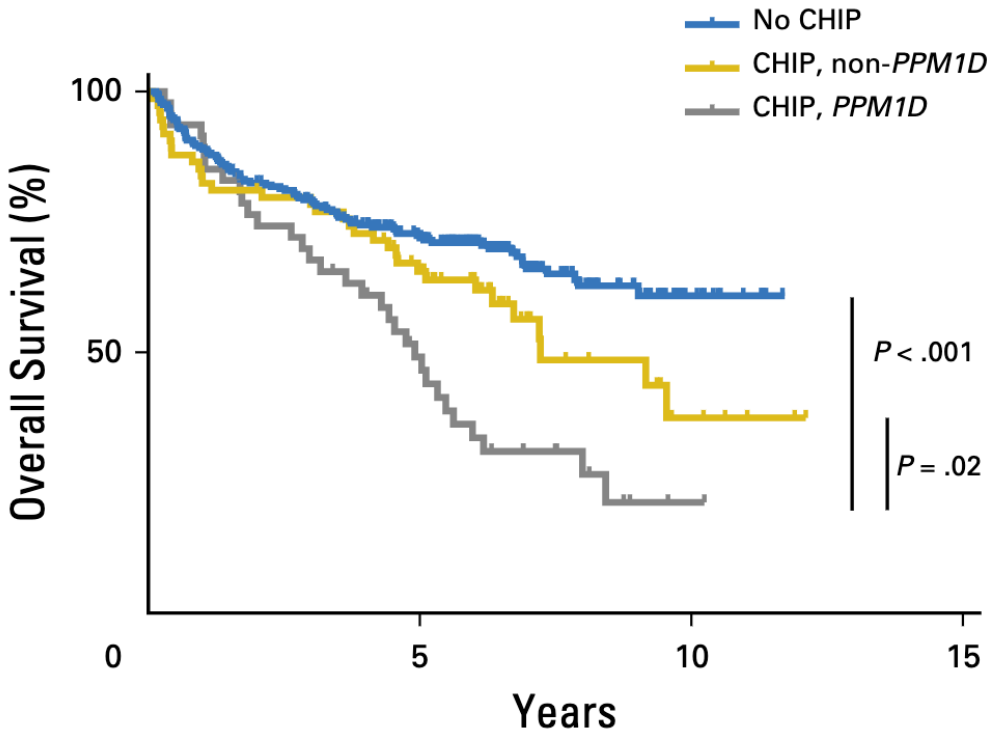
→ **Enrichment for *PPM1D* mutations lymphoma patients**

[1] Gibson et al., *J Clin Oncol* 2017

[2] Mouhieddine et al., *Nat Commun* 2020

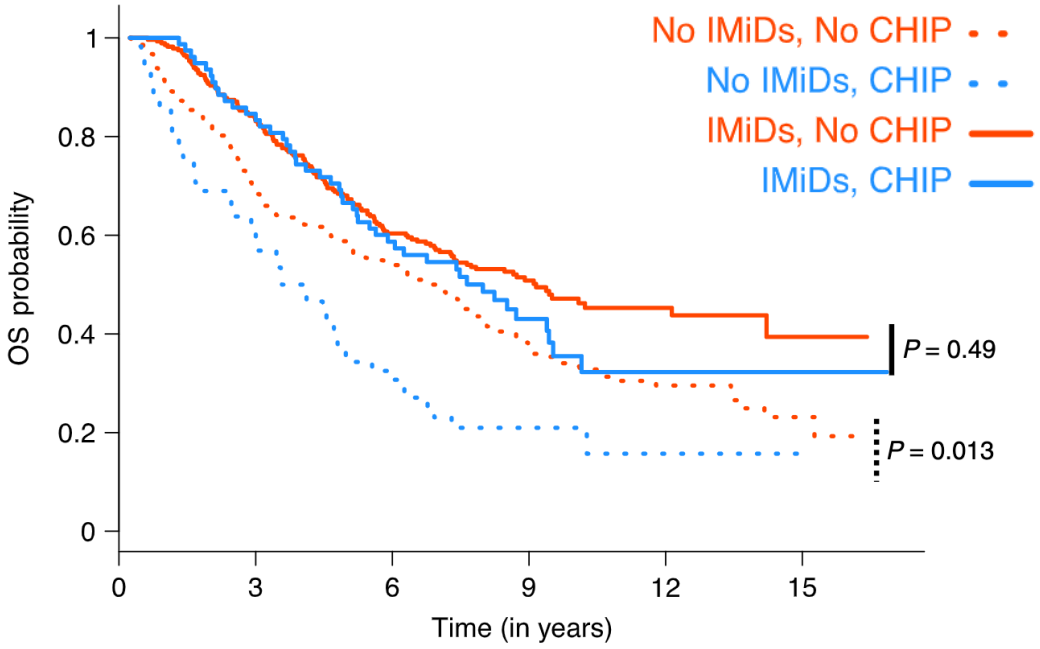
ASCT – CHIP is associated with inferior overall survival

Lymphoma patients [1]



→ **Therapy-related myeloid neoplasms & cardiovascular disease**

Plasma cell myeloma patients [2]



→ **Disease progression**

[1] Gibson et al., *J Clin Oncol* 2017

[2] Mouhieddine et al., *Nat Commun* 2020

Take-home message of CH in HSCT

Allo-HSCT

- CH is very common in the general (ageing) population (and thus in donors).
- Older donor age is associated with donor-engrafted CH.
- Donor-engrafted CH is associated with increased CI of cGvHD and decreased CIR but similar, maybe even improved OS.
- DCL is a rare but devastating complication (adverse-risk genetics, i.e., *TP53*).
- Currently, no indication for CH screening in allo-HSCT donors.

ASCT

- Therapy-related myeloid neoplasms and cardiovascular disease.
- Promotion of disease progression under certain circumstances ?

Thank you for your attention !

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