HÉMATOPOÏÈSE CLONALE (CHIP): IMPLICATIONS CLINIQUES EN ONCOLOGIE ET EN HÉMATOLOGIE

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Lyon, 17/05/2022

GUSTAVE ROUSSY
CANCER CAMPUS
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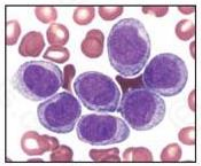
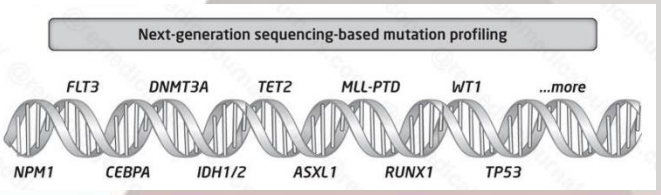
ONCO AURA
RÉSEAU RÉGIONAL DE CANCÉROLOGIE
AUVERGNE-RHÔNE-ALPES

Morphology

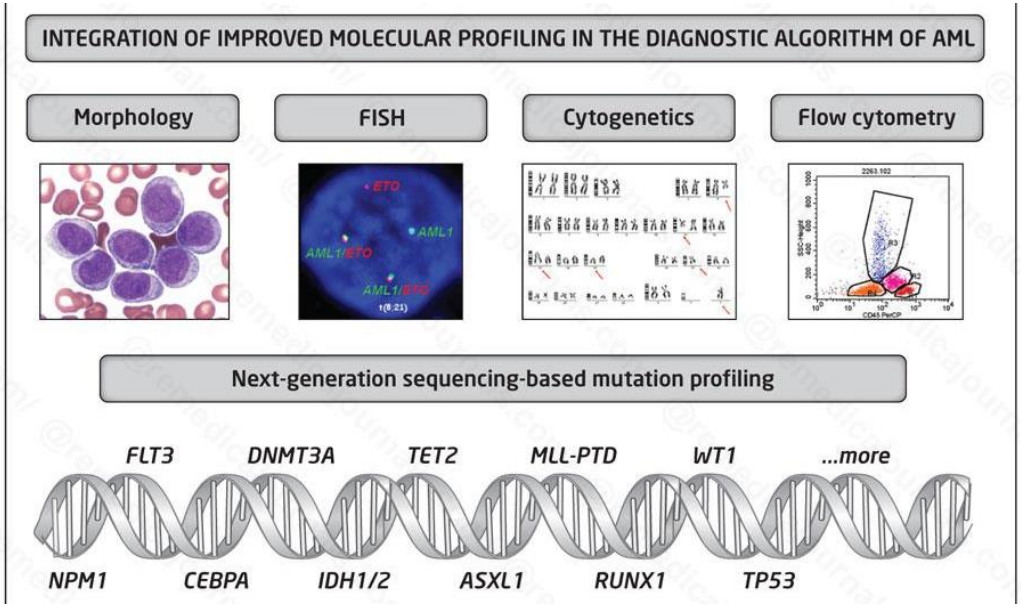


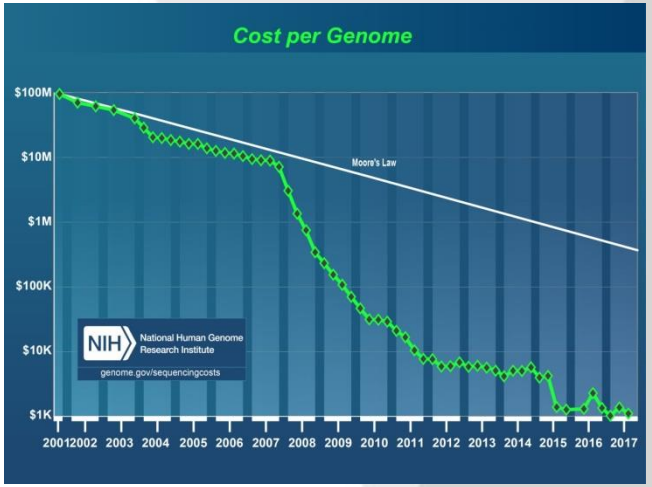
CHIP
Molecular characterization of acute myeloid leukemia



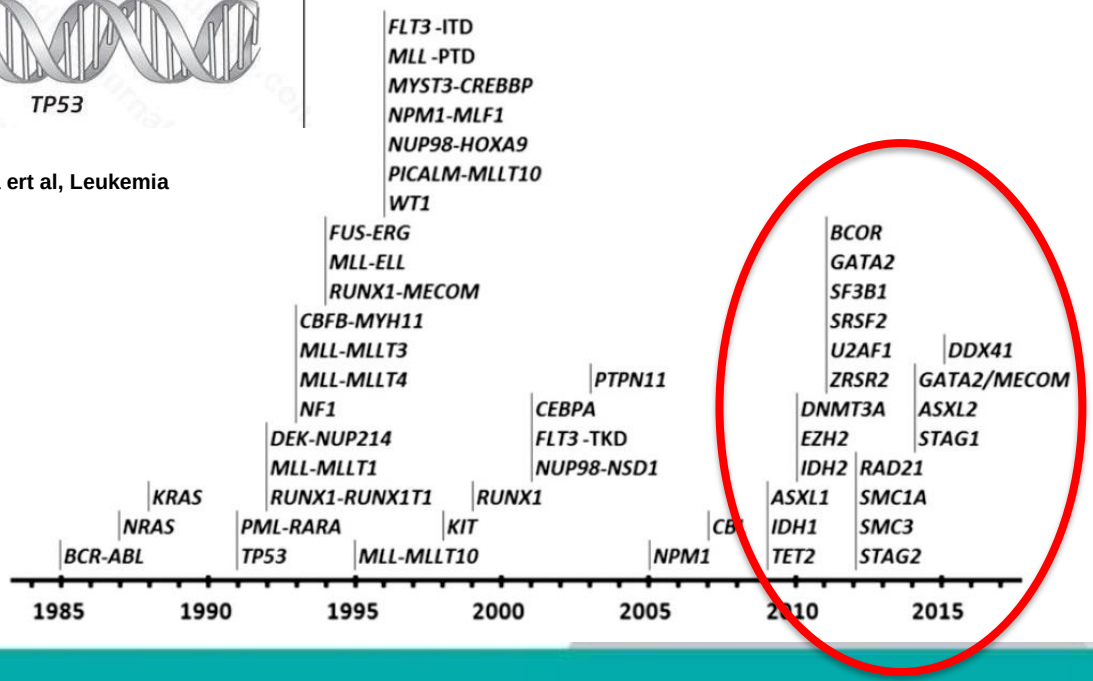
The Molecular Pathogenesis of Acute Myeloid Leukemia, K Tawana ert al, Leukemia lymphoma 2016

AML Molecular Characterization



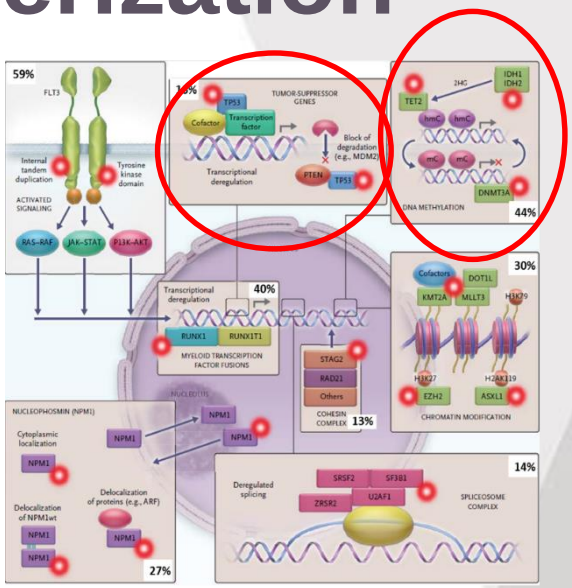


The Molecular Pathogenesis of Acute Myeloid Leukemia, K Tawana ert al, Leukemia lymphoma 2016



AML Molecular Characterization

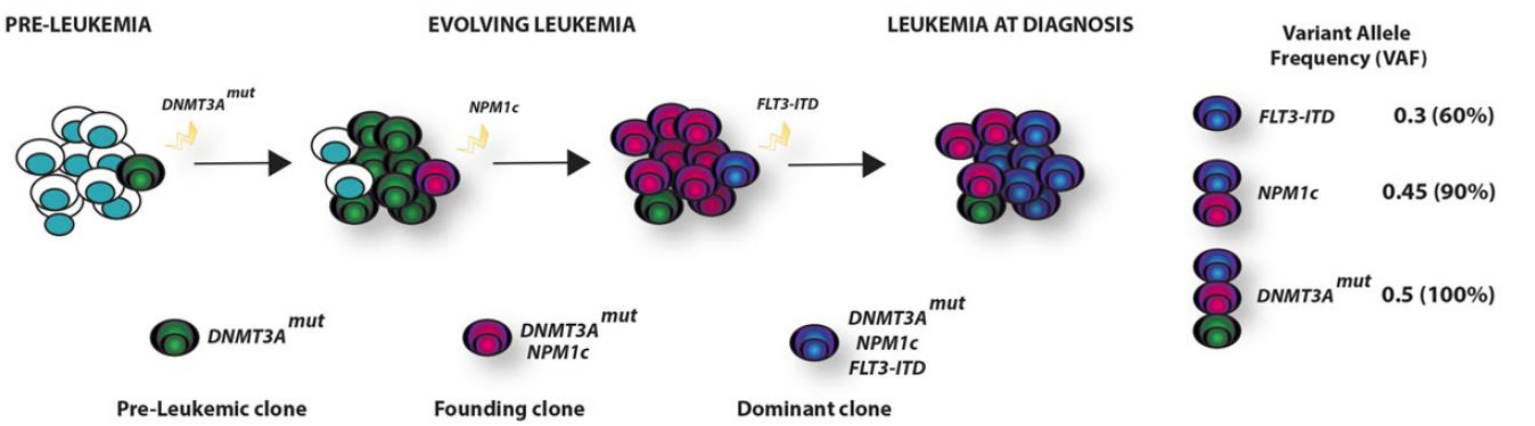
- Distinct groups of gene mutations
  - > Epigenetic mutations lead to unusual gene expression of some oncogene with no alteration of the DNA sequence
  - > DNA repair mutations



- 3 to 5 drivers mutations in AML
- Variant allele frequency (VAF) :

nbr of variant reads /nbr of total reads

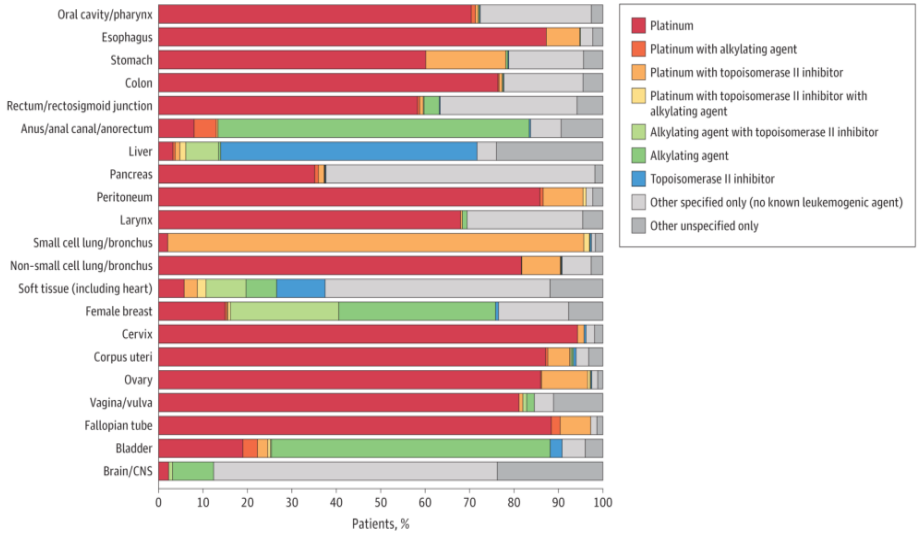
Clonal evolution and clonal heterogeneity of AML



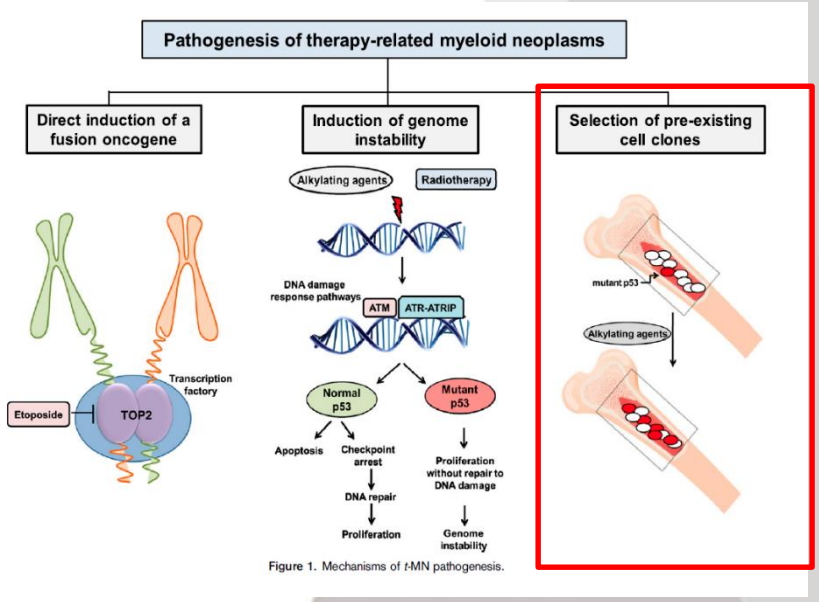
AML physiopathology, TRMN example

Therapy-related myeloid neoplasms (WHO 2016)

Therapy-related myeloid neoplasms (TRMNs) remain as a distinct category in the classification for **patients who develop myeloid neoplasms following cytotoxic therapy.**
The TRMNs may be further subdivided as therapy-related MDS or AML (t-MDS or t-AML)

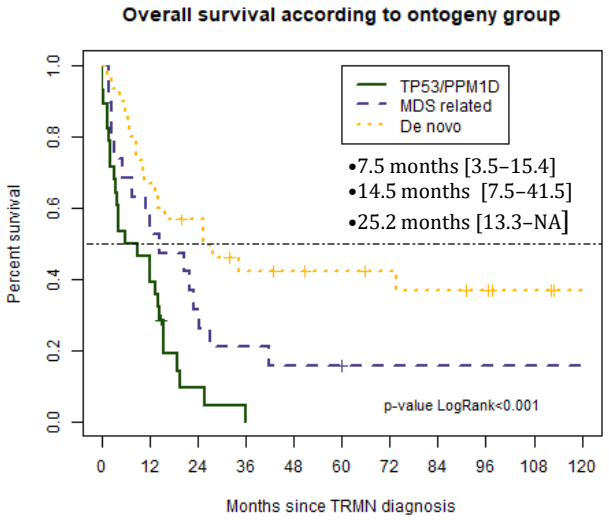


Association of Chemotherapy for Solid Tumors With Development of TRMN in the Modern Era
JAMA Oncol. 2019;5(3):318-325

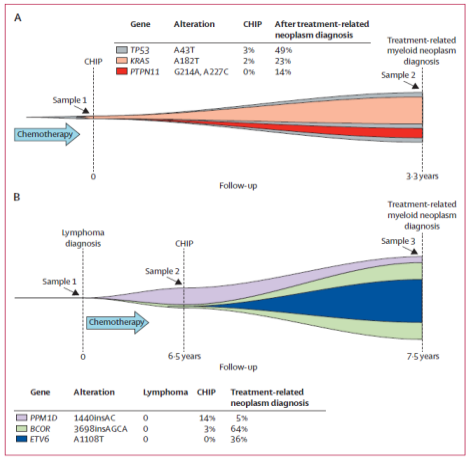


M Heuser ASH 2016

Molecular Landscape of TRMN



Khalife-Hachem *et al*, Hemasphere 2021



Gillis et al, Lancet Oncol 2017

- **TP53/PPM1D group : Clonal Selection**
  - Older
  - More treatment lines
  - Longer time btw TRMN & Cancer,
  - More complex Karyotype
  - Poor OS

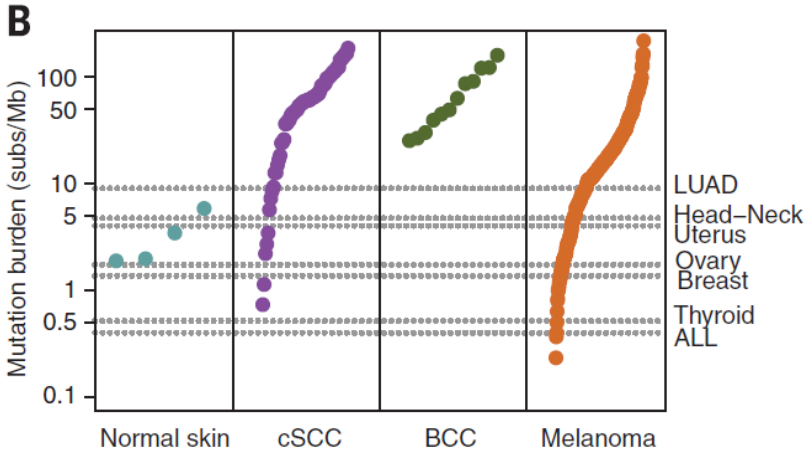
- In **78%** of TRMN cases, at least one of the mutations was detected at cancer stage (median time 3 years [1,7-7,8]).

CHIP DEFINITION

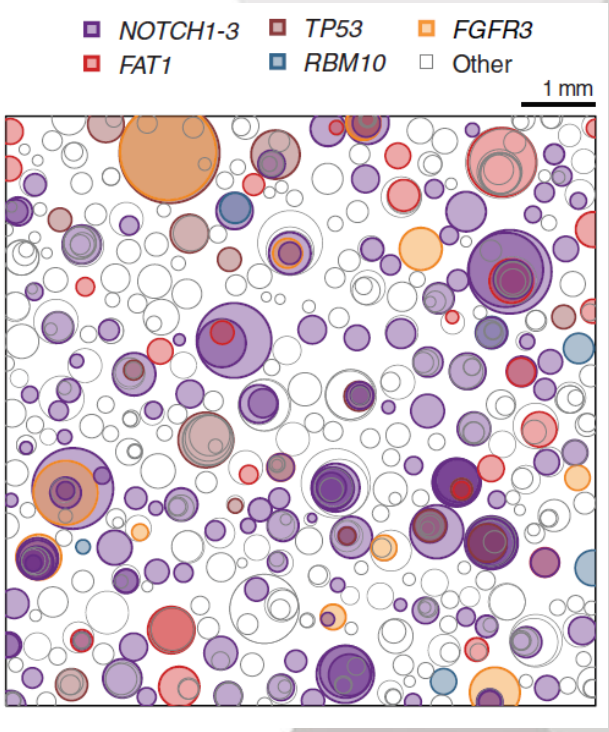
M Hübner et alRev Med Suisse 2015;volume 11. 1325-1330

New Paradigm with development of Sequencing-based approaches

- Ultradeep sequencing of normal skin



- Burden of somatic mutations 2 to 6 mutations/MB/cells
- Similar to that seen in many cancers

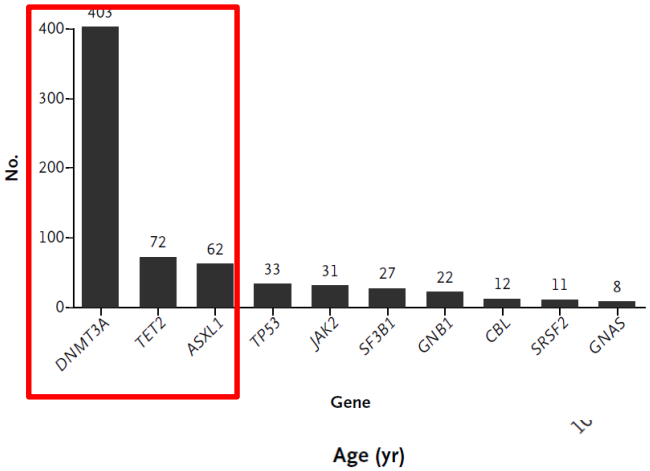


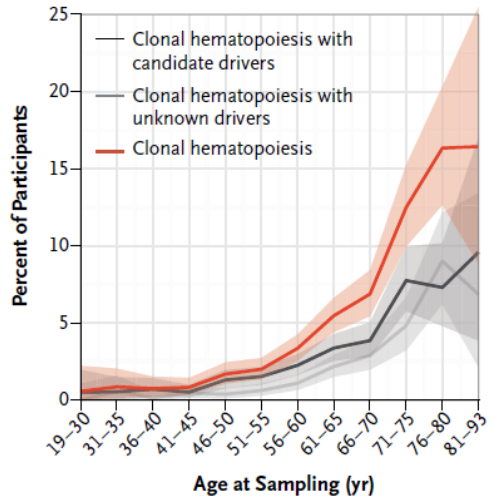
- Schematic representation of the mutant clones in 1 cm^2 of normal skin
  - > mutations were found in 18 to 32% of normal skin cells

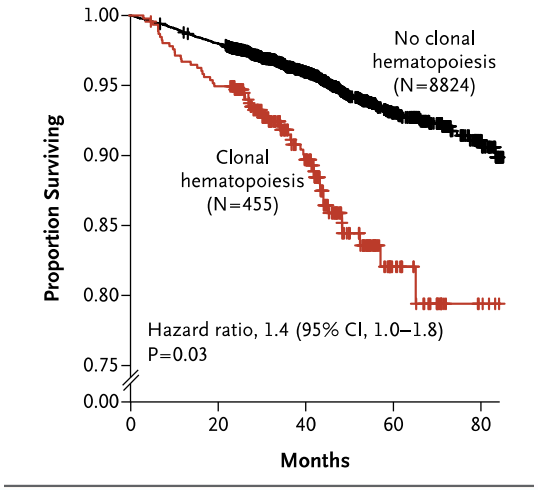
David P. Steensma et Benjamin L. Ebert, Experimental Hematology, 2020-03-01

Iñigo Martincorena et al, Science 2015

Clonal hematopoiesis of indeterminate potential (CHIP) in healthy patients



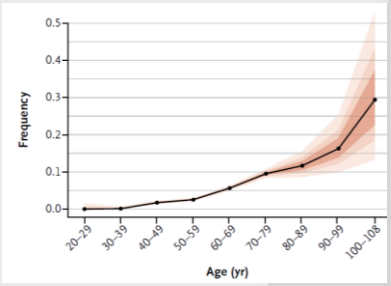


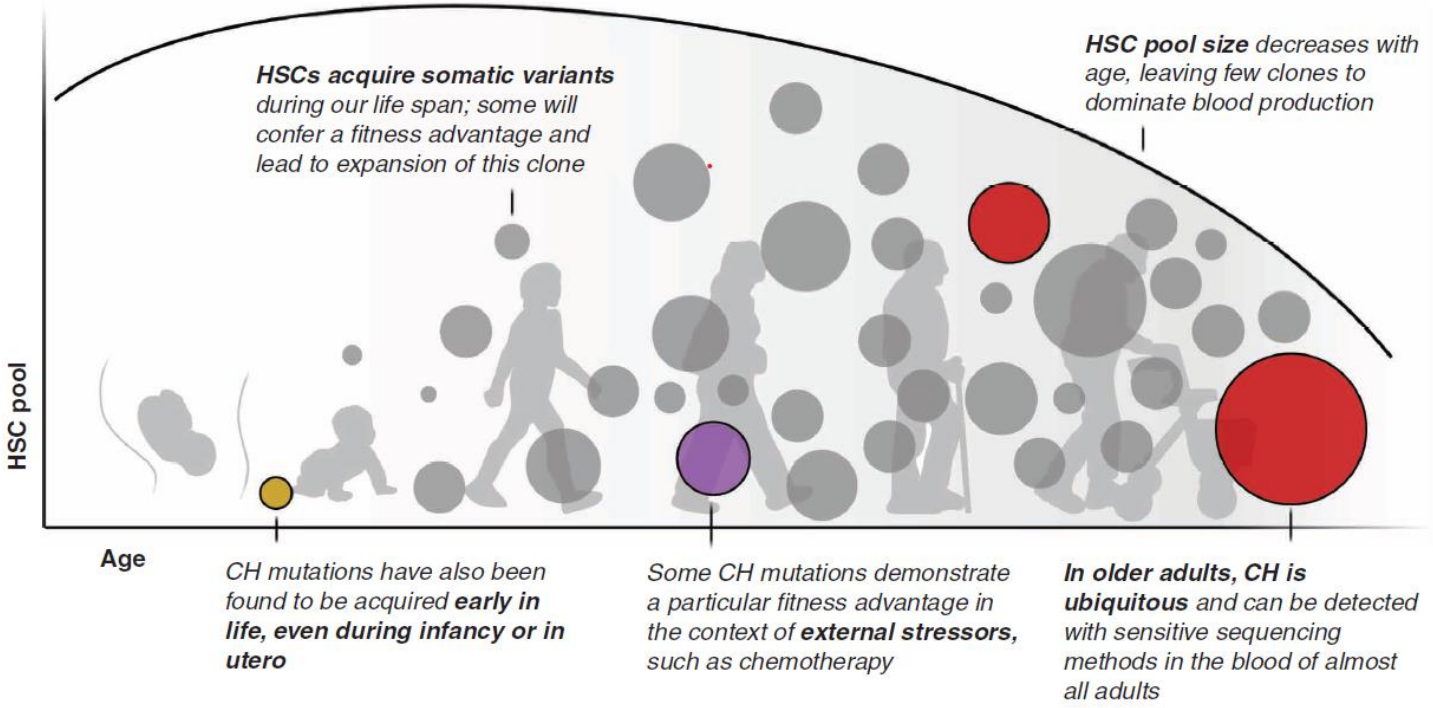


- 10 % healthy adults > 65 years
- Somatic mutations : epigenetic regulators
- 10 times the risk of a hematologic cancer VAF > 10% (LNH/AML)
- Increase in all-cause mortality (including coronary heart disease, ischemic stroke)

Jaiswal S et al, NEJM 2014.
Genovese G et al, NEJM 2014.

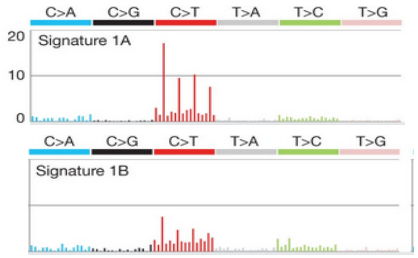
CHIP
CONTEXT DEPENDENT MECHANISM

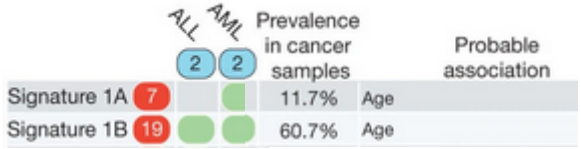




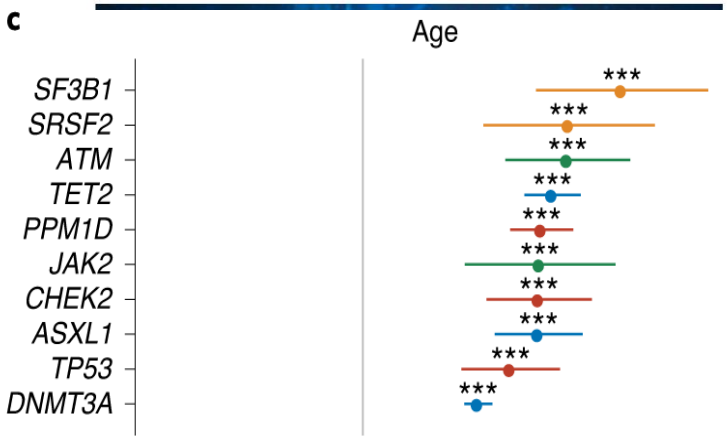
Influence of age

- **Distinct mutational signatures with age**
  - CHIP deamination of 5-methylcy-tosine to thymine is found to be a common events





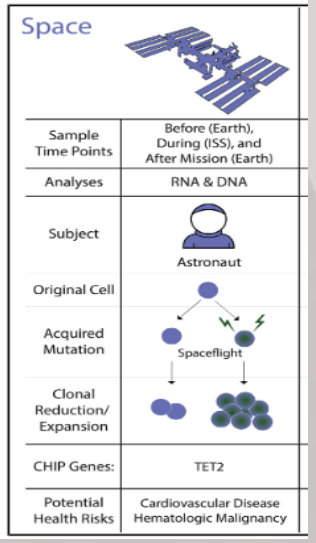
Alexandov et al, Nature 2013



Former NASA astronauts and identical twins Scott Kelly (right) and Mark Kelly. Scott spent a year on the ISS from 2015 to 2016 while Mark stayed on Earth, allowing scientists to study the effects of living in space on Scott's body and compare the changes to Mark.

PHOTOGRAPH BY ROBERT MARKOWITZ, NASA

Lack of gravity and other non-Earthly conditions cause accelerated aging effects



Trinchant et al, Cell Reports 2020

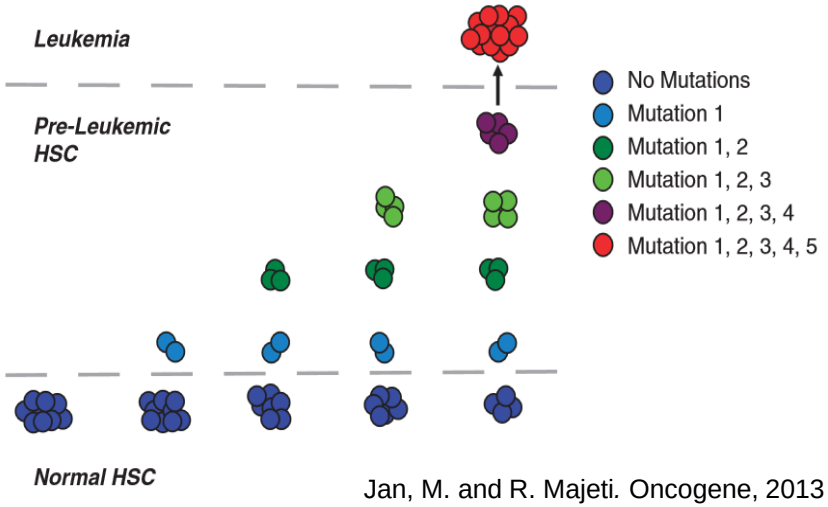
- Somatic mutations are inevitable, especially in proliferative tissue as hematopoietic system
- Age correlates with the number of cell divisions, events naturally accumulate
- Clonal advantage
  - HSC pool contraction
  - increased fitness over their wild-type counterparts (For ex TET2 & DNMT3A mice exhibit increased HSC renewal)

NHLBI Trans-Omics for Precision Medicine Consortium, Nature 2020

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele frequency of at least 2% (e.g., *DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, U2AF1, CREBBP, CUX1, SRSF2, MLL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1*)
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

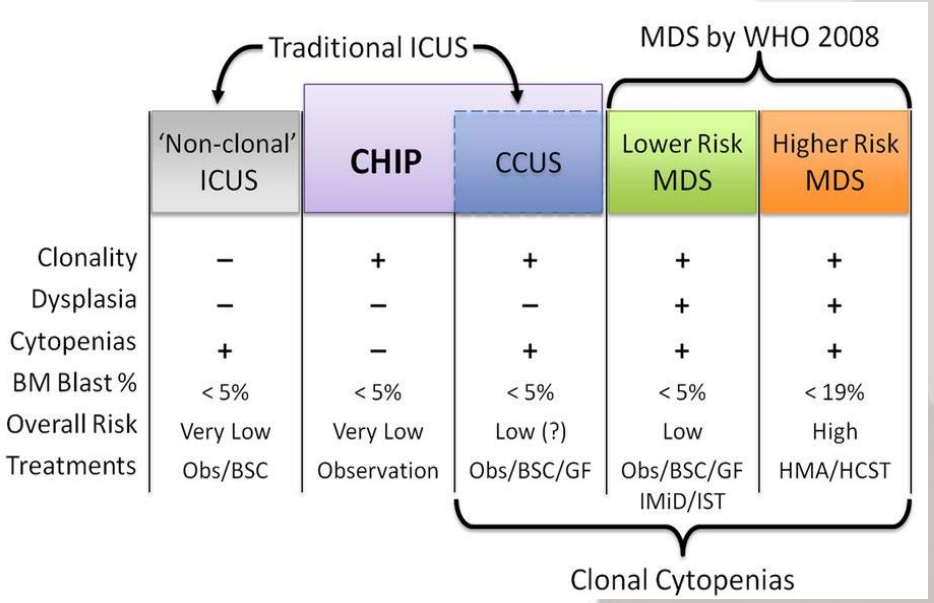
D Steensma *et al,* Blood 2015



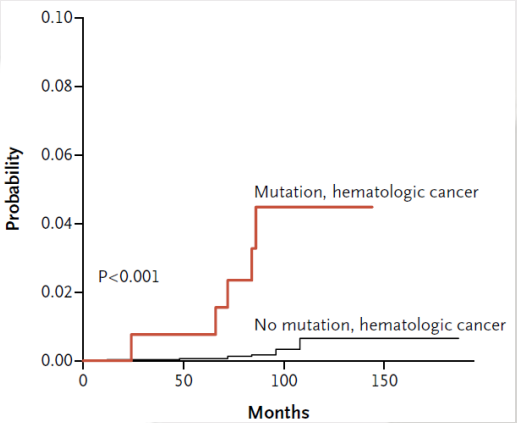
Jan, M. and R. Majeti. Oncogene, 2013

CHIP to AML : a continuum ?

- **MDS : Myelodysplastic Syndrom**
- **ICUS: Idiopathic Cytopenias of Undetermined Significance**
- **IDUS: Idiopathic Dysplasia of Undetermined significance**
- **CCUS :ClonalCytopenias of Undetermined Significance**
- **CHIP: Clonal Hematopoiesis of Indeterminate Potential**



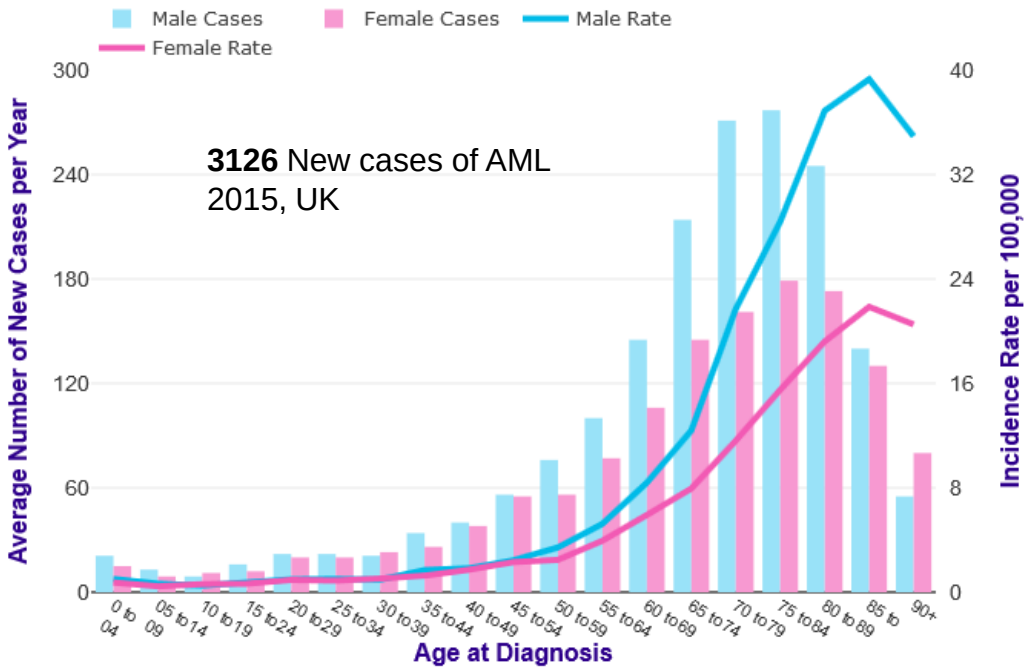
D Steensma *et al,* Blood 2015



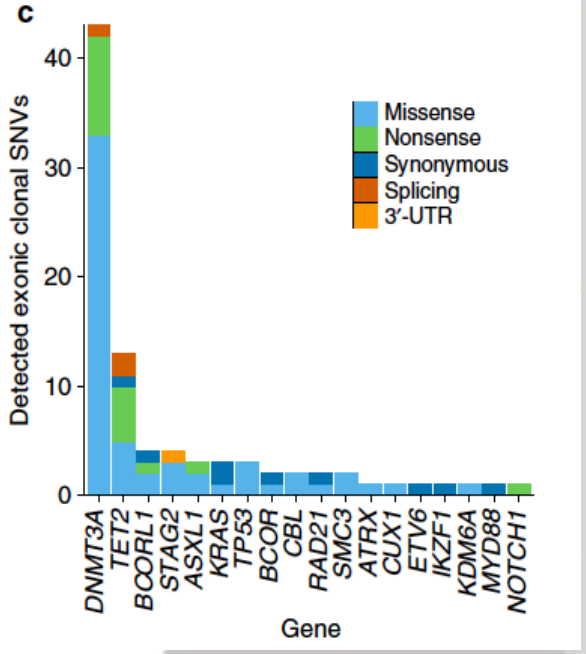
CHIP : PRE LEUKEMIC STATE ?

Are all CHIP a preleukemic state ?

- AML is a rare disease opposite to CHIP
- CHIP is ubiquitous in healthy adults



Cancer Research UK

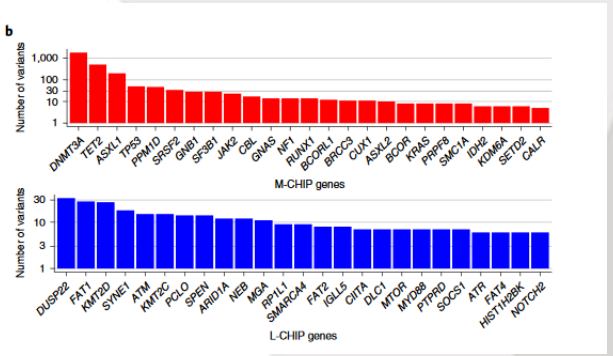


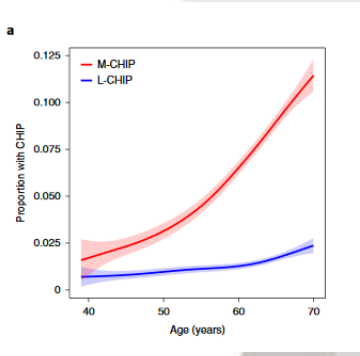
Young et al, Nat Com 2016

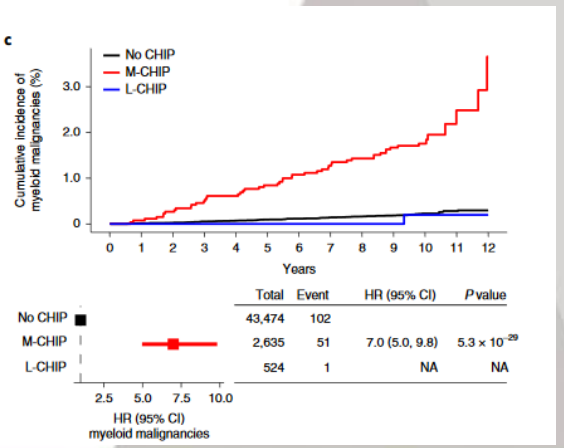
95% of individuals studied (VAF 0.0003)

CHIP or Pre Leukemic state ?

- **All CHIP are not the same**
  - Distinguished myeloid and lymphoid somatic gene mutations
  - Prevalence of both M-CHIP increased with age
  - M-CHIP was associated with a higher incidence of myeloid malignancies (hazard ratio = 7.0)

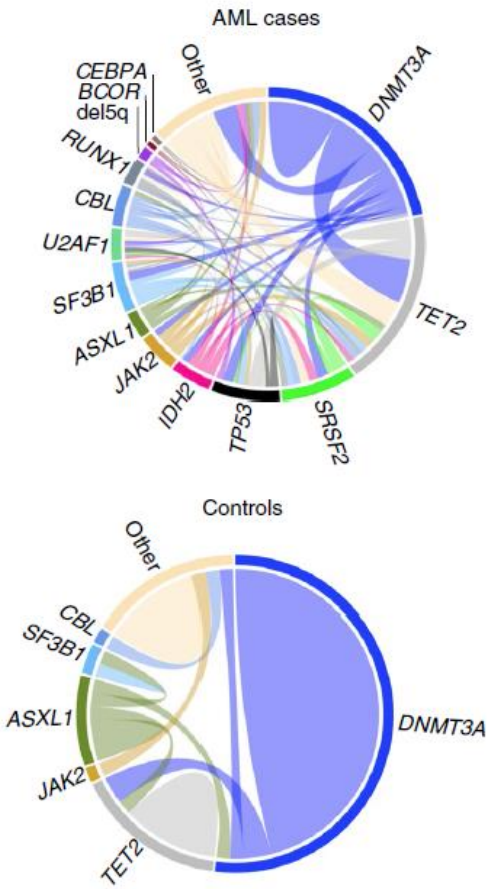






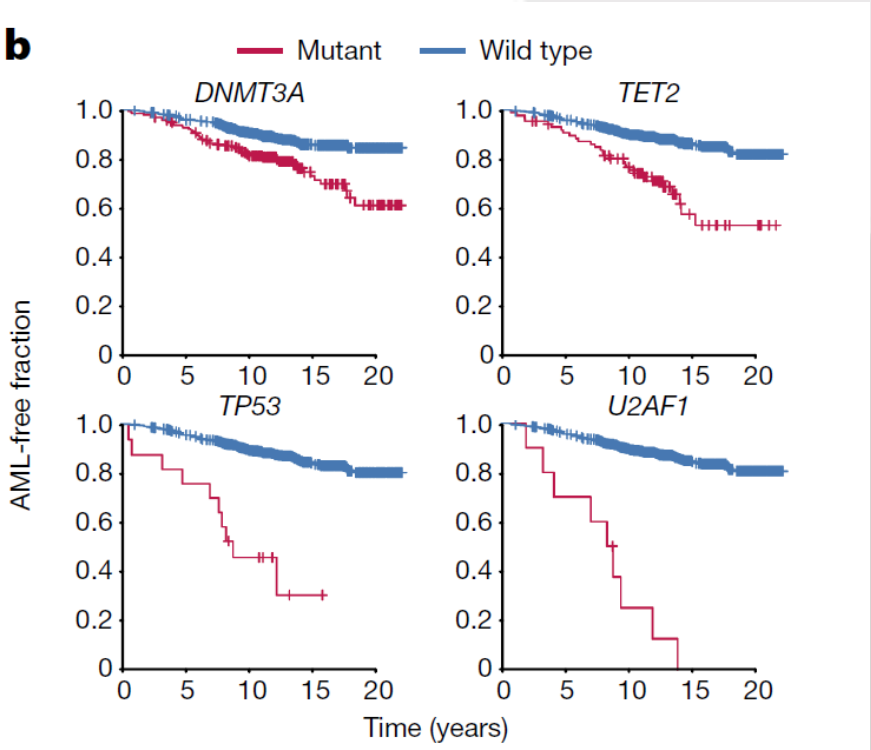
A Niroula *et al* Nat Med 2021

CHIP & AML PREDICTION



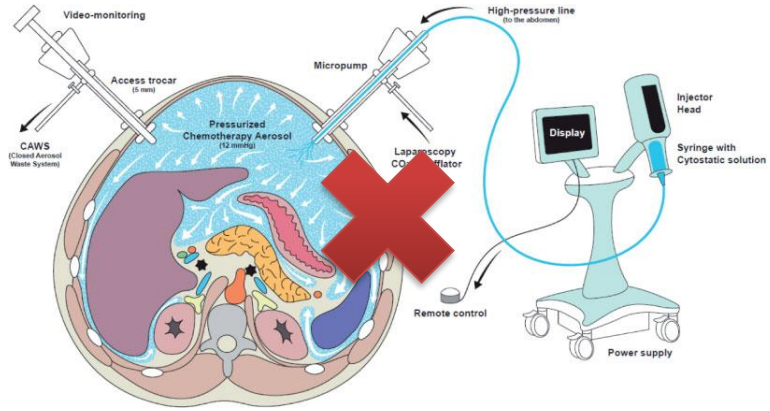
- AML demonstrated greater clonal complexity than controls

Pinkal Desai *et al*, Nat Med 2018



- Higher variant allele frequencies
- IDH2, TP53 and RUNX1 mutations almost always predictive of development of AML.

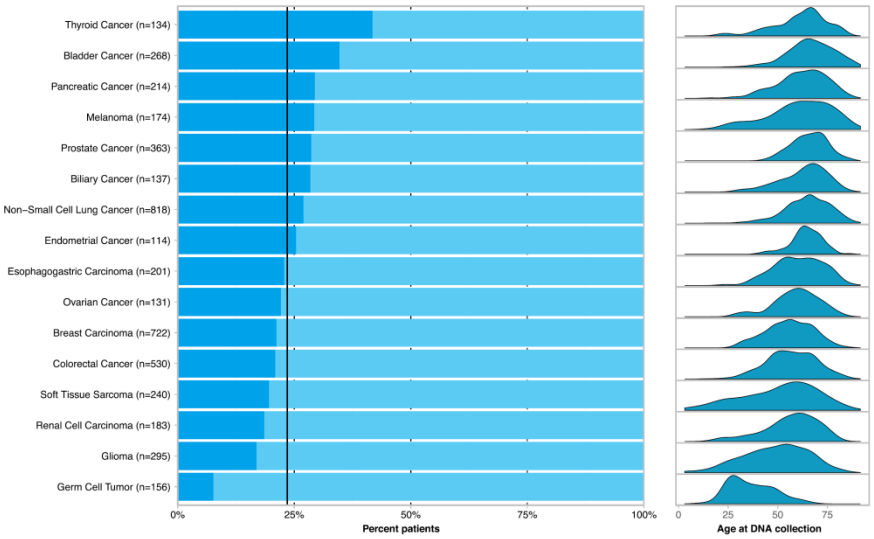
Sagi Abelson *et al*, Nature 2018

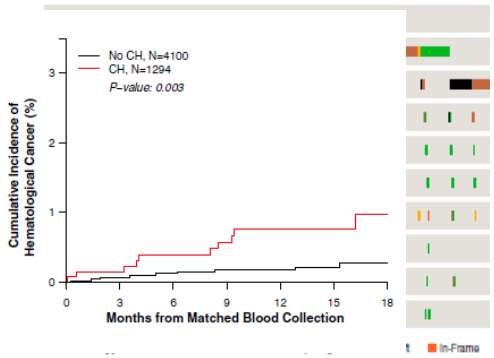

Video-monitoring
Access trocar
(5 mm)
Micropump
High-pressure line
(to the abdomen)
Pressurized
Chemotherapy Aerosol
(12 mmHg)
CAWS
(Closed Aerosol
Waste System)
Display
Injector
Head
Syringe with
Cytostatic solution
Remote control
Power supply

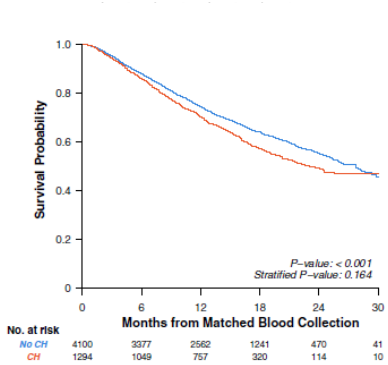
CHIP
&
CANCER


SALE%

CHIP and Cancer



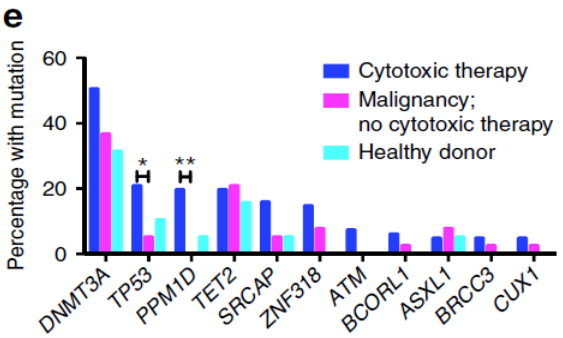




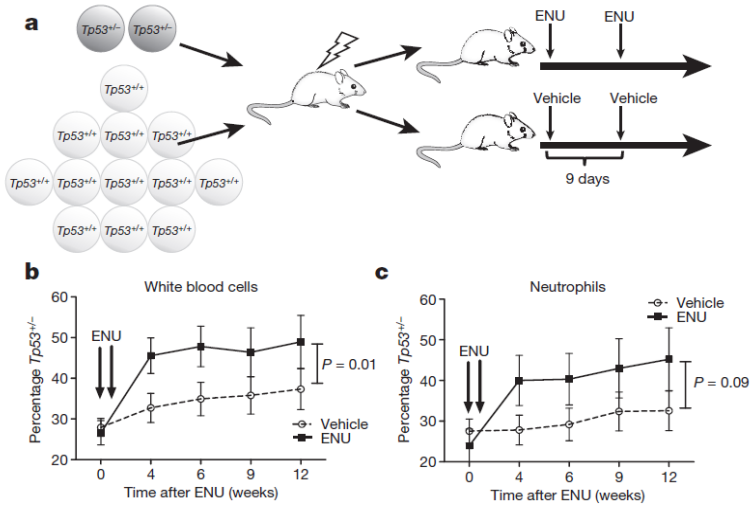
- 25% in cancer patients
- No associations across larger cancer categories
- ↗ PPM1D/TP53 mutations
- CH-PD was associated with shorter patient survival
- Increased incidence of subsequent hematologic cancers

CC Coombs, Cell stem cell 2018

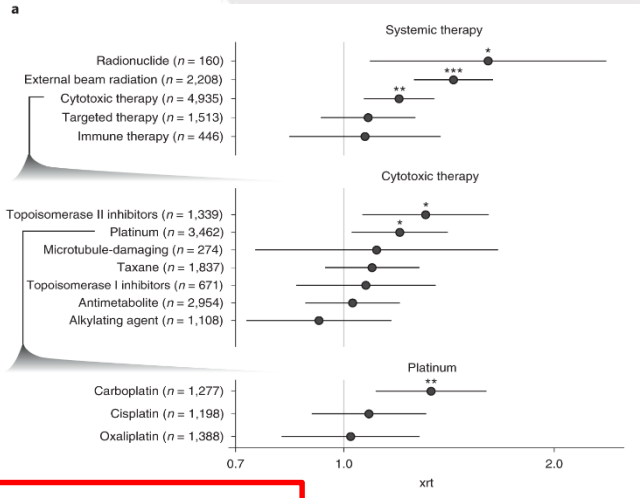
CHIP selection depends on type somatic mutation & type of Chemo

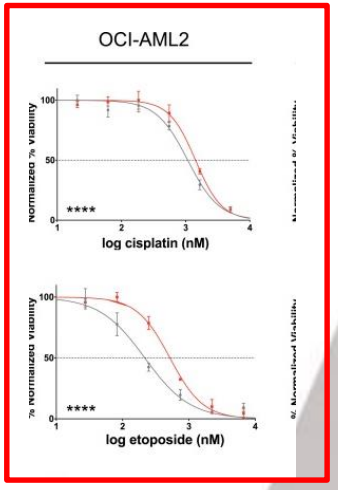


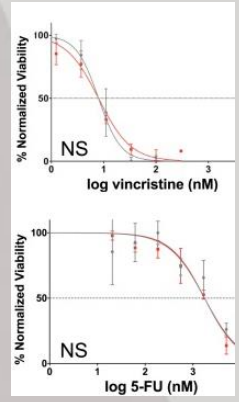
- Cytotoxic therapy expansion of clones carrying mutations in DNA damage response (TP53 and PPM1D)



- Competitive advantage Tp53+/- HSPCs after chemotherapy



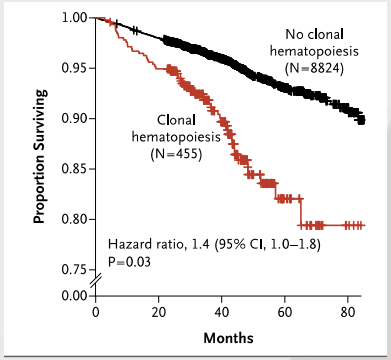


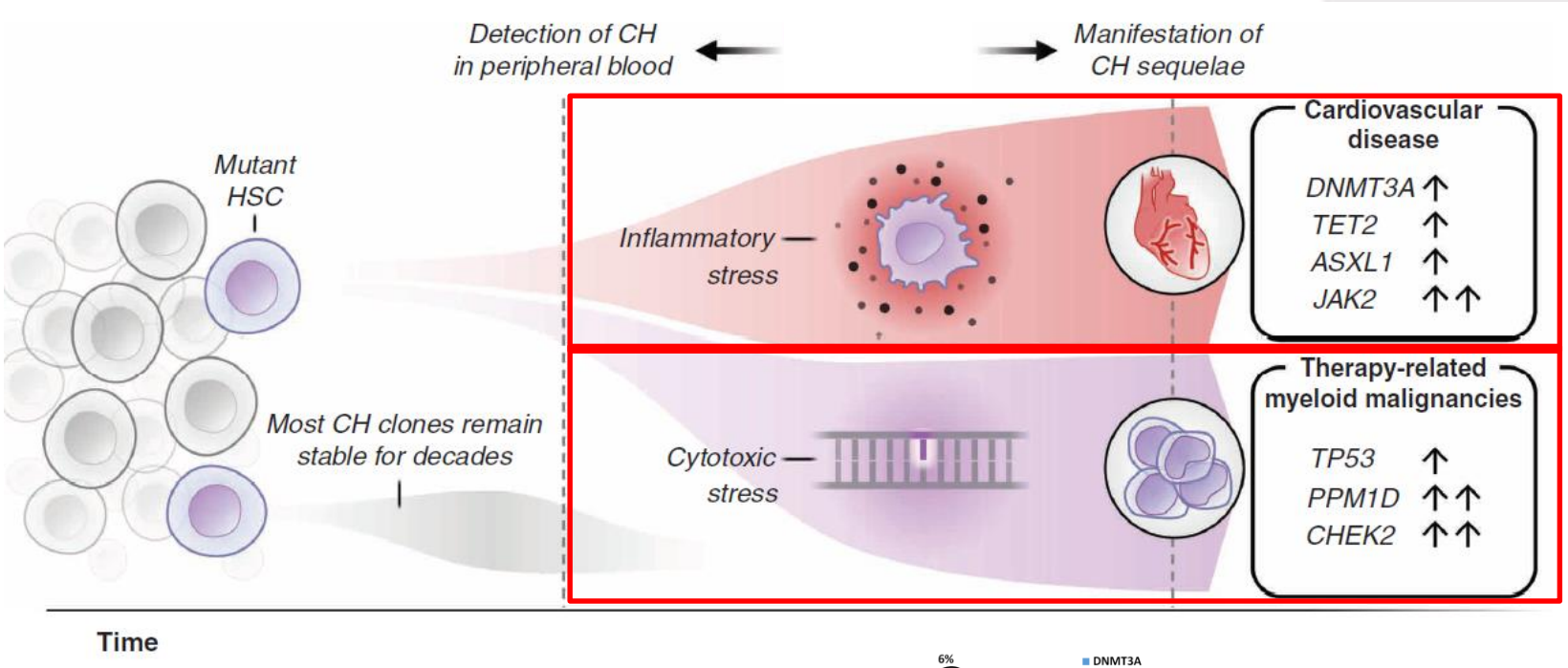


- Mutants are positively selected with some, but not all classes of agents

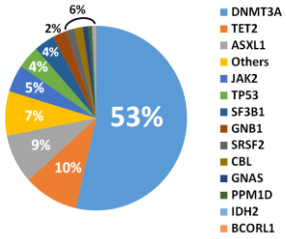
T. Wong Nat com 2018 T Wong, Nature 2015 Kelly L. Bolton, Nat Gen 20201 HSU et al, Cell Stem Cell. 2018

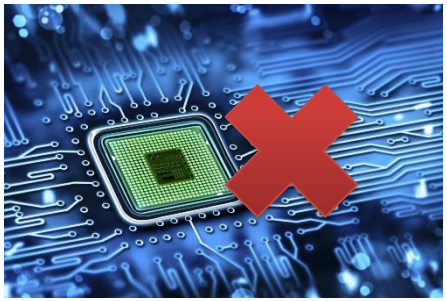
CHIP
CONTEXT DEPENDENT MECHANISM





- TP53/PPM1D less than 10% of CHIP
- DNMT3A/TET2 around 2/3 of CHIP





CHIP, CVD & Inflammation

CHIP and Cardiovascular disease

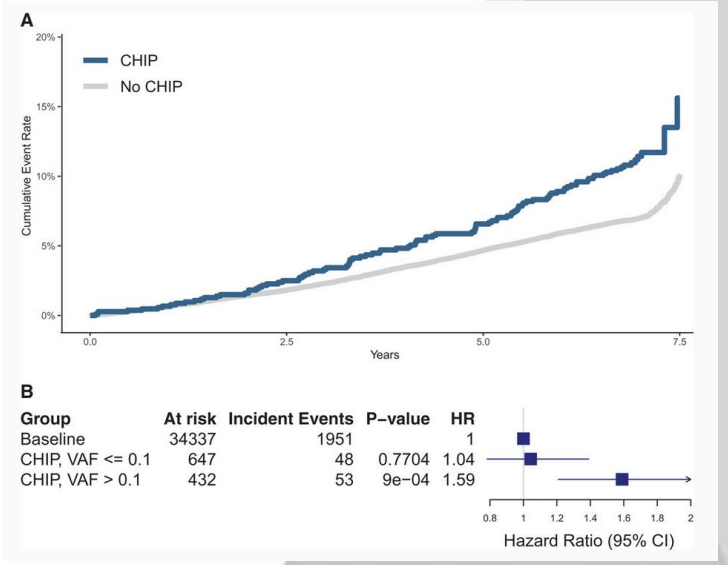
- CHIP had a 4.0 times risk of myocardial infarction
- CHIP carriers with these mutations also had increased coronary- artery calcification

- Restricted to VAF >10%.
- DNMT3A and TET2 is independently associated future risk of cardiovascular disease.

B CHIP and Myocardial Infarction, According to Mutated Gene

ATVB and PROMIS	No. of Participants with Myocardial Infarction/ No. at Risk	Odds Ratio (95% CI)	P Value
DNMT3A	31/46	1.4 (0.7–2.8)	0.29
TET2	12/13	8.3 (1.2–357.5)	0.02
ASXL1	8/8	Undefined	0.02
JAK2	16/16	Undefined	<0.001
Other	20/22	6.9 (1.7–61.6)	0.001

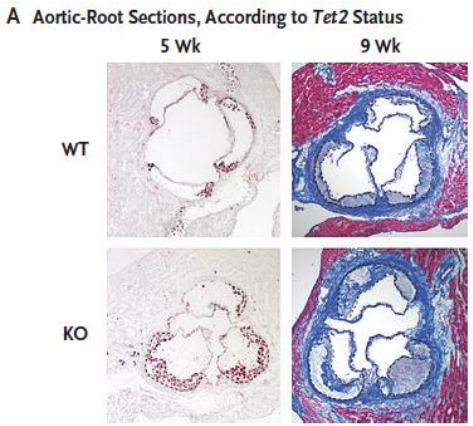
S Jaiswal, NEJM 2017

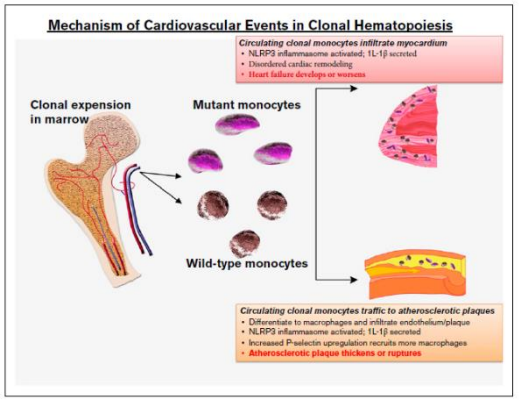


Bick et al, Circulation 2020

Cardiovascular injury associated with Inflammation

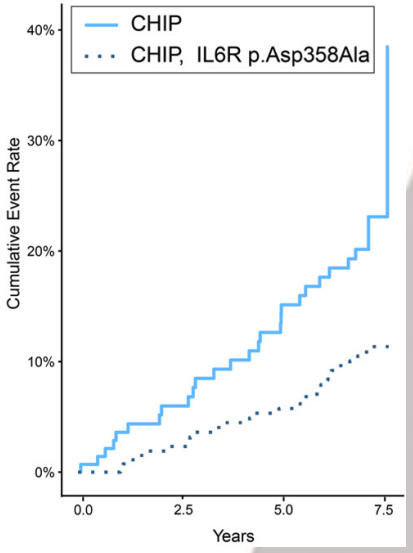
- CHIP associated with TET2 deficiency accelerates atherosclerosis in mice





- CANTOS trial :
  - Administration of anti-IL1B (canakinumab) reduce cardiovascular events in patients with TET2 CHIP (HR, 0.38)

- Individuals who develop CHIP with simultaneous genetic deficiency of IL-6 signaling had cardiovascular disease risk reduction

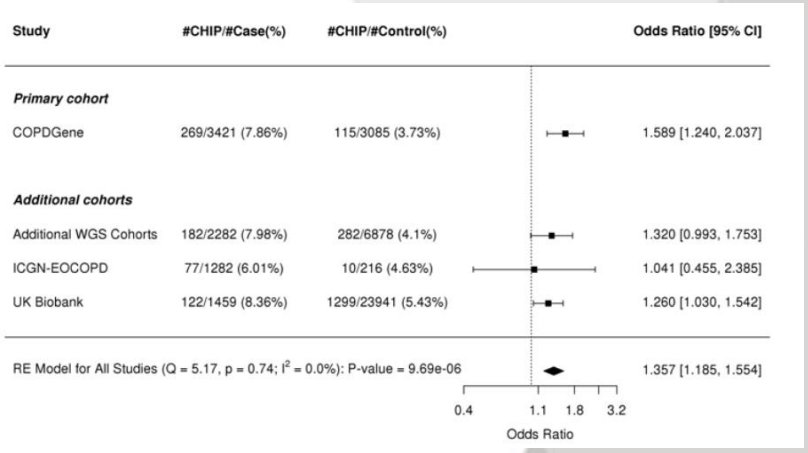


Fuster et al., Science (2017)

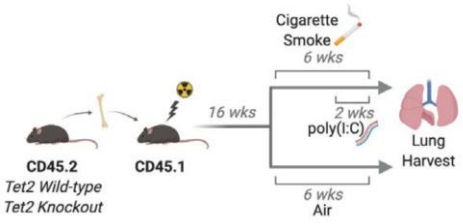
Bick et al, Circulation 2020

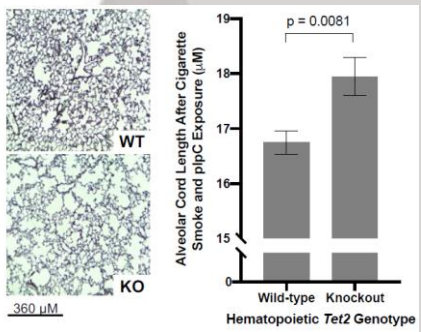
CHIP & obstructive pulmonary disease

- Individuals with CHIP had a risk of
  - moderate-to-severe COPD 1.6
  - severe or very severe COPD 2.2 times greater than non-carriers



- Inactivation of Tet2 in mouse HSC exacerbated emphysema and inflammation in cigarette smoke exposure models





Peter Miller et , Blood 2021

CHIP Summary

- **CHIP : somatic DNA mutation in genes associated with hematologic malignancies detected in the blood of « healthy patients » (normal hemogram)**
  - Very common (>10% over 65 yo)
  - DNMT3A, TET2, ASXL1 represent 75% of mutations

- **Contributing factors**
  - Age
  - Cytotoxic, especially radiotherapy & cisplatin (TP53/PPM1D/CHEK2)
  - Role of inflammation (TET2/DNMT3A)
  - Smoking (ASXL1), genetic predisposition (?)

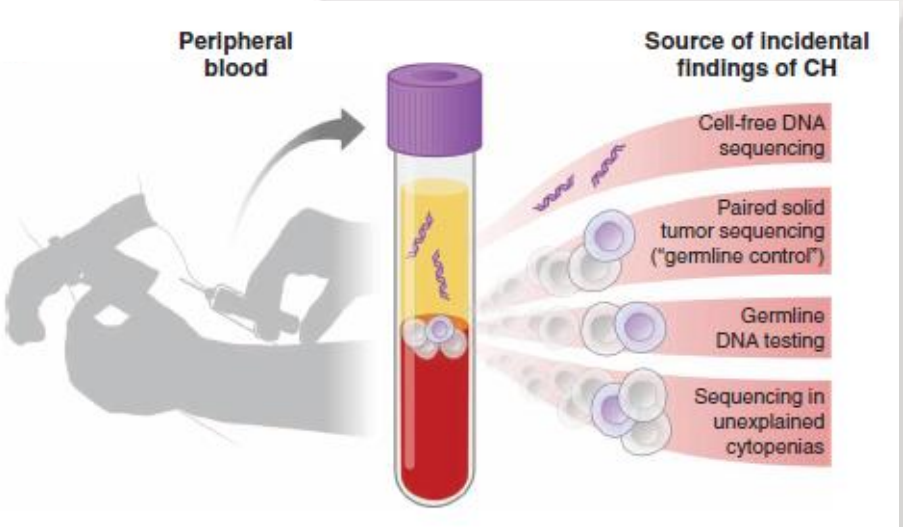
- **Not a disease but a risk factor for**
  - Haematological malignancies (TP53/PPM1D/CHEK2)
  - Cardiovascular disease (TET2/DNMT3A/JAK2)

- **Prognostic impact link to the clone size (VAF >10%)**

- **Role of CHIP in** auto-immunity, rheumatologic diseases, infection, insulin resistance, Lymphoma, GVHD, Osteoporosis, HIV, severity of COVID-19, Colon cancer, Alzheimer……

CHIP : a reality ?

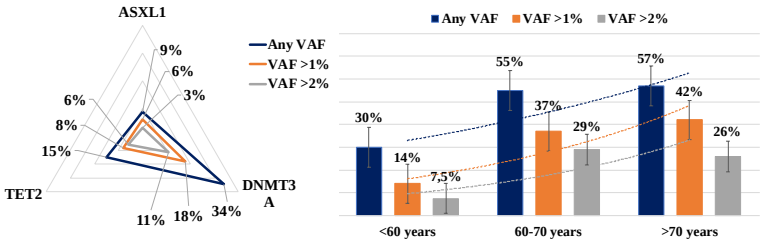
- A lot of clinical trials use cfDNA for inclusion in solid tumor trials
- Some mutations detected in cfDNA are derived from CH not tumor !

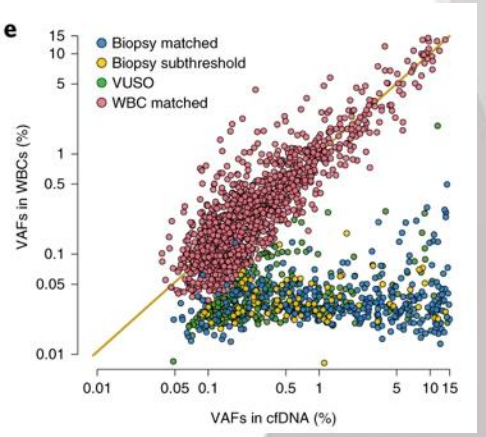


FoundationOne Liquid Biopsy :

- 33 genes screened also in myeloid panel(including JAK2, MPL, ASXL1, DNMT3A, TET2, U2AF1, SF3B1, IDH1,IDH2, TP53)

CHIP in cfDNA in patients with NSCLC (=n=290)





P Razavi, Nat Med 2019

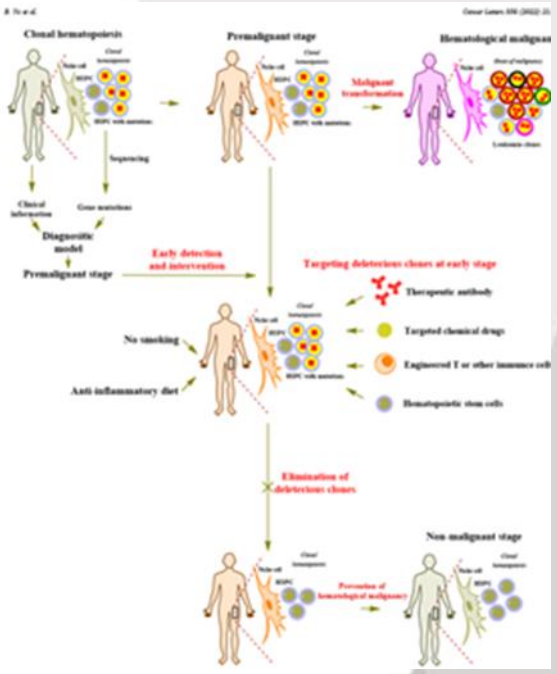
- VAFs of CHIP in blood samples correlated with CHIP in plasma samples

Thomas Köhnke and Ravindra Majeti, CANCER DISCOVERY 2021

What we do with these results…..

CHIP : an opportunity ?

- **Therapeutic intervention ?**
  - > Prevent TRMN development ?
  - > Prevent CVD ?



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Merci !

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All the patients !