Beyond the Marrow: The Detrimental Effects of Clonal Hematopoiesis

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Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

Disclosures

- Consulting: Aptitude Health
- Advisory Board: Autolus (Obe-Cel)

- I won’t be discussing NON-FDA approved label medications.

Sections

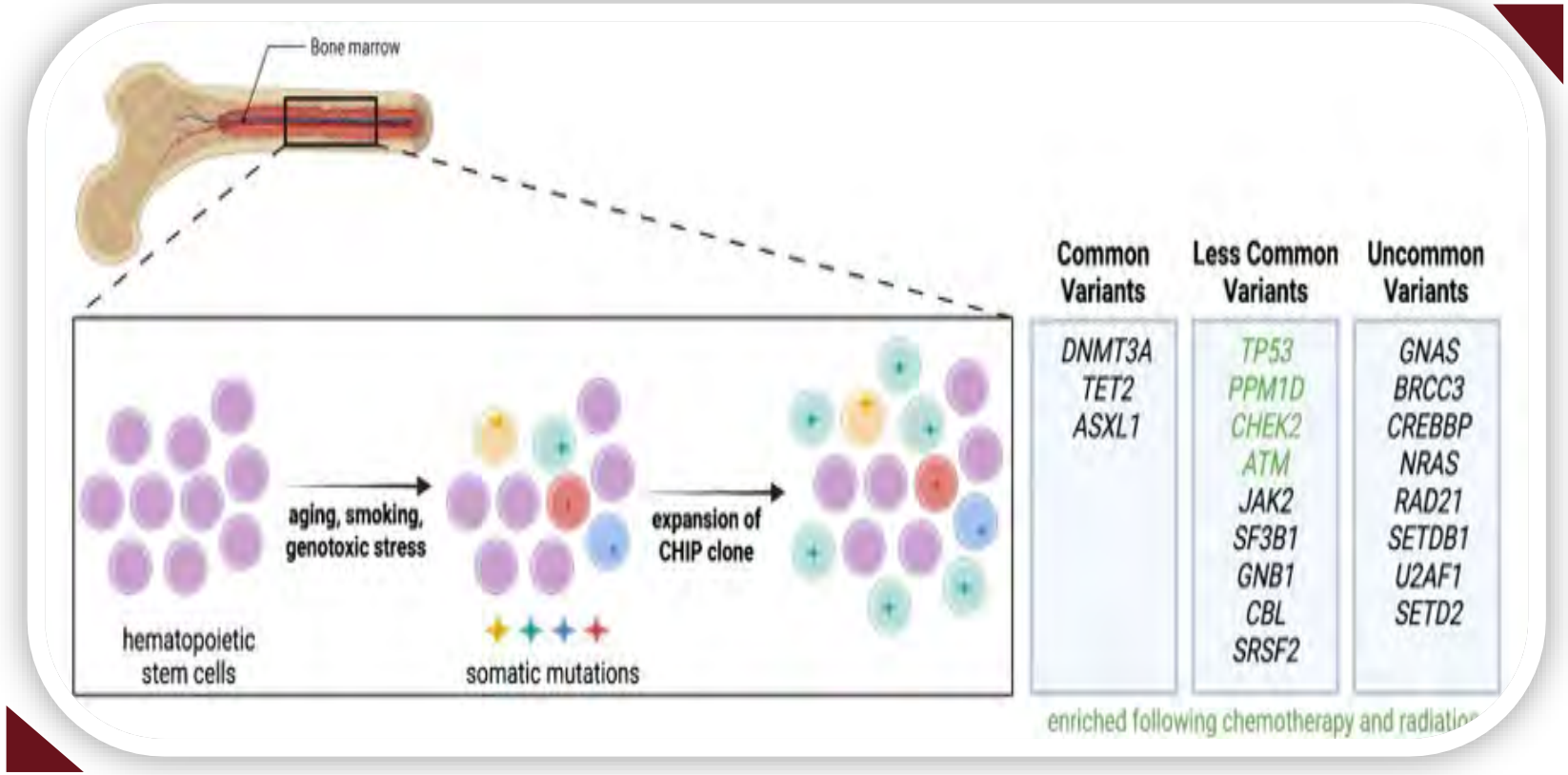
CH Nosology

- Definition of Clonal Hematopoiesis
- Incidence, History, Classification
- Diagnosis & Risk Stratification
- Hematological Consequences of CH
- Non-Hematological Consequences of CH
- Models of Management

CH Definition

Definition

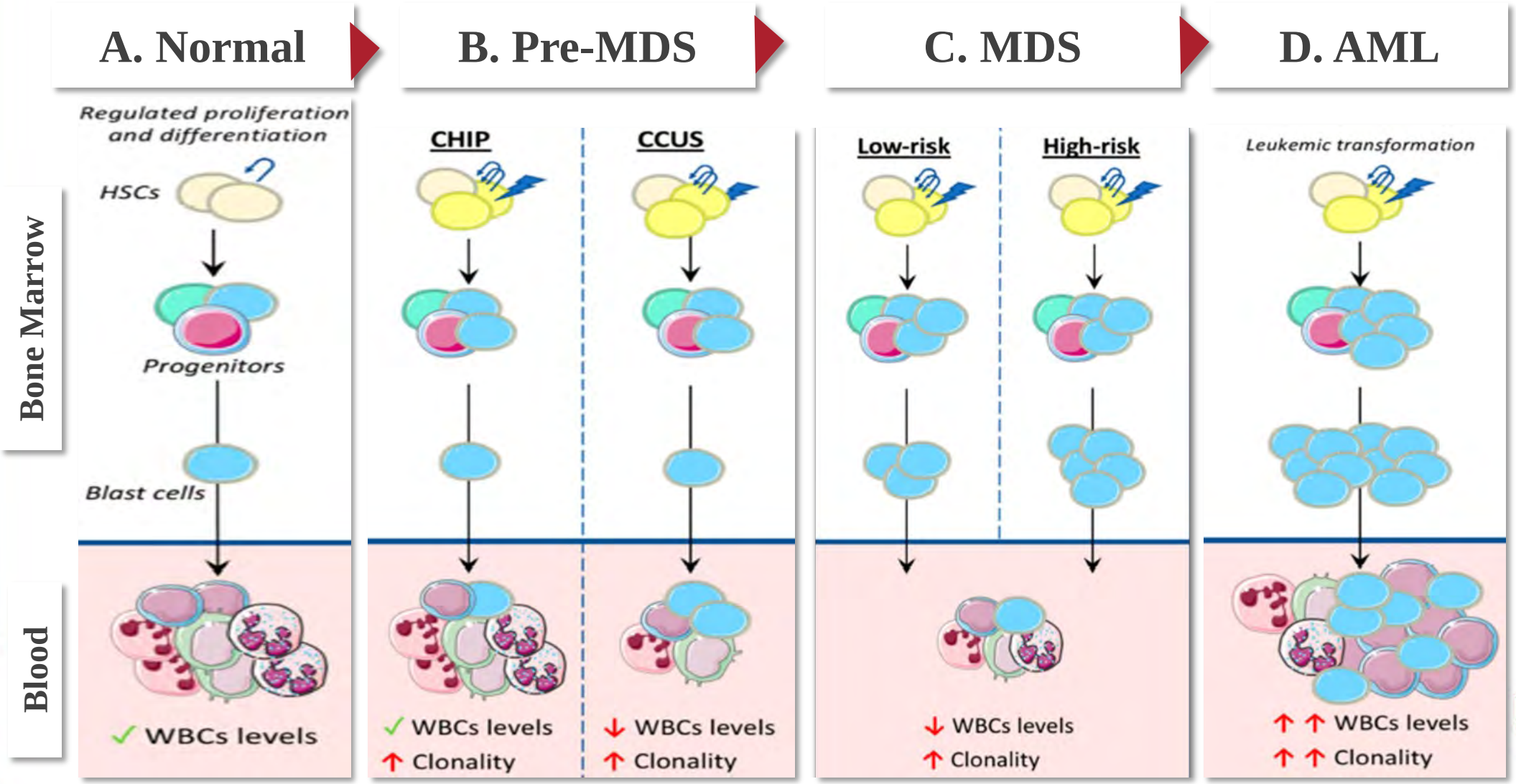
Definition ?



Anticancer therapies such as chemotherapy and radiotherapy are promoting factors for CHIP, particularly *TP53*, *PPM1D*, or *CHEK2*

Reed et al. Clin Can R; Apr 2023

Transformations From Normal Hematopoiesis To Acute Myeloid Leukemia (AML) Development



Bertuzzo Veiga et al. Cancers; Jan 2021

Incidence

CH Incidence

- Increases with Age
- Others evaluating incidence in:

  Stroke, HIV, other solid malignancy
- Estimated ~10% population

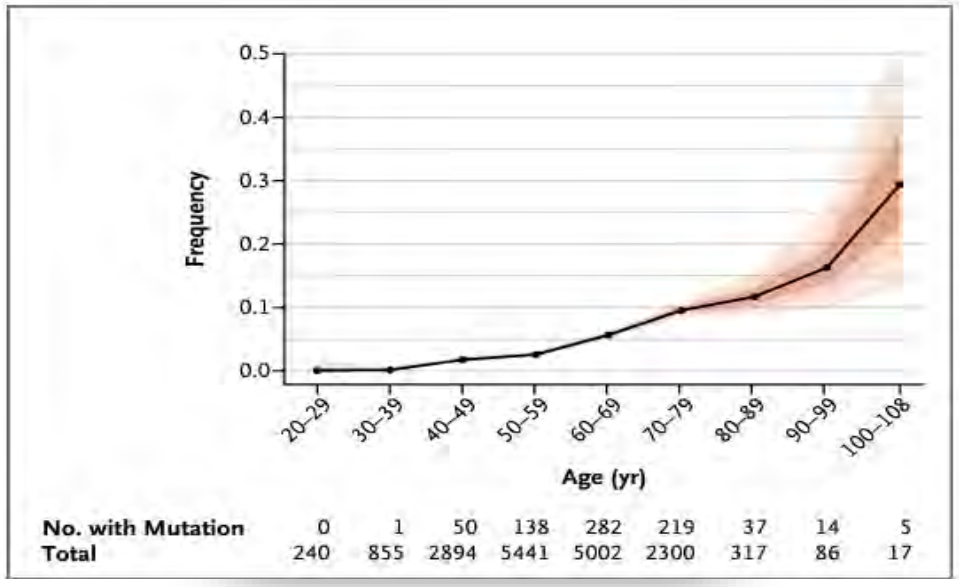


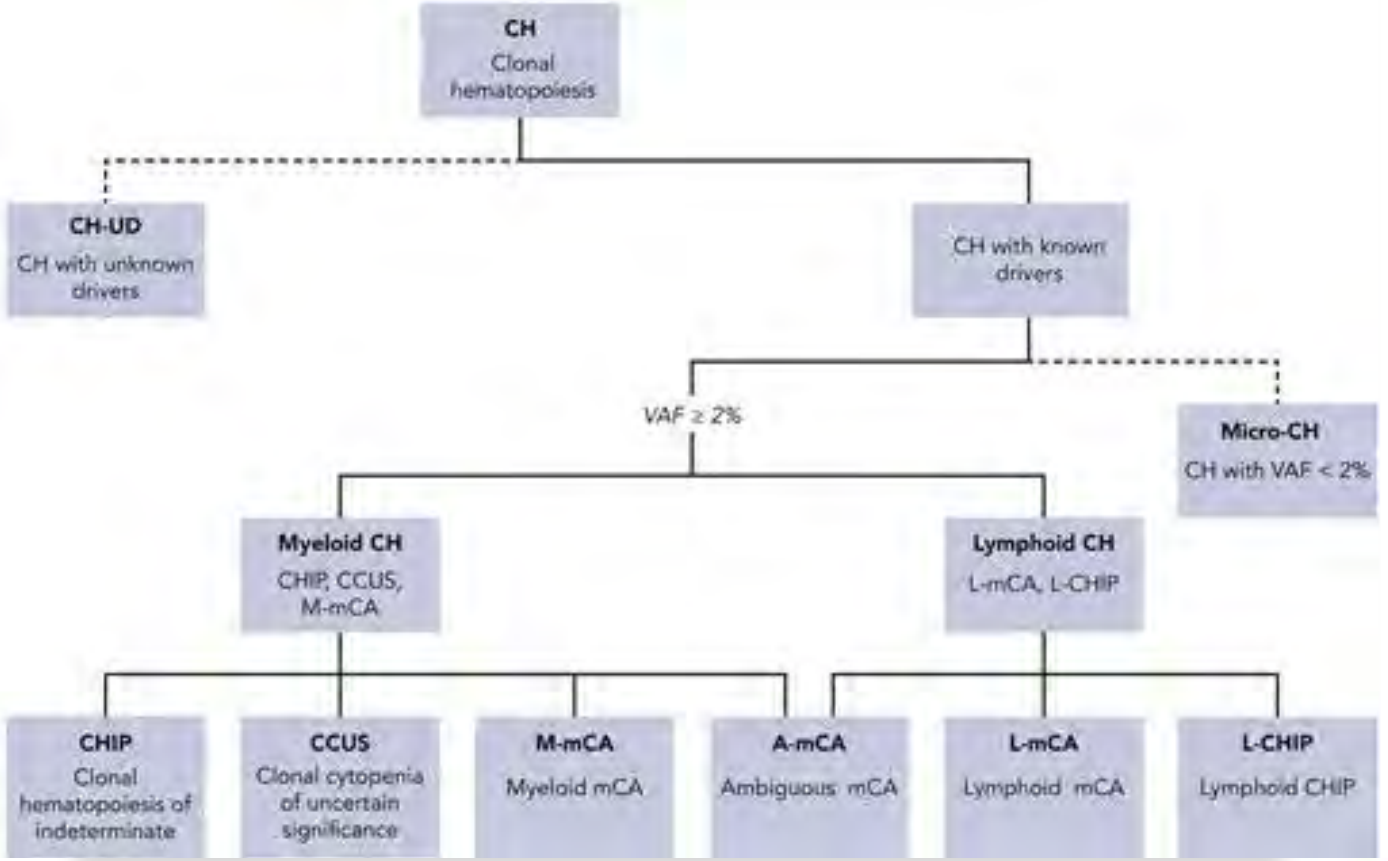
Figure 2. Prevalence of Somatic Mutations, According to Age.

Colored bands, increasingly lighter shades, represent the 50th, 75th and 95th percentiles

Jaiswal S et al. NEJM; Jan 2017
Perez-Gonzalez A, et al. Blood; Nov 2023

Myeloid CH: CHIP, CCUS, and M-mCA

- **Mutations** in *DNMT3A*, *TET2*, and *ASXL1*, which account for 70%-80% of all cases with CHIP
- **Epigenetic** regulators
- **Lymphoid** CHIP



Weeks L et al. Blood; Dec 2023

Germ line Predisposition to CH

Classification

Clonal fitness and context-dependent selection

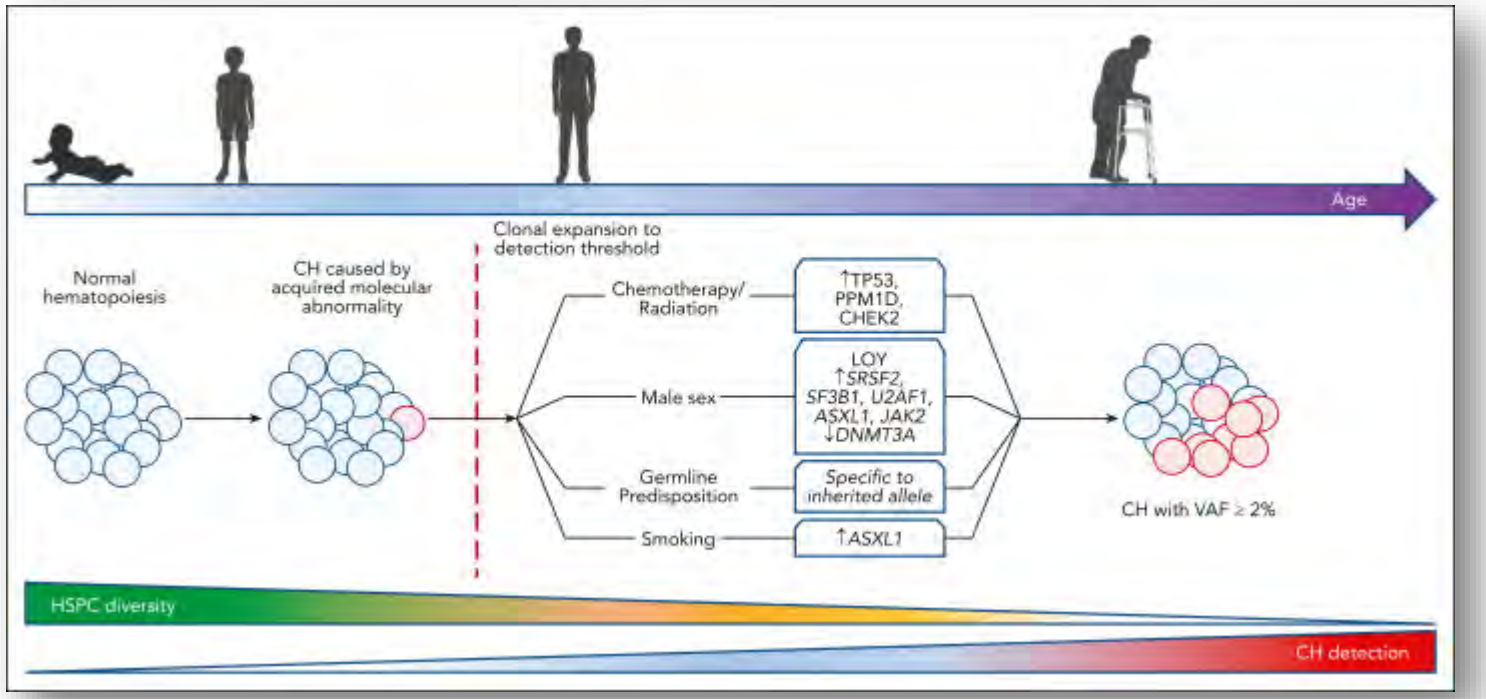


Figure 3. Causes and consequences of Clonal Haematopoiesis

Weeks L et al. Blood; Dec 2023

Integration in WHO Classification

Classification

Leukemia

www.nature.com/leu

REVIEW ARTICLE OPEN

Check for updates

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1]✉, Eric Solary[2]✉, Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]✉

CLONAL HAEMATOPOIESIS

Clonal haematopoiesis (CH) refers broadly to the presence of a population of cells derived from a mutated multipotent stem/ progenitor cell harbouring a selective growth advantage in the absence of unexplained cytopenias, haematological cancers, or other clonal disorders. The incidence of CH increases with age [6]. Substantial advances in understanding the molecular genetics and public health implications of CH took place since the last classification, including recognition of their association with

SPRINGER NATURE

Khoury J et al. ***Leukemia***; June 2022

Diagnosis

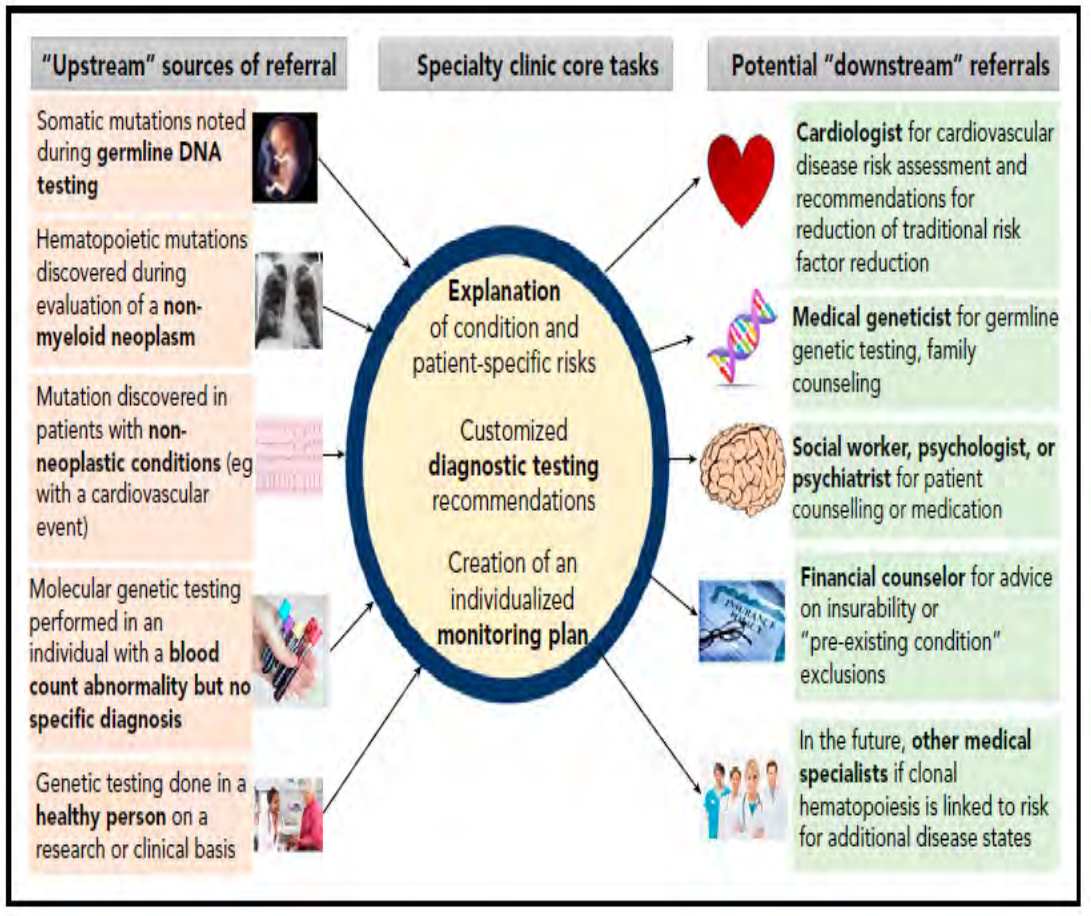


Figure 4. Referral patterns and evaluation of people with clonal Haematopoiesis.

People with clonal hematopoiesis may be identified in several different ways, including during testing for other conditions. Tasks for hematologists include helping affected persons understand clonal hematopoiesis and its implications, organizing further diagnostic testing that may be indicated in some cases (e.g., bone marrow aspiration and biopsy), and developing a monitoring plan. Referral to other specialists may be necessary, including geneticists (e.g., if a germline mutation is possible) or cardiovascular disease specialists for traditional risk factor assessment and modification.

CHRS Risk Stratification

Risk Stratification

CHIP/CCUS Patients

CHRS Risk Stratification

www.chrsapp.com

High Risk
(-1% of population)

Intermediate Risk
(-10% of population)

Low Risk
(-89% of population)

10-year Risk of Myeloid Malignancy

High Risk

> 50%

Intermediate Risk

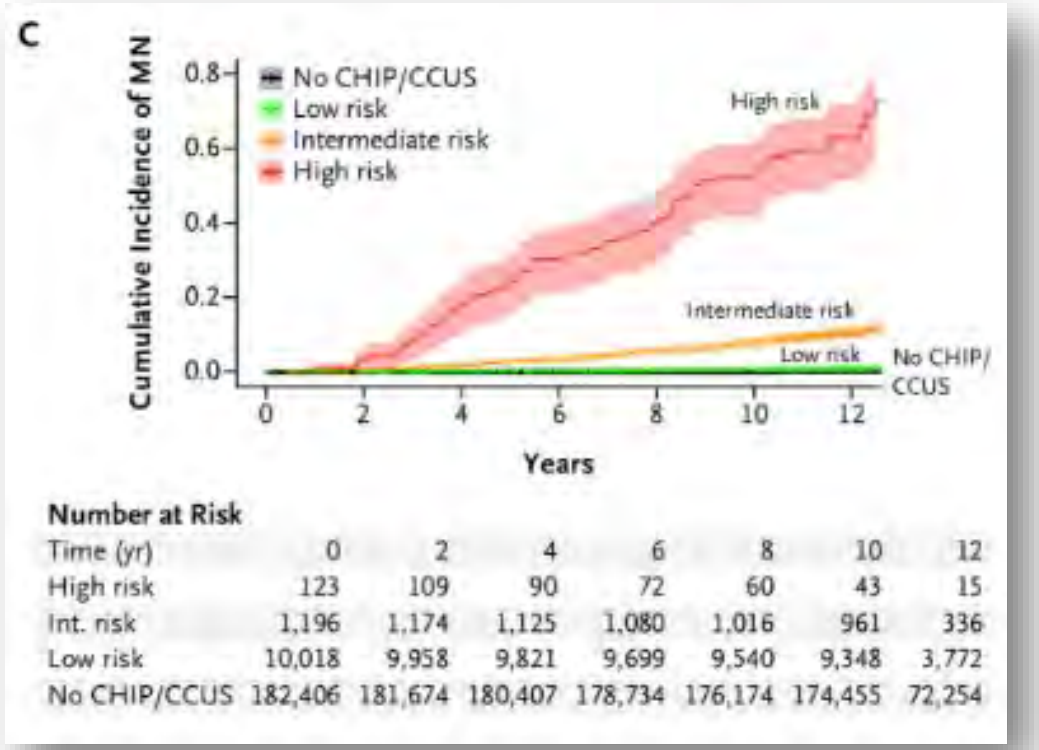
7-8 %

Low Risk

< 1%

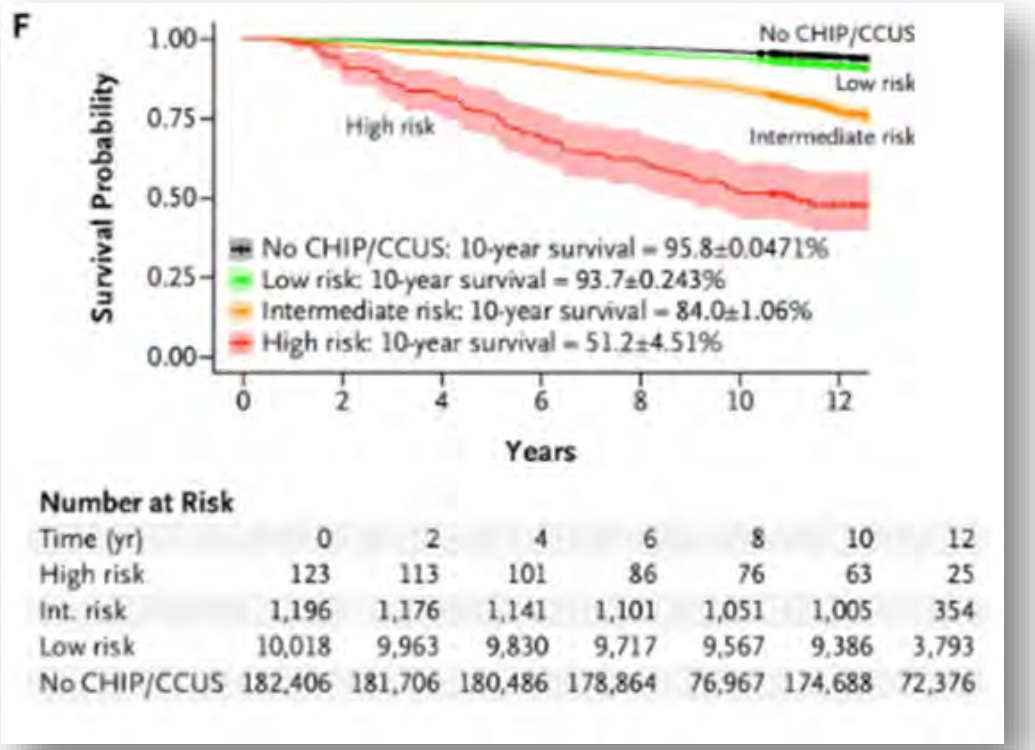
Graphical Representation of Cumulative Incidence of MN and Survival Probability over the Years

Risk



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



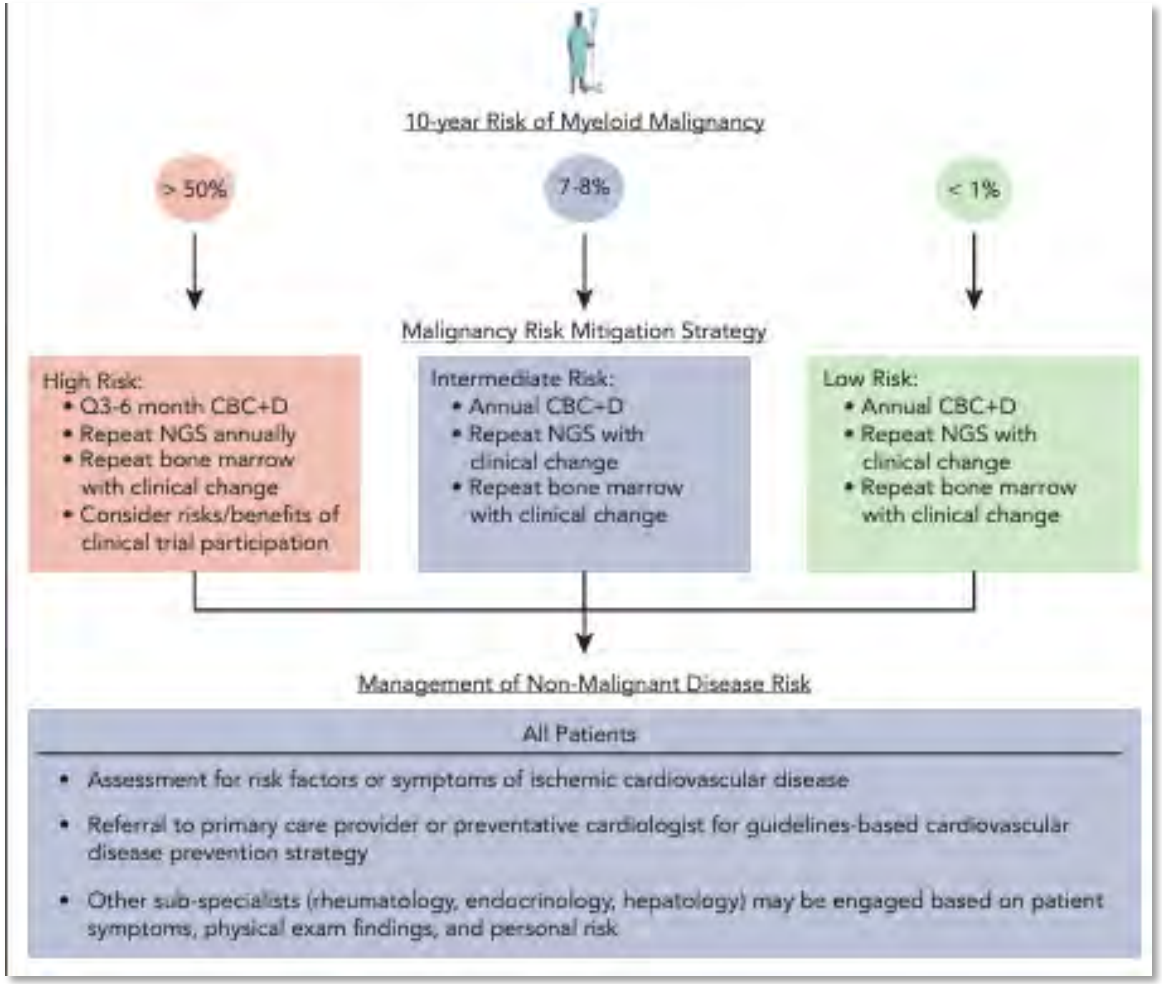
Number at Risk

Time (yr)	0	2	4	6	8	10	12
High risk	123	113	101	86	76	63	25
Int. risk	1,196	1,176	1,141	1,101	1,051	1,005	354
Low risk	10,018	9,963	9,830	9,717	9,567	9,386	3,793
No CHIP/CCUS	182,406	181,706	180,486	178,864	76,967	174,688	72,376

Weeks L et al. Blood; Dec 2023
Weeks L et al. NEJM Evi; Apr 2023

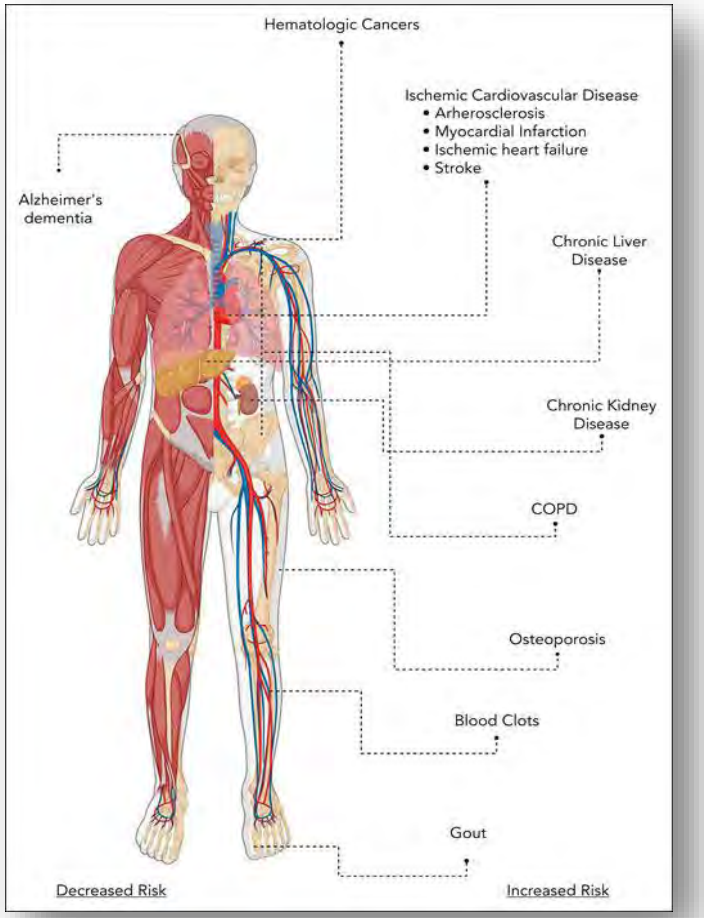
Management

Current Management Strategies for CH



Weeks L et al. Blood; Dec 2023
Weeks L et al. NEJM Evi; Apr 2023

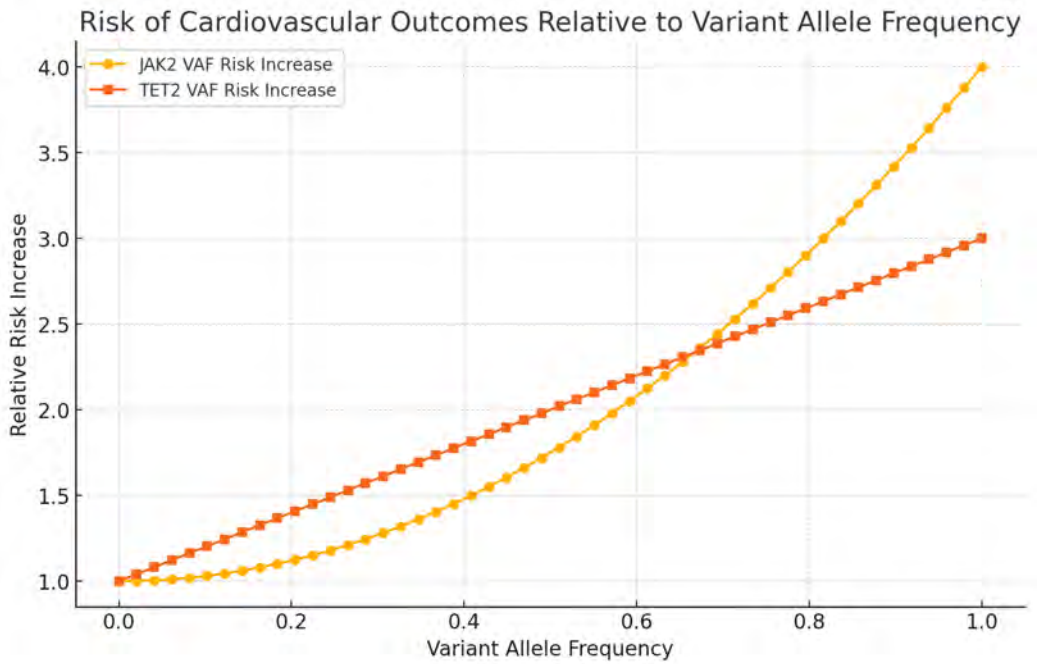
Non-Hematological Consequences of CH



Ischemic Cardiovascular Diseases

Consequences

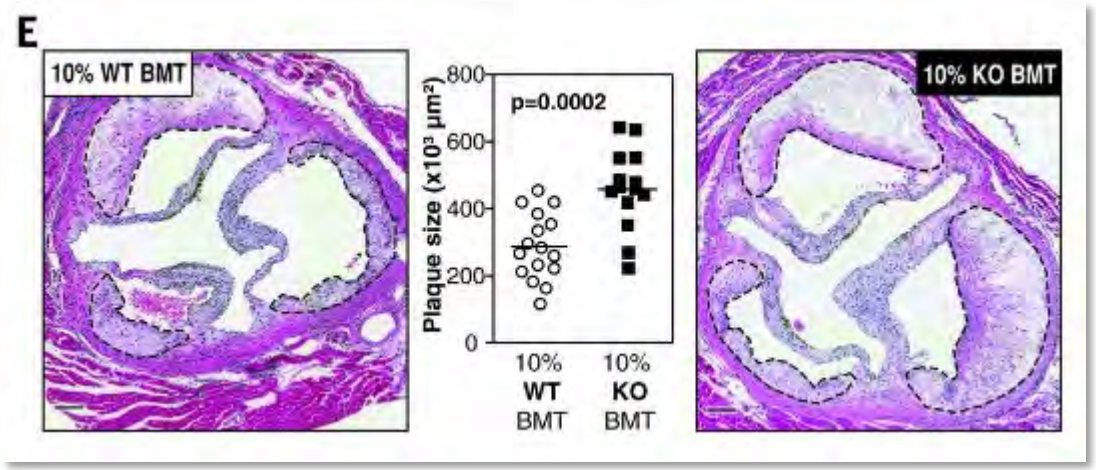
- Richest data
- Casual role already established in animal models
- Independently associated w/ Adverse Cardiac Outcomes
- Clone Size is a strong predictor; α VAF%
- Role of JAK2 and TET2 in inflammatory signaling
    - Inflammasome IL-1b, IL-6, C-RP
- Role of Canakinumab (IL-1b Inhibitor)
- Predicts secondary ischemic events
- Loss of Y-Chromosome , related to evolution of fibrosis

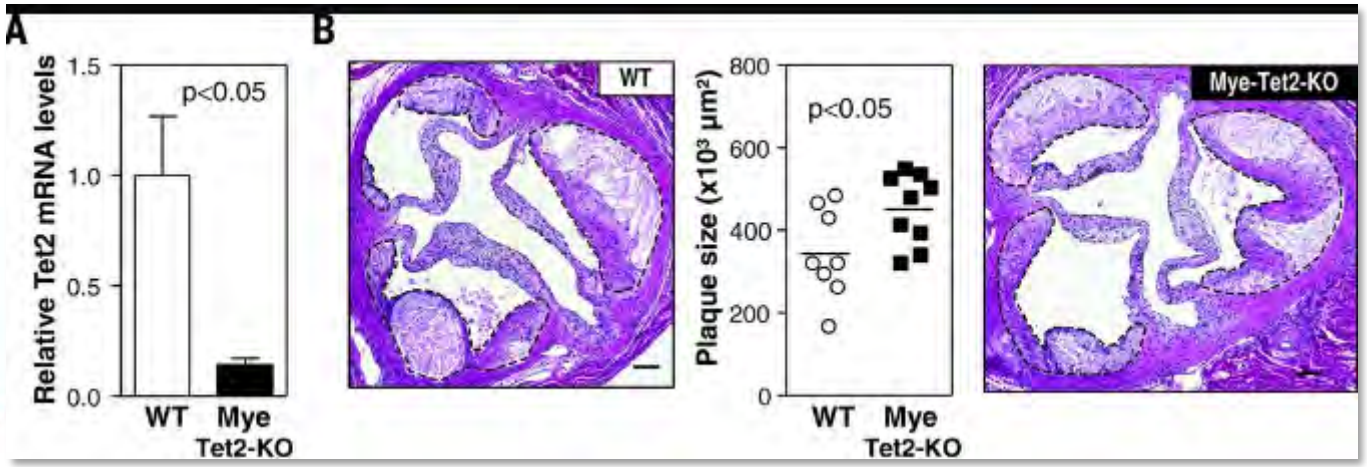


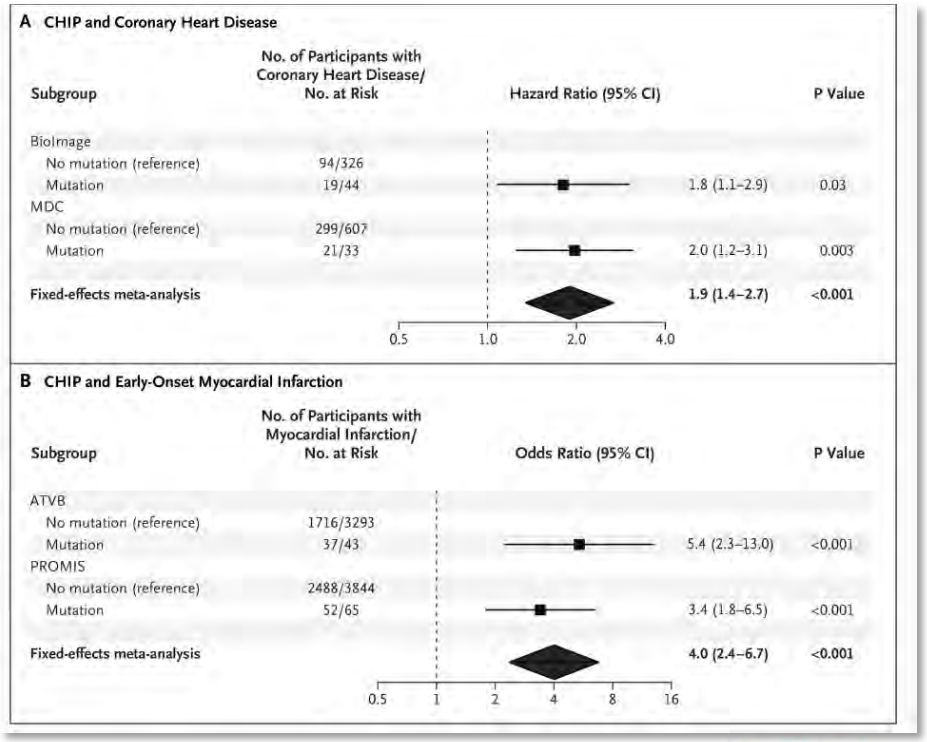
Bertuzzo Veiga et al. Cancers; Jan 2021
Weeks L et al. Blood; Dec 2023

TET2 Mutated Macrophages

Consequences



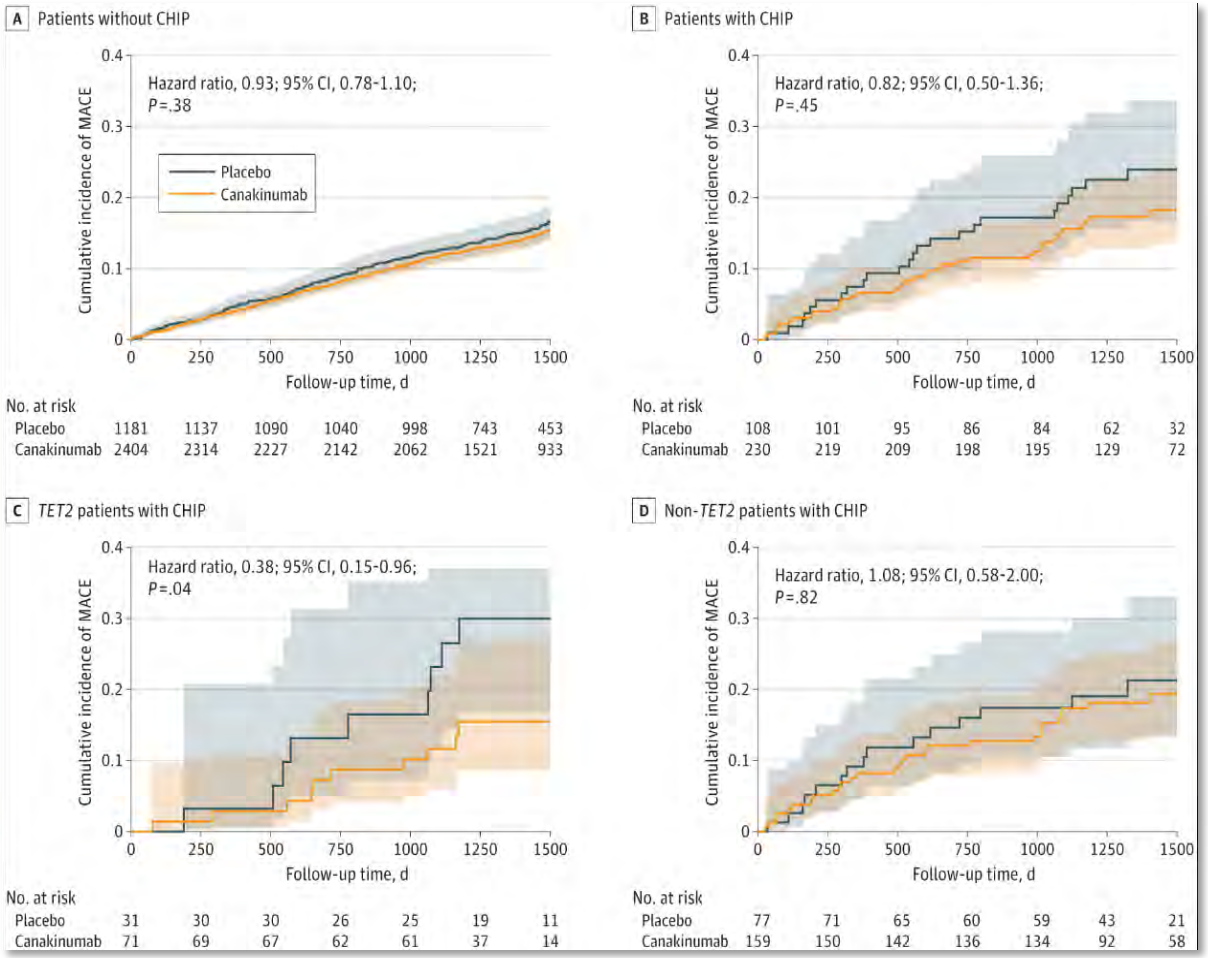


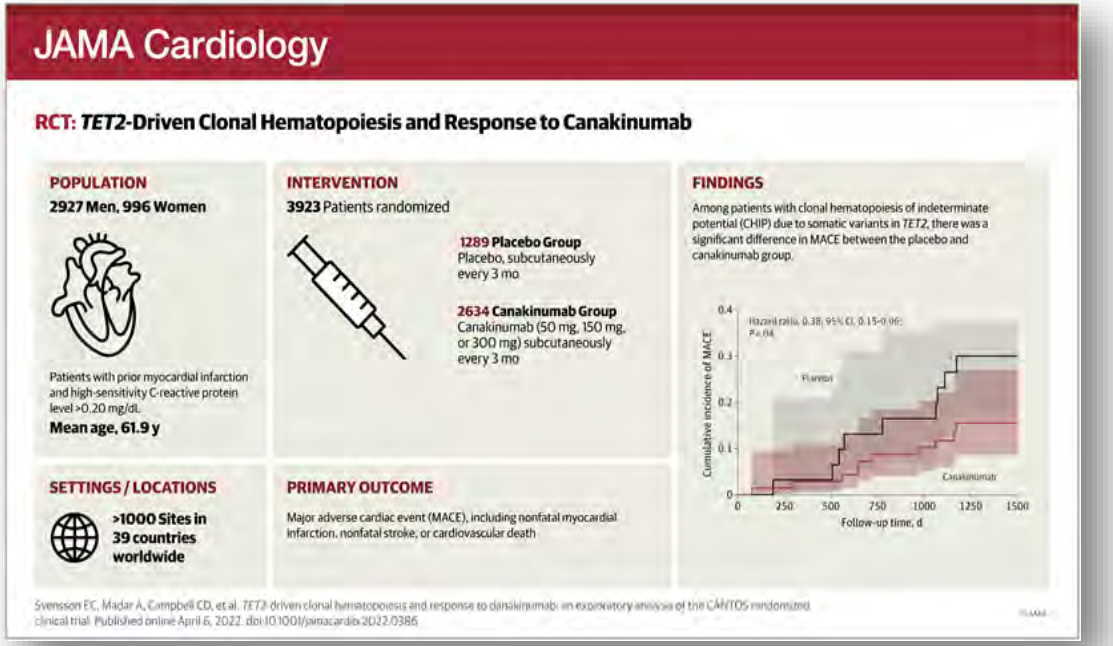


Jaiswal S et al. NEJM; Jan 2017
Fuster JJ et al. Science; Mar 2017

Canakinumab – CANTOS Trial

Consequences





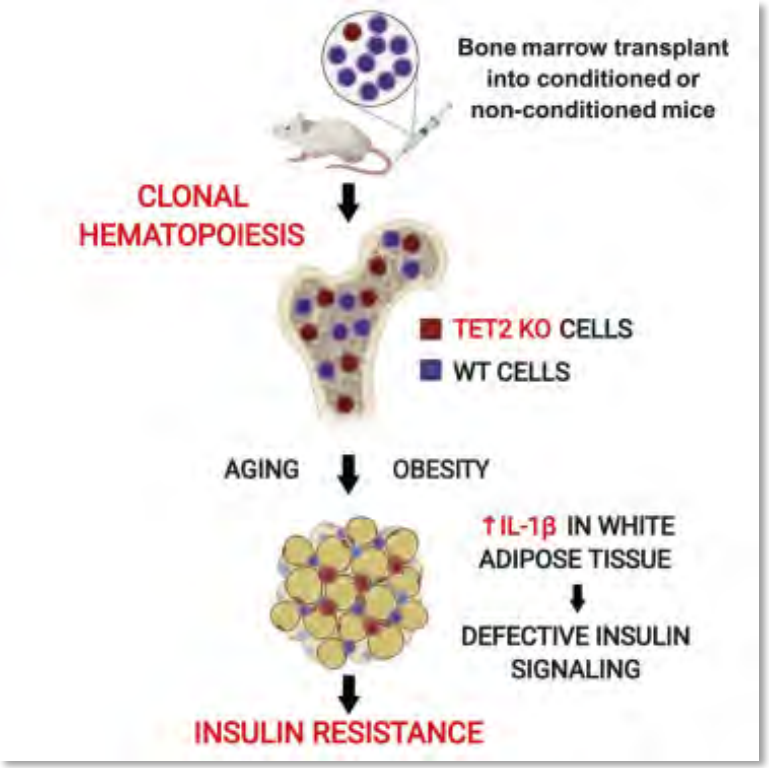
Svensson EC, et al. JAMA Cardiol; Apr 2022

Other CVD Risk Factors: T-II Diabetes Mellitus

- TET2-deficiency-driven clonal hematopoiesis aggravates insulin resistance in aged mice

- TET2-deficiency-driven clonal hematopoiesis aggravates insulin resistance in obese mice

- NLRP3 inhibition prevents the effects of TET2-deficient cells on insulin sensitivity

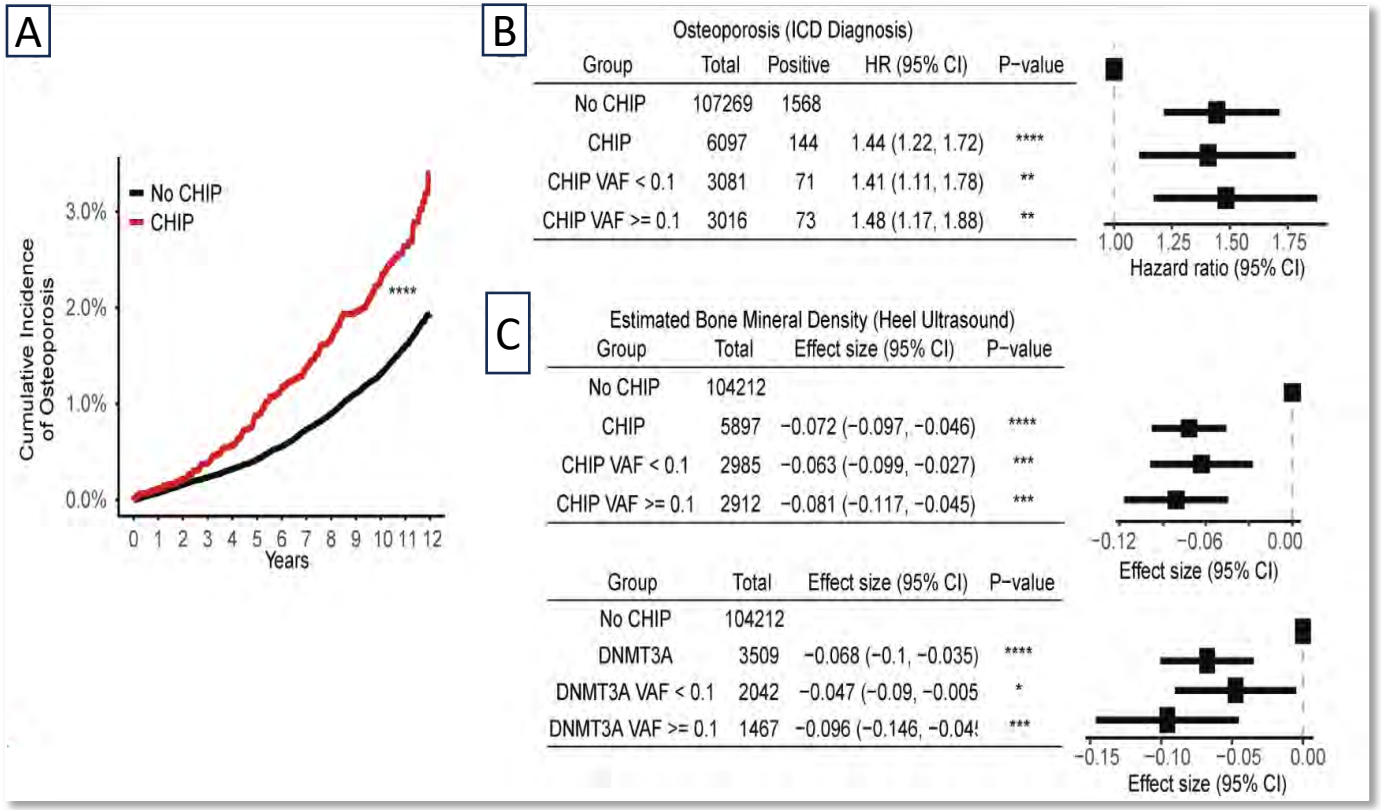


Fuster JJ, et al. Cell Rep. Oct 2020

Osteoporosis

Consequences

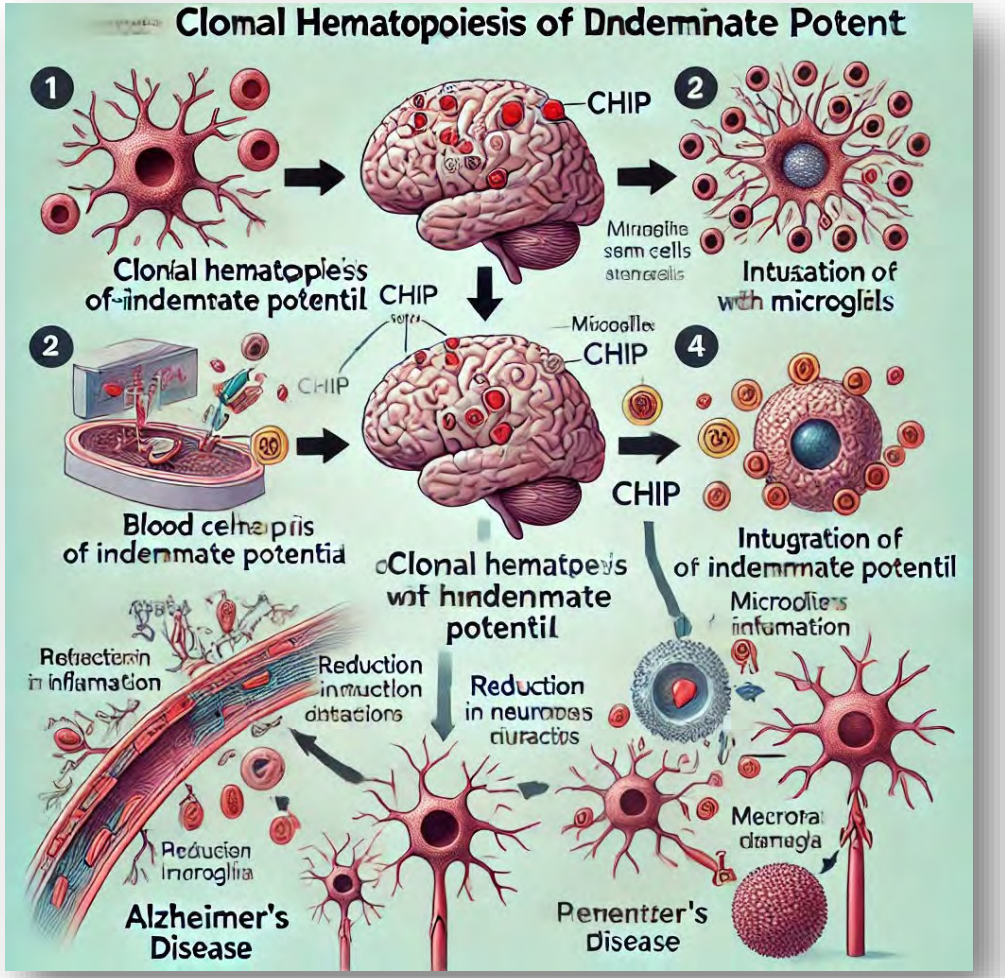
- DNMT3A
- Incidence α VAF
- Osteoclasotogenesis IL-20
- Rapamycin



Wang H, et al. Cell; Jul 2024

Neurocognitive Function

Consequences

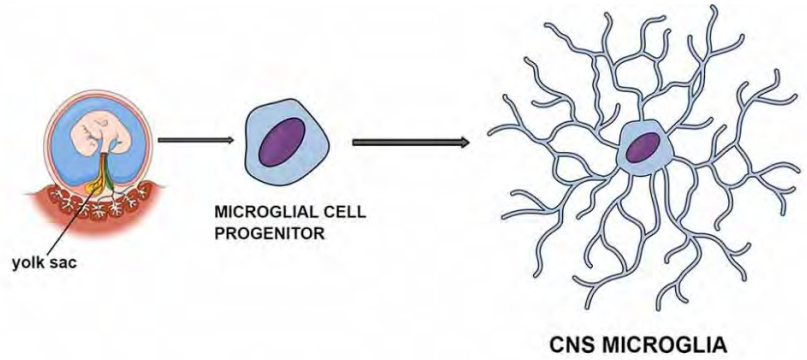


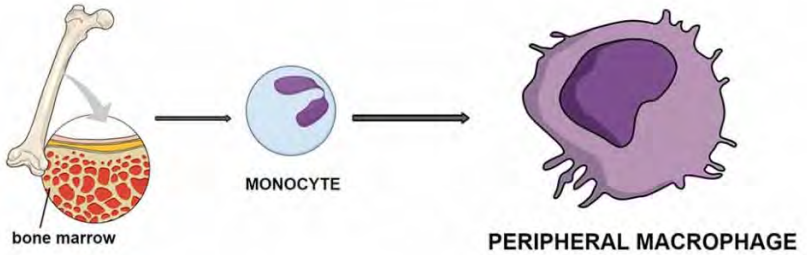
Bouzid H, et al. Nature; Jun 2023
Yun J, et al. Ann Lab Med; Nov 2024
Bouzid H, et al. Nature; Jun 2023
Liu X, et al. JIM; Jul 2024

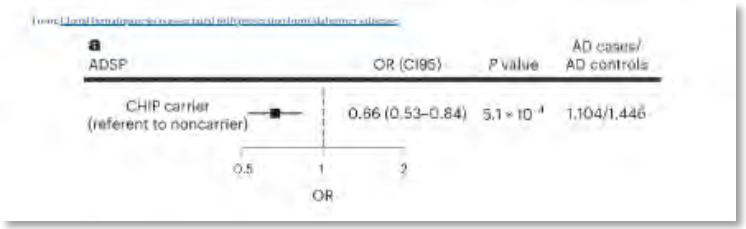
Effect of CHIP on the risk of AD dementia and ADNC

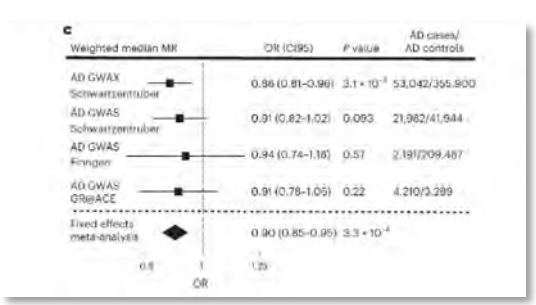
Consequences

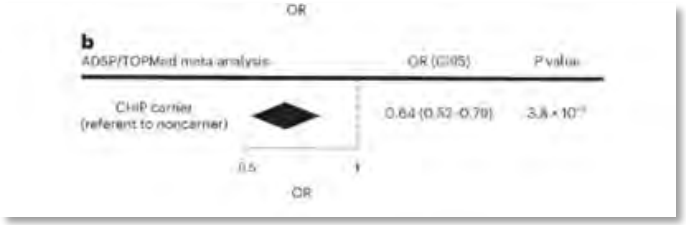
- Multiple Types of Analyses demonstrate that CHIP is associated with reduced risk of AD or AD related pathology; Longitudinal Cohort Study, Case Control Study and Brain Pathology
- Altered phagocytic activity of bone marrow–derived microglial-like cells

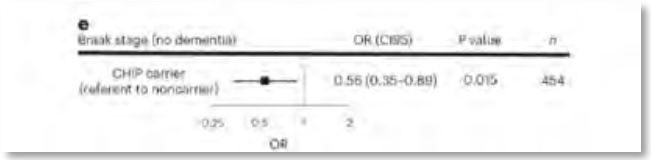


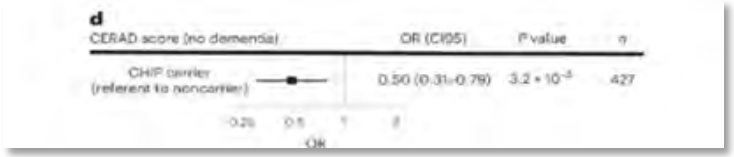












Bouzid H, et al. Nature; Jun 2023

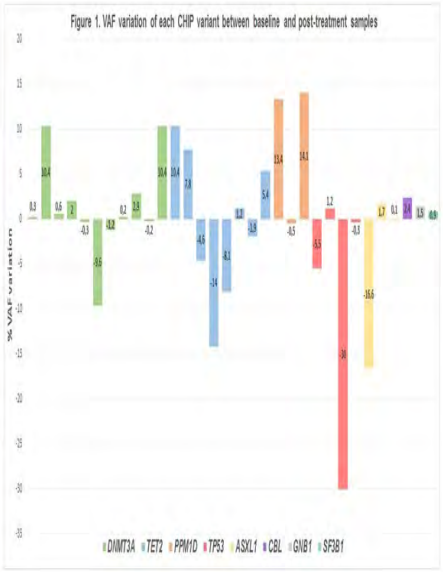
CH with Solid Tumors

Consequences

- Agents, timing
- Mitigate the risk of subsequent risk of t-MN
- Cytotoxic Chemotherapy vs I.O.
- Post-PARP (33% of patients w/ t-MN had Tp53 CHIP)
- NET w/ Peptide Receptor Radionuclide Therapy

Table 1. Baseline characteristics

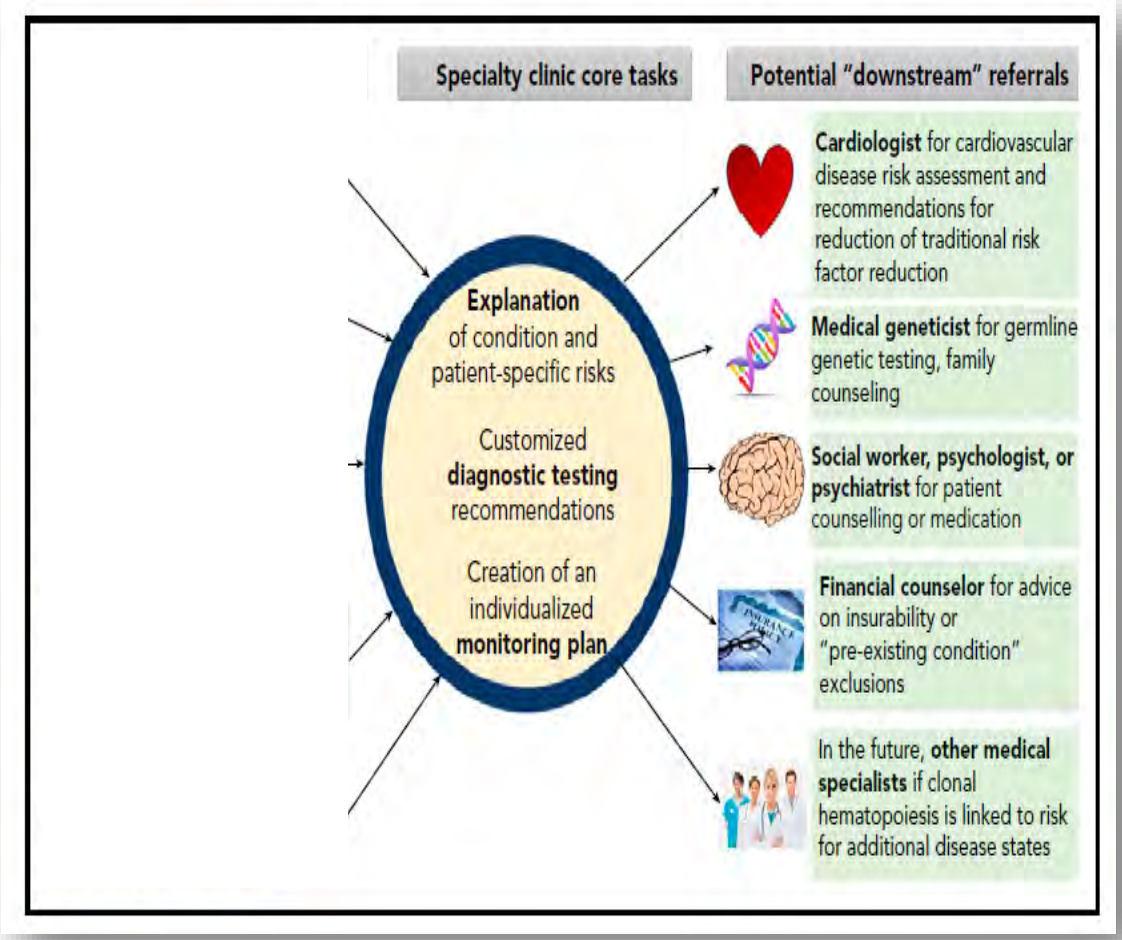
Variables	Total cohort (n=102)	CHIP (n=35)	CHIP negative (n=67)	P-value
General				
Median age (range)	70 (64-77)	75 (69-78)	70 (64-76)	0.04
Female gender, n (%)	56 (54%)	26 (67%)	32 (48%)	0.11
Median hemoglobin (IQR), g/dl	13.2 (11-14.7)	12.2 (10.4-13.3)	13.5 (11.3-14.9)	0.16
Median leukocyte count nl/L (IQR)	7.1 (5.9-9.2)	7.3 (5.4-9.3)	7.7	0.5
Median platelet count nl/L (IQR)	236 (171-293)	232 (152-293)	253	0.4
Active smoking, n (%)	13 (13%)	4 (11%)	9 (14%)	0.48
Type of neoplasm				
Breast neoplasm, n (%)	16 (16%)	10 (67%)	6 (37%)	0.01
Ovarian neoplasm, n (%)	17 (17%)	5 (29%)	12 (71%)	0.8
Head and neck carcinoma n (%)	11 (11%)	3 (27%)	8 (73%)	0.81
Colorectal+esophageal neoplasm, n (%)	21 (20%)	6 (29%)	15 (71%)	0.49
Bladder neoplasm, n(%)	7 (7%)	0 (0%)	7 (100%)	0.04
Lymphoproliferative syndrome, n(%)	23 (22%)	10 (43%)	13 (57%)	0.88
Multiple myeloma, n(%)	8 (8%)	2 (25%)	6 (75%)	0.53
Treatment				
Chemotherapy, n (%)	59 (58%)	24 (54%)	35 (67%)	0.52
Alkylating agents, n (%)	34 (33%)	16 (44%)	18 (27%)	0.06
Platinum agents, n (%)	58 (56%)	15 (42%)	43 (64%)	0.03
Anti-tubulin agents, n (%)	44 (43%)	20 (56%)	24 (34%)	0.04
Antimetabolites, n (%)	34 (33%)	6 (17%)	28 (42%)	0.01
Anthracyclines, n (%)	19 (19%)	10 (28%)	9 (13%)	0.07
Radiation therapy, n (%)	37 (36%)	16 (44%)	21 (31%)	0.2
Outcomes and complications				
CR, %	72%	68%	68%	0.8
ORR, %	89%	86%	83%	0.3
Grade 1-2 cytopenias, %	54%	56%	55%	0.9
Grade 3-4 cytopenias, %	14%	16%	14%	0.9
Grade 1-2 infections, %	11%	16%	8%	0.2
Grade 3-4 infections, %	8%	3%	10%	0.2



Plan

Rx Plan

- Work up
- Monitoring Counts
- CH-associated adverse outcomes
  - Hematological malignancies
  - **Non-hematological conditions**
  - **Referrals**
  - **Trials and interventional studies**



Steensma D et al. Blood; Oct 2020

Ongoing Clinical Trials !

Rx Plan

- Canakinumab
- IDH ½ inhibitors
- Statins
- Colchicine
- Vitamin C

TABLE 4 Table summarizing planned/active/recruiting interventional clinical trials for patients with clonal hematopoiesis (source: www.clinicaltrial.gov).

Sr No.	Name	Type (planned accrual)	Key inclusion criteria	Primary end-point(s)	NCT identifier
1.	A study of enasidenib in people with clonal cytopenia of undetermined significance	Pilot study (Phase 1, N = 15)	CCUS with *IDH2* mutations	Rate of hematologic improvement	NCT05102370
2.	A pilot study of ivosidenib for Patient(s) with clonal cytopenia of undetermined significance and mutations in IDH1	Pilot study (Phase 2, N = 15)	CCUS with *IDH1* mutations	Rate of hematologic improvement	NCT05030441
3.	Ascorbic acid and combination chemotherapy for the treatment of relapsed or refractory lymphoma or clonal cytopenia of undetermined significance	Phase 2 (N = 15, for CCUS)	CCUS arm (arm D): Diagnosis of CCUS with one or more *TET2* mutations with or without splicing gene or epigenetic mutations with hemoglobin <10 gm/dL, absolute neutrophil count less than 1000/mm^3, or platelet count less than 100, 000/mm^3.	CCUS arm (arm D): Hematologic response defined as objective status of HI-E (minor or major response), HI-P, or HI-N evaluated by MDS IWG 2018 criteria at 20 weeks.	NCT03418038
4.	Epigenetics, vitamin C and abnormal blood cell formation—vitamin C in patients with low-risk myeloid malignancies	Prospective, randomized, placebo-controlled trial (N = 109)	CCUS defined as persistent cytopenia in one or more lineages, normal cytogenetics (except -Y), bone marrow morphology not diagnostic of MDS or any other malignancy. OR, a diagnosis of MDS as according to World Health Organization (WHO) 2016 diagnostic criteria with revised international prognostic scoring system (IPSS-R) risk score ≤3 AND bone marrow blast % <5 OR diagnosis of CMML-0 or -1 as according to WHO 2016 diagnostic criteria. AND (for all the categories above) the presence of a detectable mutation in genes recurrently affected in myeloid malignancy (excluding germline mutations)	Median change from baseline in variant allele frequency at 12 months	NCT03682029
5.	Canakinumab for the prevention of progression to cancer in patients with clonal cytopenias of unknown significance. IMPACT Study	Phase 2 (N = 110)	CCUS with high-risk mutations defined as any spliceosome mutations (at any VAF), isolated *TP53* mutation at >5% VAF, at least 1 *TET2*, *DNMT3A*, or *ASXL1* mutation at any VAF plus 1 other somatic or germline myeloid predisposition mutation, presence of two or more myeloid somatic or germline mutations each at ≥10% VAF.	Time to overt myeloid malignancy	NCT05641831

TABLE 4 (Continued)

Sr No.	Name	Type (planned accrual)	Key inclusion criteria	Primary end-point(s)	NCT identifier
6.	Statins in patients with clonal cytopenia of undetermined significance (CCUS) and myelodysplastic syndromes (MDS)	Pilot study (Phase 2, N = 16)	CCUS defined by the presence of somatic mutation(s) with VAF >2% in absence of morphology/cytogenetic changes diagnostic for MDS plus unexplained cytopenia in at least one lineage ORMDS is defined using the WHO 2016 definition and classified into lower-risk if IPSS-R score is ≤3.5. Lower-risk MDS will be required to have at least one mutation in a recurrent mutated gene with a VAF ≥2%.	Change in allele burden (VAF) of somatic mutation (assessed in peripheral blood or bone marrow)	NCT05483010
7.	Repurposing metformin as a leukemia-preventive drug in CCUS and LR-MDS	Phase 2 (N = 24)	Lower risk MDS according to revised International prognostic scoring system (IPSS-R score ≤3), ORCCUS defined as the presence of somatic mutations and persistent unexplained cytopenia(s).	Change in variant allele frequency of somatic mutation	NCT04741945

Collaboration

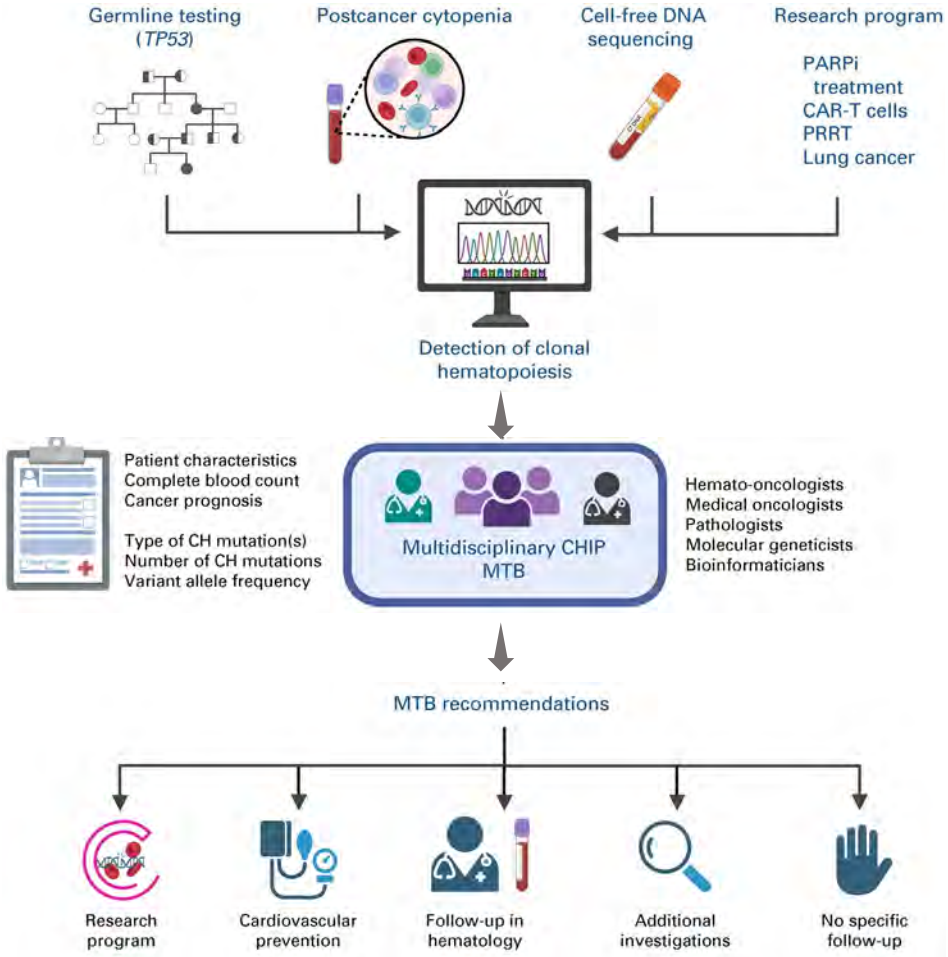
Consequences

- Assessment for risk factors & / or symptoms of IHD
- Referral to PCP or preventative cardiologist for guidelines based cardiovascular disease prevention strategy
- Other subspecialties
  - > Guide specific interventions for nonmalignant comorbidities

Models

Rx Plan

- Post Allo HSCT
- Research Programs
- Gustave Roussy Model
- MSKCC Model



Who Should Be Referred?

Service Area

- Incidentally during work up for Cytopenia
- Solid tumors NGS
- Diagnose germ line cancer predisposition syndromes
- Investigate suspected donor cell leukemia after HSCT
- Orthopedics Surgeries
- Gyn Onc & Breast Ca Clinics
- Referrals solid malignancies undergoing Foundation One Liquid CDX
- Challenges with Origin of Certain mutations, Prognosis of Solid Tumors

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Conclusion

CH Nosology

- CHIP Incidence in our Aging Population
- Risk of Leukemia and Other Hematological Neoplasms
- Risk of Non-Hematological Conditions
- Sources of Referral – i.e. Genetic Counseling
- Incidence + Consequences = Significance
- Collaboration is a Key !
- A big room of intervention !

THANK YOU !

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