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Clonal Hematopoiesis in Cancer and Cardiovascular Disease

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Emerging evidence suggests a dynamic relationship exists between cancer and cardiovascular disease (CVD). CVD is common among cancer survivors; however, it also may increase the risk of developing cancer. The underlying factors driving this connection remain poorly understood. Aging, chronic inflammation, and perturbed immune signaling are shared hallmarks of cancer and CVD. Clonal hematopoiesis (CH), the age-related accumulation of somatic mutations in hematopoietic cells leading to cells with a growth advantage, is associated with immune dysregulation in elderly people. Growing evidence suggests that CH is a risk factor for CVD. Although the link between CH and hematological cancer is well established, its relationship to solid organ cancers is far less understood. This review provides an in-depth analysis of the evidence linking CH with solid organ malignancies and explores its role as a shared risk factor for the development of both CVD and cancer. Furthermore, it discusses the potential mechanisms by which CH may contribute to CVD among cancer survivors. (JACC CardioOncol. 2025;7:470–495) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide. Despite being considered distinct diagnoses, both conditions share common risk factors, such as aging, smoking, obesity, physical inactivity, and metabolic disorders, as well as overlapping pathological hallmarks, including chronic inflammation, oxidative stress, and cellular senescence.[1,2] It is also now well understood that among cancer survivors, CVD is a prominent cause of mortality. Indeed, in cancer survivors, CVD accounts for 27% of all deaths and 56% of noncancer deaths.[3] This has primarily been attributed to the cardiotoxic effects of cancer treatments, such as anthracyclines, chest radiation, and immunotherapies, and in some instances, can manifest long after cessation of therapy. In addition, evidence has emerged that CVD is an independent risk factor for cancer, suggesting a bidirectional relationship exists between the 2 conditions.[4] Given their prevalence and substantial impact on human health, understanding the intricate relationship between these conditions is crucial for developing prevention, risk stratification, and treatment approaches to improve patient outcomes.

Aging and chronic inflammation, which are often collectively given the term inflammaging, are common risk factors for CVD and cancer. Among the numerous mechanisms contributing to inflammaging, one gaining significant attention is clonal hematopoiesis (CH)—the age-related acquisition of

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HIGHLIGHTS

- Cancer and cardiovascular disease share overlapping features, with clonal hematopoiesis perhaps representing as a previously unrecognized link.
- Studies suggest clonal hematopoiesis is a novel cancer risk factor, with mutant leukocytes contributing to tumorigenesis.
- Clonal hematopoiesis may also contribute to cardiotoxicity among cancer survivors.
- Screening for clonal hematopoiesis may aid risk stratification and personalized therapies to improve patient outcomes.

somatic driver mutations in hematopoietic cells, which facilitate clonal expansions in the blood.[5] Recently, it has emerged that CH is an independent risk factor for a range of cardiovascular conditions. Experimental studies have supported a causal relationship, indicating that mutant leukocytes exacerbate disease by promoting inflammation and disrupting immune function. Although CH is a well-established precursor to hematological malignancies, its connection to solid cancers remains far less understood. Immune cells and chronic inflammation are known contributors to tumorigenesis. Therefore, it is reasonable to speculate that CH may play a causal role in the development of solid organ malignancies. Recent studies are beginning to support this notion, perhaps suggesting that CH represents a shared risk factor between cancer and CVD. Moreover, new work indicates that CH may, in part, explain the elevated risk of CVD observed in cancer survivors. This review provides an up-to-date overview of CH and its relationship with cancer and CVD, exploring how these 2 distinct diseases may be interconnected.

AGE-RELATED CLONAL HEMATOPOIESIS

Over a lifetime, we sporadically accumulate mutations in all cells throughout the body. Although these mutations are usually neutral or lead to cellular demise, sometimes they may be advantageous.[5] This provides the cell with a competitive fitness advantage, allowing it to outcompete "less-fit" neighboring cells. As a result, cells with the mutation grow and constitute an increasingly larger portion of the tissue. The lifelong acquisition of mutations and clonal outgrowth of cells with advantageous mutations contribute to a phenomenon known as somatic mosaicism.[5,6] Although somatic mosaicism represents a pathway to malignancy, it has been detected in all otherwise healthy tissues throughout the body. Despite this, its biological significance and impact on human health, outside the realm of malignancy, is only beginning to be appreciated.

CH is a form of somatic mosaicism within the hematopoietic system. It occurs when a hematopoietic stem or progenitor cell (HSPC) acquires a driver mutation, which provides the cell with an enhanced trait such as increased self-renewal, proliferation, survival, or a combination of these, enabling the mutant HSPC to expand at a disproportionate rate compared with surrounding HSPCs. As a result, the mutation grows and is carried into leukocyte progeny, where it can be detected in mature blood cells by DNA sequencing.[5] With the emergence of next-generation sequencing (NGS), our understanding of CH has grown, and it has come to light that several subtypes (Figure 1) of this phenomenon exist, which are primarily defined by the type of genetic aberration involved. Driver gene–mediated CH involves mutations (ie, single-nucleotide variants, and small insertions and deletions) to a single driver gene, although often to a preleukemic driver gene.[7-9] This subtype encompasses clonal hematopoiesis of indeterminate potential (CHIP), marked by an expanded blood clone with a preleukemic driver mutation and a variant allele frequency (VAF) of 2% or higher in the blood. Mosaic chromosomal alterations (mCAs) have also been described in blood cells, such as losses and gains of sections or entire chromosomes and loss of heterozygosity.[10-12] A subset of this includes the entire loss of the sex chromosomes, specifically the loss of the X chromosome (LOX) in females and the loss of the Y (LOY) in males.[12-15] As these subtypes of CH become more frequent with age, the term age-related clonal hematopoiesis can be used to collectively describe the genetic aberrations that drive clonal events within the aged hematopoietic system.[16] This review primarily focuses on driver gene–mediated CH, although mCAs also are discussed wherever appropriate and where the literature is available.

ABBREVIATIONS AND ACRONYMS

AIC = anthracycline-induced cardiotoxicity

CAD = coronary artery disease

CH = clonal hematopoiesis

CHIP = clonal hematopoiesis of indeterminate potential

DNMT3A = DNA methyltransferase 3 alpha

HSPC = hematopoietic stem or progenitor cell

IL = interleukin

LOX = loss of the X chromosome

LOY = loss of Y chromosome

mCAs = mosaic chromosomal alterations

NGS = next-generation sequencing

NSCLC = non-small-cell lung cancer

PPM1D = protein phosphatase, $Mg2+/Mn2+$ dependent 1D

tCH = therapy-related clonal hematopoiesis

TET2 = ten eleven translocation 2

TGF = transforming growth factor

TI-CH = tumor-infiltrating clonal hematopoiesis

t-MPN = therapy-related myeloproliferative neoplasms

TP53 = tumor protein p53

UKB = UK Biobank

VAF = variant allele frequency

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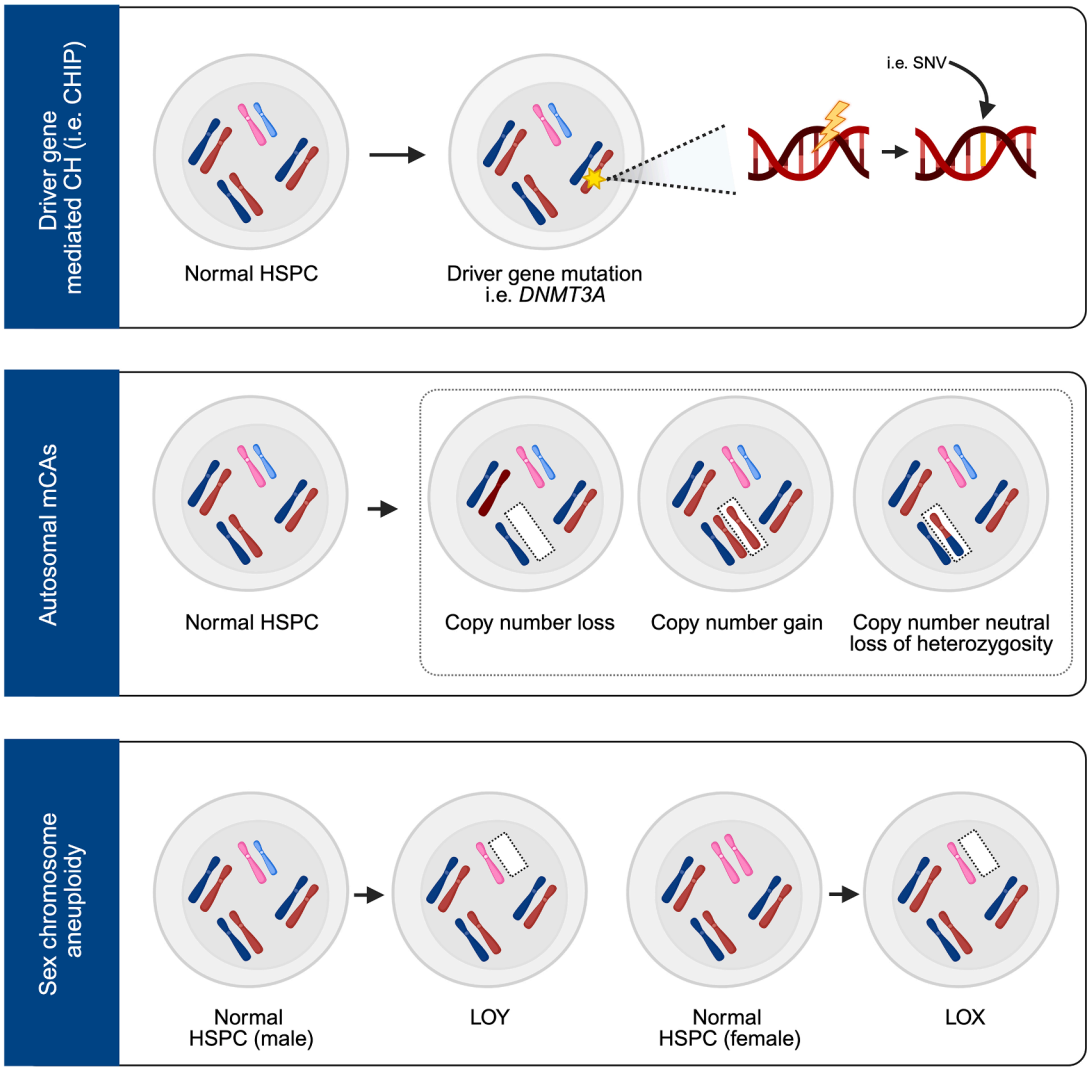
FIGURE 1 Overview of the Types of Mutations Observed in Age-Related CH



CH = clonal hematopoiesis; CHIP = clonal hematopoiesis of indeterminate potential; DNMT3A = DNA methyltransferase 3α; HSPC = hematopoietic stem and progenitor cell; LOX = loss of the X chromosome; LOY = loss of the Y chromosome; mCAs = mosaic chromosomal alterations; SNV = single-nucleotide variant. Created with BioRender.com, with permission.

DRIVER GENES AND CHIP. In 2014, 3 large longitudinal studies used whole exome sequencing to examine the prevalence of common blood cancer driver mutations in the blood across the life span.[7-9] It was found that the frequency of hematopoietic clones carrying driver mutations increased sharply with age with estimates that 10% of individuals older than 70 had at least 1 mutation in their blood cells.[9] Mutations occurred in a range of candidate driver genes, with most occurring in the epigenetic regulators, DNA methyltransferase 3 alpha (*DNMT3A*), ten eleven translocation 2 (*TET2*), and additional sex combs like 1 (*ASXL1*). A smaller proportion of mutations were found in other driver genes encoding proteins involved in DNA damage response (ie, tumor protein p53 [*TP53*] and protein phosphatase, Mg2+/Mn2+ dependent 1D [*PPM1D*]), spliceosome (ie, *SF3B1*), and cytokine signaling, (ie, *JAK2*). As would be expected, individuals carrying a mutant clone had a substantially higher risk of developing a hematological malignancy, with an absolute risk of progression of ~0.5% to 1% per year compared with <0.1% in individuals without detectable clones. However, most did not develop a hematological malignancy, as these conditions are relatively rare and generally require the acquisition of multiple

mutations.[8,9] From these observations, the term "CHIP" was born to help explain the occurrence of a blood cancer mutation with an undefined potential for malignancy.[17] To meet the criteria for "CHIP," an individual must have an expanded blood cell clone carrying a mutation in a known blood cancer driver gene at a VAF of at least 2% without meeting the standard diagnostic criteria for malignancy (ie, cytopenia, dysplasia, or neoplasia). Nevertheless, the 2% VAF threshold is an artifactual construct that was likely proposed based on the low depth of earlier NGS methods and the inherent error of NGS. Since, studies using deep error-corrected sequencing, capable of detecting clones at ~0.03% VAF, have begun to challenge this threshold, suggesting clones smaller than 2% VAF may also be of clinical importance.[18-21] Furthermore, it is also known that mutations can occur in unknown drivers outside those recurrently mutated in hematological malignancies, that is, non-CHIP driver genes.[8,22,23] Given the limitations of the CHIP definition and the emergence of studies using sequencing methodologies with lower mutation detection thresholds with improved accuracy, we refer to this form of CH as driver gene-mediated CH. However, when citing original research using the term CHIP, we will continue to use this definition to accurately represent the findings.

Since these landmark studies, other studies have examined the frequency of driver gene mutations in the blood across the life span and in distinct cohorts of individuals.[22,24-27] The reported prevalence of CH varies and largely depends on 3 main factors: variant calling, sequencing depth, and the study cohort. Although these issues have been discussed elsewhere,[5,28] studies using non-biased sequencing approaches,[22,29] which identify a broader range of clonally expanded events, and ultradeep error-corrected sequencing,[27] which detect mutations at lower VAFs, have shown that CH is far more prevalent than previously thought. Recent work suggests that driver gene mutations are acquired earlier in life, and the clones expand in a subset of individuals as a function of age.[24,25,30] Exactly what drives clonal expansion in some individuals and not others remains enigmatic, although mutation type, heritable traits, inflammation, infection, smoking, and cancer therapy exposure may play a role and these factors have been reviewed elsewhere.[5,31,32] Furthermore, studies examining the prevalence of preleukemic driver mutations in the blood in different cohorts suggest its prevalence can vary, particularly in disease cohorts where driver gene mutations appear to be enriched.[33-36] Thus, when interpreting data that report the prevalence of driver gene-mediated CH, these previously mentioned factors should be considered to ensure accurate comparisons and meaningful conclusions can be made.

MOSAIC CHROMOSOMAL ALTERATIONS. Expanded clones carrying mCAs have been detected in the blood of otherwise healthy individuals and become more frequent with age.[10-13,15,37] These large-scale mutations involve the loss and/or gain of chromosomal segments or entire chromosomes and loss of heterozygosity. Although mCAs can occur throughout the genome, they are more commonly found in specific chromosomal regions.[12,37] Notably, sex chromosome loss represents the most frequent mCA, with loss of the X chromosome occurring in females and loss of the Y chromosome in males.[13,15] Large epidemiological studies report that autosomal mCAs are present in ~2% to 5% of individuals younger than 45 years, ~5% to 15% of those at 65 years, and up to 30% to 40% in individuals older than 90 years.[12,37] Differences in reported prevalence have been attributed to possible ancestral differences between study cohorts.[12,37-39] Regarding sex chromosome aneuploidy, the reported prevalence of these aberrations varies across studies and is influenced by detection limits, with Y chromosome loss in men being considerably more frequent. More specifically, studies suggest that the prevalence of LOX ranges from approximately 0.5% to 7% in elderly women depending on the study threshold[12,15,40,41] and preferentially affects the inactivated X chromosome.[15] LOY studies indicate that in elderly men, between 10% and 40% have lost their Y chromosome in at least 10% of their blood cells.[13,14,22,42-44] The factors that promote the expansion of mutant clones carrying mCAs are ill defined. Associations with heritable traits have been described, some of which include cancer susceptibility loci.[14,39,42,44] It has thus been suggested that these mutations may be biomarkers of genomic instability originating from heritable traits and could explain their association with cancer. In addition, expansion of LOY has been associated with smoking[42,44-47] and pollutant exposure,[48,49] which are also risk factors for the development of various types of cancer.

AGE-RELATED CH AND CVD

DRIVER GENES. In 2014, 2 landmark longitudinal studies discovered that CHIP was associated with an increase in all-cause mortality.[8,9] Cause-specific analyses revealed that the elevated mortality risk far exceeded that linked to hematologic malignancies. Interestingly, in an unplanned secondary analysis, Jaiswal et al[9] made the unexpected discovery that cardiovascular causes drove this increased risk, as it

was found that individuals with CHIP had an increased risk of developing coronary heart disease (HR: 2.0; 95% CI: 1.2-3.4) and ischemic stroke (HR: 2.6; 95% CI: 1.4-4.8). Jaiswal et al[50] conducted a follow-up study to substantiate these findings and directly test the hypothesis that CHIP is associated with elevated cardiovascular risk. These findings have been summarized in **Table 1** and support the previous findings that CHIP is a risk factor for CVD. Since these studies, numerous investigations have been conducted to examine the connection between CH and CVD, corroborating the initial findings by Jaiswal et al[9] and revealing new associations between driver gene-mediated CH and CVD incidence/risk. In addition, studies have also found that CH is associated with poorer prognoses of various cardiovascular conditions. An extensive list of these clinical studies is summarized in **Table 1**. Experimental studies using murine models of CH have provided causal support for these associations, demonstrating that different driver mutations promote CVD. Furthermore, they have provided insight into the underlying mechanisms, revealing that leukocytes with driver mutations have an enhanced inflammatory profile, thereby contributing to the inflammatory processes that drive CVD. These murine studies alongside the described mechanism are summarized in **Table 2**. Most importantly, several of these mechanisms have been supported by clinical studies and have also shown that patients with CH respond more favorably to certain therapies targeting these proinflammatory mechanisms (**Table 3**). These findings open the door for the development of personalized therapies for individuals with driver gene mutations in their blood and CVD.

mCAs. The putative link between mCAs and CVD risk has received considerably less attention than driver gene CH, with current data suggesting that LOY may primarily drive this association. In particular, data from the UK Biobank (UKB) indicate that LOY is associated with self-reported myocardial infarction and stroke,[46] incident atrial fibrillation[51] (HR: 1.06; 95% CI: 1.03-1.11), and an increased risk of death from various cardiovascular causes, including hypertensive heart disease (HR: 3.48; 95% CI: 1.54-7.89), heart failure (HR: 1.76; 95% CI: 1.01-3.05), congestive heart failure (HR: 2.42; 95% CI: 1.14-5.15), and aortic aneurysm and dissection (HR: 2.76; 95% CI: 1.21-6.29).[52] Similarly, LOY has been linked to an increased risk of mortality (HR: 2.58; 95% CI: 1.33-5.03) and heart failure (HR: 2.30; 95% CI: 1.23-4.27) in patients with chronic kidney disease[53] and higher mortality (HR: 2.59; 95% CI: 1.00-6.68) in patients with wild-type transthyretin cardiac amyloidosis.[54] LOY also appears to have clinical prognostic significance, as it has been associated with poorer outcomes in high-risk individuals undergoing cardiac procedures due to underlying CVD, such as carotid endarterectomy (HR: 2.28; 95% CI: 1.11-4.67),[55] transcatheter aortic valve replacement (HR: 2.2; 95% CI: 1.4-3.4),[56] and coronary angiography (HR: 1.41; 95% CI: 1.09-1.82).[57] Moreover, LOY is associated with poor functional outcomes following ischemic stroke (OR: 2.2; 95% CI: 1.6-3.1).[58] Cardiovascular associations with LOX have begun to emerge from analyses of UKB data. One study identified an inverse association with incident atrial fibrillation (HR: 0.90; 95% CI: 0.83-0.98)[51] and another suggested possible connection with several other cardiovascular conditions.[41]

Experimental studies have begun to explore whether the relationship between LOY and CVD is causal, providing insights into underlying mechanisms. To investigate hematopoietic LOY, Sano et al[52] developed a mouse model using CRISPR-Cas9 to ablate the Y chromosome in lineage-negative bone marrow cells from male mice. LOY or control cells were then transplanted into lethally irradiated male mice. In this model, mice developed age-related cardiac dysfunction and more severe heart failure following transverse aortic constriction, accompanied by increased indices of fibrosis. By way of mechanism, LOY macrophages exhibited a profibrotic gene signature enriched in transforming growth factor (TGF)-β1 signaling. TGF-β1 blockade with a monoclonal antibody partially reversed heart failure and fibrosis post transverse aortic constriction. Follow-up studies using additional mouse models of LOY have extended the findings from this initial work, showing that disruption of the Y-linked gene, UTY, in immune cells, mimics the profibrotic effects of LOY in heart failure.[59]

Clinical findings have since strengthened this experimental work. Single-cell sequencing has shown that LOY monocytes and macrophages from men with dilated cardiomyopathy or those who have undergone transcatheter aortic valve replacement or cardiac angiography display an enhanced profibrotic gene signature.[56,57,59] Notably, in men with dilated cardiomyopathy, LOY macrophages were linked to increased cardiac fibroblast activation, further supporting LOY's contribution to cardiac fibrosis.[59] It has also been found that men undergoing coronary angiography with a high percentage of LOY cells in their blood (>17%) have elevated plasma levels of profibrotic and proinflammatory mediators.[57] The authors of this study also examined the effect of a myocardial fibrosis genetic risk score on all-cause mortality and death due to cardiovascular causes in men who have undergone cardiac angiography. This

TABLE 1 CH and CVD: Clinical Studies

		Incidence		
First Author, Year	Disease Focus	Population and CH Prevalence	Sequencing Method	Findings
Bick et al, 2020[139]	CV events (MI, coronary artery revascularization, stroke, or death)	35,416 individuals from UKB 3% *DNMT3A*/*TET2* CHIP	Whole exome sequencing	*DNMT3A*/*TET2* CHIP was associated with increased incident CVD event risk (HR: 1.27; 95% 95% CI: 1.04-1.56), which was stronger for larger clones (HR: 1.59; 95% CI: 1.21-2.09)
Yokokawa et al, 2021[140]	CVD	832 hospitalized patients with any CVD; 462 with vascular disease, 370 without vascular disease 1.8% with *JAK2*^{V617F} mutations	qPCR	Individuals with *JAK2*^{V617F} mutations were enriched in those with vascular diseases compared with those with nonvascular diseases *JAK2*^{V617F} mutations were independently associated with higher risk of cardiovascular events (HR: 3.35; 95% CI: 1.22-9.21)
Marston et al, 2024[141]	CVD	63,700 individuals from 5 TIMI randomized trials 8.2% CHIP	Whole exome sequencing	Individuals with CHIP had no increase in cardiovascular events (HR: 1.07; 95% CI: 0.99-1.16) Individuals with CHIP had an increase in first-ever MI (HR: 1.31; 95% CI: 1.05-1.64) but no increase in recurrent MI (HR: 0.94; 95% CI: 0.79-1.13)
Jaiswal et al, 2017[50]	CAD	4 case-control studies: 4,726 CAD cases and 3,529 controls CHIP: 2.73 % cases vs 1.59% controls 3 prospective cohorts, unselected for coronary events: JHS, FUSION, FHS	Whole exome sequencing	CHIP was associated with CHD (HR: 1.9; 95% CI: 1.4-2.7) *DNMT3A*, *TET2*, *ASXL1*, *JAK2* all associated with CHD, which was strongest for JAK2 mutations (HR: 12.0; 95% CI: 3.8-38) CHIP was associated with early-onset MI (HR: 4.0; 95% CI: 2.4-6.7) VAFs ≥10% associated with coronary artery calcification (HR: 12; 95% CI: 2.4-64)
Honigberg et al, 2022[116]	CAD	11,495 women from UKB and 8111 women from WHI 3.6% and 8.6% CHIP respectively	Whole exome sequencing (UKB) Whole genome sequencing (WHI)	In women from UKB and WHI <70 years old, any CHIP was associated increased risk of CAD (HR:1.36; 95% CI: 1.07–1.73) Risk stronger for CHIP with VAF >10% (HR:1.48; 95% CI: 1.13-1.94)
Vlasschaert et al, 2023[142]	CAD	451,180 individuals from UKB	Whole exome sequencing	CHIP associated with cumulative incident CAD and increased risk of CAD Risk greater for non-*DNMT3A* CHIP
Zekavat et al, 2023[126]	PAD	37,657 individuals from UKB and 12,465 individuals from MGBB 5.8% and 5.4% CHIP respectively	Whole exome sequencing	CHIP associated with increased risk of PAD in UKB (HR: 1.58; 95% CI: 1.11-2.25) and MGBB (HR: 1.66; 95% CI: 1.31-2.11) Risk of PAD strongest for VAF >10% (HR:1.97; 95% CI: 1.44-2.71) and significant associations found for drivers other than *DNMT3A*
Bhattacharya et al, 2021[143]	Stroke	86,178 individuals from 8 prospective cohorts: WHI, MESA, JHS, FHS, CHS, ARIC, MGBB, UKB 6% CHIP combined	Deep coverage whole genome sequencing (CHS, JHS, MESA, FHS, WHI) Whole exome sequencing (ARIC, UKB, MGBB)	Any CHIP was associated with increased risk of hemorrhagic (HR: 1.24; 95% CI: 1.01-1.51) but not ischemic stroke (HR: 1.11; 95% CI: 0.98-1.25) *DNMT3A*-CHIP was associated with hemorrhagic stroke (HR: 1.43; 95% CI: 1.03-1.98). *TET2*-CHIP was associated with ischemic stroke (HR: 1.90; 95% CI: 1.18-3.05) CHIP was associated with small vessel ischemic and subarachnoid hemorrhage stroke subtypes
Yu et al, 2021[114]	HF	56,597 individuals from CHS, JHS, WHI, ARIC, and UKB 6% CHIP combined	Whole genome sequencing (CHS, JHS, WHI) Whole exome sequencing (ARIC and UKB)	Any CHIP associated with increased risk of HF (HR: 1.25; 95% CI: 1.13-1.38) Risk strongest for *TET2*, *JAK2*, and *ASXL1* mutations *ASXL1* mutations associated with reduced LVEF
Schuermans et al, 2024[113]	HF	2,927 individuals from JHS and 5,163 individuals from WHI 6.3% CHIP combined	Whole genome sequencing	Cumulative incidence of any HF and HFpEF higher among CHIP carriers vs noncarriers *TET2*-CHIP was significantly associated with HFpEF (HR: 2.35; 95% CI: 1.34-4.11)
Wolach et al, 2018[144]	Thrombosis	10,893 individuals from a case-control cohort that included healthy controls and patients with schizophrenia 4% CHIP	Whole exome sequencing	CHIP was associated with increased rate of thrombotic events that was particularly prominent in individuals with *JAK2*^{V617F} mutations
Zon et al, 2024[145]	Thrombosis	425,399 individuals from UKB 3.4% CHIP	Whole exome sequencing	Any CHIP was associated with an incident venous thromboembolism (HR: 1.17; 95% CI 1.09-1.3) *JAK2* mutations had the strongest association with incident venous thromboembolism (HR: 4.2; 95% CI: 2.18-8.08) *JAK2* mutations associated with prevalent venous thromboembolism

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TABLE 1 Continued

First Author, Year	Disease Focus	Population and CH Prevalence	Sequencing Method	Findings
		Incidence		
Saadatagah et al, 2024[146]	AF	4,131 individuals from ARIC and 195,851 individuals from UKB 24.7% and 5.8% CHIP, respectively	Whole exome sequencing	Large CHIP (VAF >10%) was associated with increased risk AF (HR: 1.12; 95% CI: 1.01-1.25) Any *TET2* (HR: 1.18; 95% CI: 1.01-1.38) or *ASXL1* (HR: 1.33; 95% CI: 1.02-1.73) mutation was associated with increased risk of AF
Lin et al, 2024[147]	AF	358,097 individuals from UKB 3.5% CHIP	Whole exome sequencing	CHIP was associated with incident AF (HR: 1.11; 95% CI: 1.04-1.19)
Ahn et al, 2024[148]	AF	1,004 patients with AF and 3,341 healthy controls 10.7% and 23.6% CHIP in controls and AF cases, respectively	Deep targeted sequencing	CHIP mutations were more prevalent in patients with AF (OR: 1.38; 95% CI: 1.10-1.74)
Nakao et al, 2023[149]	Thoracic aortic aneurysm	417,759 individuals from UKB 0.028% with *JAK2*^{V617F} CHIP	Whole exome sequencing	*JAK2*^{V617F} CHIP associated with incident thoracic aortic aneurysm (HR: 12.8; 95% CI: 4.8-34) No association with abdominal aortic aneurysms (HR: 1.4; 95% CI: 0.19-9.7)
		Prognosis		
Dregoesc et al, 2024[150]	CAD	218 patients with stable CAD 33% with CH driver mutations	Ultrasensitive single-molecule molecular inversion probe sequencing	CH associated with MACE (HR: 3.19; 95% CI 1.27-8.01) CH with VAF >1.07% predictive of MACE
Gumuser et al, 2023[151]	Atherosclerotic CVD	13,129 individuals from UKB with established ASCVD 5.1% CHIP	Whole exome sequencing	Any CHIP was associated with incident ASCVD events (HR: 1.24; 95% CI: 1.08-1.43) or all-cause mortality (HR: 1.28; 95% CI: 1.09-1.51) This association was stronger for large CHIP
Dorsheimer et al, 2017[34]	Chronic ischemic HF	200 patients with chronic ischemic HF 18.5% CHIP	Deep targeted amplicon sequencing	*DNMT3A*/*TET2* CH was associated with progression of chronic ischemic HF and a shorter survival (HR: 2.1; 95% CI: 1.1-4.0)
Cremer et al, 2020[19]	Chronic ischemic HF	419 patients with chronic ischemic HF 36.75% CH carriers	Deep error-corrected targeted amplicon sequencing	CH, including mutations <2% VAF, was associated with a poorer survival Multiple CH mutations with a collective VAF >3% are associated with a shorter survival
Assmus et al, 2021[18]	Chronic ischemic HF	419 patients with chronic ischemic HF 56.2% carriers of *DNMT3A* or *TET2* mutation with VAF >0.5%	Deep error-corrected targeted amplicon sequencing	*DNMT3A* clones >1.15% VAF and/or *TET2* clones >0.73% VAF were associated with poor clinical prognosis (HR: 1.77; 95% CI: 1.08-2.90)
Pascual-Figal et al, 2021[33]	Heart failure with reduced ejection fraction	62 patients ≥60 years with ischemic and non-ischemic HF with reduced left ventricular ejection fraction 38.7% CHIP	Error-corrected targeted amplicon sequencing	Patients with mutations in either *DNMT3A* or *TET2* showed accelerated HF progression in terms of death (HR: 2.79; 95% CI: 1.31-5.92), death or HF hospitalization (HR: 3.84; 95% CI: 1.84-8.04), and HF-related death or HF hospitalization (HR: 4.41; 95% CI: 2.15-9.03)
Cochran et al, 2023[20]	HFpEF	81 patients with HFpEF and 36 controls from Alberta HEART 40% CH 59 patients with HFpEF from SCAN-MP cohort 61% CH	Ultradeep error-corrected sequencing	*TET2* mutations were enriched in patients with HFpEF CH-positive patients had worse diastolic dysfunction and elevated levels of HF markers CH was associated with increased risk of CV-related hospitalization in individuals ≥70 y (HR: 5.06; 95% CI: 1.06-24.15)
Sikking et al, 2024[21]	DCM	500 patients with DCM 21% CH	Single-molecule molecular inversion probe technique	CH with a VAF cutoff of 0.36% was associated with a higher risk of cardiac death (HR: 2.33; 95% CI: 1.24-4.40) CH with a VAF cutoff of 0.06% was associated with an increased risk of all-cause mortality (HR: 1.72; 95% CI: 1.10-2.69)
Ahn et al, 2024[148]	AF	21,286 UKB patients with AF 6.1% CHIP	Whole exome sequencing	AF patients with CHIP, particularly those with *TET2* mutations, were more likely to have clinical characteristics consistent with poor prognosis CHIP associated with higher risk of composite clinical event (HF, ischemic stroke, or death) in patients with AF (HR:1.32; 95% CI: 1.20-1.45)
Wang et al, 2022[152]	STEMI	485 patients with STEMI 16.5% with CHIP	Deep targeted sequencing	*DNMT3A*/*TET2* mutations were an independent predictor of increased incidence of death (HR: 1.97; 95% CI: 1.10-3.51) and MACE (HR: 1.83; 95% CI: 1.15-2.91)
Bohme et al, 2022[187]	Cardiogenic shock complicating acute MI	12.4% with *DNMT3A* and/or *TET2* CHIP; 446 patients from the CULPRIT-SHOCK trial 29% CHIP	Targeted amplicon sequencing	CHIP was associated with all-cause mortality or severe renal failure in patients with cardiogenic shock complicating acute MI (OR: 2.05; 95% CI: 1.35-3.12)
Arends et al, 2023[153]	Ischemic stroke	581 patients with first-ever ischemic stroke 40.6% with CH	Deep targeted sequencing	Patients with CH had a higher risk of recurrent vascular events and death (HR: 1.55; 95% CI: 1.04-2.31), which was higher among those with large clones and *TET2* or *PPM1D* mutations

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TABLE 1 Continued

Prognosis				
Mas-Piero et al, 2020[154]	Valve disease	279 patients with severe aortic valve stenosis undergoing TAVI 33.3% *DNMT3A*/*TET2* CHIP	Targeted amplicon sequencing	Patients with *DNMT3A* or *TET2* CHIP had an increased medium-term all-cause mortality following TAVI (HR: 3.1; 95% CI:1.17-8.08) Patients with *DNMT3A*/*TET2* CHIP showed increases in inflammatory markers
Lassalle et al, 2023[36]	Valve disease	258 patients with aortic valve stenosis undergoing TAVR 68% with CHIP	Captured-based high-throughput sequencing	Patients carrying low VAF (2%-10%) *TET2* driver mutation had a significantly decreased overall survival in the 5 years post-TAVR *DNMT3A* mutations had no effect on survival Patients with both a *TET2* and *DNMT3A* mutation had a slightly improved survival post-TAVR

AF = atrial fibrillation; Alberta HEART = Alberta Heart Failure Etiology and Risk Translation; ARIC = Atherosclerosis Risk in Communities; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CH = clonal hematopoiesis; CHD = coronary heart disease; CHIP = clonal hematopoiesis of indeterminate potential; CHS = Cardiovascular Health Study; CULPRIT-SHOCK = Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock; CV = cardiovascular; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; DNMT3A = DNA methyltransferase 3 alpha; FHS = Framingham Heart Study; FUSION = Finland, United States Investigation of NIDDM (Genetics); HF = heart failure; HFpEF = heart failure with preserved ejection fraction; JHS = Jackson Heart Study; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MESA = Multi-Ethnic Study of Atherosclerosis; MGBB = Mass General Brigham Biobank; MI = myocardial infarction; PAD = peripheral artery disease; qPCR = quantitative polymerase chain reaction; SCAN-MP = Screening for Cardiac Amyloidosis with Nuclear Imaging in Minority Populations; STEMI = ST-elevation myocardial infarction; TAVI = transcatheter aortic valve implantation; TAVR = transcatheter aortic valve implantation; TET2 = ten eleven translocation 2; TIMI = Thrombolysis in Myocardial Infarction (study group); UKB = UK Biobank; VAF = variant allele fraction; WHI = Women's Health Initiative.

genetic risk score comprises 11 single-nucleotide variants that have been previously associated with higher T1 intensity on magnetic resonance imaging, indicative of myocardial fibrosis. Interestingly, LOY was only associated with increased all-cause mortality and death due to cardiovascular causes in men with an elevated genetic risk score.[57] This finding further supports the role of hematopoietic LOY in promoting CVD through profibrotic mechanisms. Moreover, it suggests a potential interaction between LOY and genetic susceptibility to fibrosis, although follow-up studies are needed to clarify this relationship.

CH AND SOLID ORGAN TUMORS

Solid organ malignancies can occur at any age; however, their prevalence rises significantly with advancing age. This age-related increase in prevalence coincides with various immune-related changes, including those driven by CH. As detailed in the preceding section, CH is linked with chronic inflammation and perturbed immune function. Given the well-established roles of immune cells in both anticancer defense and tumorigenesis, it has been of interest to examine the putative link between CH and solid organ malignancy. The following section discusses the clinical studies that provide support of a link between CH and solid organ tumors. In addition, we examine experimental studies that offer mechanistic insights into how CH may contribute to tumor development and progression.

CLINICAL STUDIES: DRIVER GENES. Enrichment. In terms of driver gene–mediated CH, it has been noted that it is common in patients with solid tumors and possibly more prevalent than in the general population.[35,60-63] It is conceivable that this may, at least in part, be explained by cancer therapies selecting the clone (ie, therapy-related CH) or shared risk factors such as smoking.[35,61] Thus, further studies are needed to interrogate this connection. In addition, CHIP mutations also have been identified in solid organ tumor biopsies, although controversy exists as to whether these mutations reflect blood contamination or true enrichment.[64-66] It is well established that leukocytes infiltrate solid organ tumors and contribute to tumor growth. Thus, it is possible that the tumor microenvironment could select for clonal expansion of leukocytes carrying driver mutations. Consistent with this idea, one study found that leukocytes with driver mutations were enriched in untreated breast tumors, with some mutations undetectable in blood samples.[65] Another study, currently in preprint form, reported that mutant clones carrying *TET2* mutations were selectively enriched in patients with anaplastic thyroid cancer.[67] The authors corroborated these findings using a mouse model of anaplastic thyroid cancer, showing that *TET2* mutant macrophages selectively expand within the tumor. In addition, a recent study investigated tumor-infiltrating clonal hematopoiesis (TI-CH) in cancer patients with CHIP.[68] In patients with non-small-cell lung cancer (NSCLC), TI-CH (VAF ≥2%) was detected in 42% of CHIP cases, with higher prevalence in lung squamous cell carcinoma than in adenocarcinoma. Consistent with the previously mentioned study, *TET2* mutations were most frequently associated with TI-CH, followed by *ASXL1*, *DNMT3A*, and *PPM1D*. In a cohort of 31,556 patients with cancer with matched blood and tumor samples, TI-CH was enriched in NSCLC, head and neck, pancreatic cancers, and

TABLE 2 CH and CVD—Experimental Murine Studies

First Author, Year	Driver Gene	CH Model	Disease and Model	Central Phenotype	Mechanism
Fuster et al, 2017[155]	*Tet2*	Myeloablative competitive BMT (10% *Tet2*$^{-/-}$, *Tet2*$^{-/+}$ or WT donor cells) Lyz2-Cre × *Tet2*$^{flox/flox}$ mice	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	*Tet2*$^{-/-}$ macrophages have heightened IL-1β production and NLRP3 activation; phenotype mitigated by NLRP3 inflammasome inhibitor
Jaiswal et al, 2017[50]	*Tet2*	Myeloablative BMT (*Tet2*$^{-/-}$, *Tet2*$^{-/+}$ or WT donor cells) Lyz2-Cre × *Tet2*$^{flox/flox}$ mice	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	*Tet2*$^{-/-}$ macrophages have elevated proinflammatory cytokine production
Liu et al 2023[156]	*Tet2*	Myeloablative competitive BMT (40% *Tet2*-deficient or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed Western diet	Worsened atherosclerosis	*Tet2*-deficient plaque macrophages have superior survival via IL-6/CSF1R signaling; phenotype blocked by anti-IL-6R antibody or CSF1R inhibitor
Yalcinkaya et al, 2023[157]	*Tet2*	Myeloablative competitive BMT (10% *Tet2*$^{-/-}$, *Tet2*$^{-/+}$, or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	*Tet2*$^{-/-}$ macrophages have elevated JNK1-BRCC3 signaling leading to deubiquitination and activation of the NLRP3 inflammasome; phenotype blocked by BRCC3 deubiquitinase inhibition or genetic deficiency of BRCC3 scaffolding protein
Rauch et al, 2023[158]	*Tet2*	Myeloablative competitive BMT (10% *Tet2*$^{-/-}$ or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet		*Tet2*$^{-/-}$ plaque macrophages show altered immune signaling and elevated inflammatory gene signatures
Zuriaga et al, 2024[159]	*Tet2*	Myeloablative competitive BMT (10% *Tet2*$^{-/-}$ or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	Elevated IL-1β/NLRP3 signaling in the atherosclerotic plaque by *Tet2*$^{-/-}$ macrophages; phenotype blocked by colchicine
Sano et al, 2018[160]	*Tet2*	Myeloablative competitive BMT (10% *Tet2*$^{-/-}$, *Tet2*$^{-/+}$ or WT donor cells) Lyz2-Cre × Tet2$^{flox/flox}$ mice	MI: permanent LAD ligation Pressure overload HF: TAC	Worsened cardiac function and remodeling	*Tet2*$^{-/-}$ macrophages have heightened IL-1β production and NLRP3 activation; phenotype attenuated by NLRP3 inflammasome inhibitor
Sano et al 2018[161]	*Tet2*	Myeloablative BMT (CRISPR-Cas9 targeted *Tet2* disrupted or WT lineage-negative donor cells)	Pressure overload HF: high-dose angiotensin II infusion	Worsened cardiac function and remodeling	Mutant macrophages show elevated expression levels of proinflammatory cytokines, *Il1b*, *Il6*, and *Ccl5*
Wang et al, 2020[162]	*Tet2*	Nonmyeloablative BMT (*Tet2*$^{-/-}$ or WT donor cells)	Age-related HF: biological aging	Accelerated age-related cardiac dysfunction and remodeling	*Tet2*$^{-/-}$ cardiac macrophages show heightened inflammatory signature and reduced expression of cell differentiation and neurogenesis genes
Cochran et al, 2023[20]	*Tet2*	Nonmyeloablative BMT (*Tet2*$^{-/-}$ or WT donor cells)	HFpEF: High-fat diet + L-NAME	Worsened diastolic dysfunction and cardiac remodeling	
Lin et al, 2024[147]	*Tet2*	Myeloablative BMT (*Tet2*-deficient or WT donor cells)	AF: Ldlr$^{-/-}$ mice fed Western diet and WT mice fed prolonged Western diet	Higher likelihood of developing cardiac arrythmias	*Tet2*$^{-/-}$ macrophages cause calcium handling defects in cardiomyocytes via NLRP3-mediated production of IL-1β and IL-6; phenotype reduced by genetic deletion or pharmacological inhibition of the NLRP3 inflammasome
Polizio et al, 2024[163]	*Tet2*	Nonmyeloablative BMT (*Tet2*$^{-/-}$ or WT donor cells) Lyz2-Cre × *Tet2*$^{flox/flox}$ mice	Hypertension: slow-pressor angiotensin II infusion to mice	Enhanced pressor response and increased sodium reabsorption	CCL5-driven renal infiltration of Tet2$^{-/-}$ macrophages, with elevated IL-1β/NLRP3 signaling, promotes expression of renal sodium transporters; phenotype blocked by NLRP3 inflammasome or CCL5 receptor inhibition
Polizio et al, 2025[164]	*Tet2*	Nonmyeloablative BMT (*Tet2*$^{-/-}$ or WT donor cells)	Hypertension: slow-pressor angiotensin II infusion	Enhanced pressor response	Increased renal sympathetic activity mediated through NLRP3 inflammasome activity; phenotype attenuated by NLRP3 inflammasome inhibition
Rauch et al, 2023[158]	*Dnmt3a*	Mechanism: myeloablative competitive BMT (10% *Dnmt3a*-deficient or WT donor cells) Phenotype: Lyz2-Cre × *Dnmt3a*$^{flox/flox}$ mice	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	Altered immune signaling and elevated proinflammatory mediators in Dnmt3a-deficient plaque macrophages
Sano et al, 2018[161]	*Dnmt3a*	Myeloablative BMT (CRISPR-Cas9 targeted *Dnmt3a* disrupted or WT lineage-negative donor cells)	Pressure overload HF: High-dose angiotensin II infusion	Worsened cardiac function and remodeling	Elevated expression of proinflammatory cytokines, *Cxcl2*, *Il6*, and *Ccl5* in mutant macrophages
Shumliakivska et al, 2024[165]	*Dnmt3a*^{R882H}	Myeloablative BMT (*Dnmt3a*$^{+/R882H}$ or WT donor cells)	MI: Permanent LAD ligation	Elevated cardiac fibrosis	Heightened macrophage production of HB-EGF activating cardiac fibroblasts

Continued on the next page

TABLE 2 Continued

First Author, Year	Driver Gene	CH Model	Disease and Model	Central Phenotype	Mechanism
Sato et al, 2024[166]	*Asxl1*	Myeloablative BMT (*Asxl1*-mutant KI or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	Exacerbated inflammation through loss of IRAK-TAK1 inhibition; pharmacological inhibition of IRAK1/4 alleviates phenotype
Min et al, 2022[167]	*Asxl1*	Myeloablative competitive BMT (30% *Asxl1*$^{tm/+}$ or WT donor cells)	MI: Permanent LAD ligation Pressure overload–induced HF: High-dose angiotensin II infusion	Worsened cardiac function and remodeling	Elevated expression of *Il1β* and *Il6* in mutant macrophages
Liu et al, 2022[168]	*Jak2*^{V617F}	EpoR-Cre × *Jak2*$^{+/flox}$ mice	Atherosclerosis: mice fed HFHC diet + LDLR antisense oligonucleotides	Increased indices of plaque instability, erythrophagocytosis, and ferroptosis	Increased ROS and lipid peroxidation in *Jak2*^{V617F} RBCs, leading to endothelial damage and increased RBC entry into plaques; administration of ferroptosis inhibitor reverses phenotype
Wang et al, 2018[169]	*Jak2*^{V617F}	Myeloablative BMT (*Jak2*^{VF} mutant or WT donor cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	Enhanced inflammasome activation and defective erythrophagocytosis by *Jak2*^{VF} macrophages; *Jak2*^{VF} RBCs more susceptible to erythrophagocytosis
Fidler et al, 2021[170]	*Jak2*^{V617F}	Phenotype: myeloablative BMT (Cx3cr1-cre × *Jak2*$^{+/flox}$ or WT donor cells) Mechanism: myeloablative competitive BMT (20% *Jak2*^{VF} or WT donor cells cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	Increased AIM2 activation, ROS production and DNA damage in *Jak2*^{VF} macrophages; inhibition of IL-1β improves plaque stability
Liu et al, 2024[171]	*Jak2*^{V617F}	Myeloablative competitive BMT (1.5% *Jak2*^{VF} or WT cells)	Atherosclerosis: Ldlr$^{-/-}$ mice fed HFHC diet	Worsened atherosclerosis	IL-1β production by mutant macrophages promotes MERTK and TREM2 cleavage on WT macrophages and induces NETosis in WT neutrophils; treatment with agonistic TREM2 antibody eliminates phenotypic differences between groups
Sano et al, 2019[172]	*JAK2*^{V617F}	Myeloablative BMT (lentiviral transduced lineage-negative cells with human *JAK2*^{V617} or *JAK2*^{WT} under myeloid promotor)	MI: permanent LAD ligation Pressure overload HF: traverse aortic constriction	Worsened cardiac function and cardiac remodeling	*Jak2*^{V617F} macrophages show increased STAT1 activity and upregulated expression of interferon-response and inflammatory genes
Wolach et al, 2019[144]	*Jak2*^{V617F}	Myeloablative BMT (*Jak2*^{V617F} mutant or WT c-Kit+ donor cells)	Thrombosis: surgical stenosis of IVC	Increased predisposition to thrombosis	Increased PAD4 expression and consequent NETosis in Jak2^{V617F} mutant neutrophils
Liu et al, 2024[173]	*Jak2*^{V617F}	Myeloablative competitive BMT (1.5 or 20% *Jak2*^{VF} or WT cells) Gp1ba-Cre × *Jak2*$^{+/flox}$ mice EpoR-Cre × *Jak2*$^{+/flox}$ mice	Arterial thrombosis: FeCl3-injury in WT and Ldlr$^{-/-}$ fed HFHC diet	Accelerated arterial thrombosis and increased platelet activity	Increased COX-1/2 expression, enhanced cPLA2 phosphorylation, and elevated production of thromboxane A2 and ROS in *Jak2*^{VF} platelets; low-dose aspirin ameliorated phenotype

AIM2 = absent in melanoma 2; BMT = bone marrow transplant; BRCC3 = BRCA1/BRCA2-containing complex 3; CCL-5 = CC-chemokine ligand 5; COX1/2 = cyclooxygenase 1/2; cPLA2 = cytosolic phospholipase A2; CSF1R = colony stimulating factor 1 receptor; Cx3cr1 = CX3C motif chemokine receptor 1; Cxcl2 = CXC motif ligand 2; EpoR = erythropoietin receptor; Gp1ba = glycoprotein 1b alpha; HB-EGF = heparin-binding epidermal growth factor-like growth factor; HFHC = high-fat, high-cholesterol; IL-1β = interleukin 1β; Il6 = interleukin 6; IRAK = interleukin-1 receptor-associated kinase; IVC = inferior vena cava; KI = knockin; L-NAME = Nω-Nitro-L-arginine methyl ester; LAD = left anterior descending artery; Ldlr = low density lipoprotein receptor; Lyz2 = lysozyme 2; MERTK = MER tyrosine-protein kinase; NET = neutrophil extracellular trap; NLRP3 = nod like family pyrin domain containing 3; PAD4 = peptidylarginine deiminase 4; RBC = red blood cell; ROS = reactive oxygen species; STAT1 = signal transducer and activator of transcription 1; TAC = transverse aortic constriction; TAK1 = transforming growth factor β-activated kinase 1; TREM2 = triggering receptor expressed on myeloid cells 2; WT = wild-type; other abbreviations as in Table 1.

mesothelioma, whereas it was less common in prostate, endometrial, ovarian, and small-cell lung cancers. These findings raise the possibility that mutant leukocytes are involved in the development of certain cancers.

Incidence. There are a growing number of studies that have examined the relationship between driver gene-mediated CH and the risk and/or incidence of solid organ cancers. Most studies published thus far have used data from the UKB, either alone or in combination with other study cohorts. These studies are summarized in **Table 4**. It would appear that CH is associated with increased risk of certain tumor types and different driver genes appear to confer increased risk for different tumors, perhaps suggesting that divergent mechanisms are at play.

Outcomes. Recent studies have also begun to investigate whether CH influences prognosis following a cancer diagnosis. This area of research remains in its very early stages, and the findings thus far have varied. A study that prospectively followed 5,394 patients with non-hematological cancer reported that CH with known driver mutations was associated with worse survival, an effect independent of the development of therapy-related myeloid neoplasms.[35] This inferior survival appeared to be linked to the progression of the primary tumor, perhaps suggestive that CH may drive cancer

TABLE 3 CH and CVD—Mechanistic Clinical Studies

First Author, Year	Disease Focus	Population and CH Prevalence	Sequencing Method	Study Intention	Findings/Mechanism
Bick et al, 2020[139]	Cardiovascular events (MI, coronary artery revascularization, stroke, or death)	35,416 individuals from UKB 3% with *DNMT3A*/*TET2* CHIP	Whole exome sequencing	Evaluate effect of IL-6R p.Asp358Ala variant, which results in genetically attenuated IL-6 signaling, on CVD risk conferred by CHIP	Individuals with large *DNMT3A*/*TET2* CHIP clones carrying IL-6R p.Asp358Ala variant have lower cardiovascular risk vs those without the variant (HR: 0.46; 95% CI: 0.29-0.73)
Abplanalp et al, 2021[174]	Chronic heart failure	10 HF patients: *DNMT3A*+ (n = 6), CHIP-negative (n = 4)	Deep targeted amplicon sequencing	Single-cell sequencing analysis of gene signatures in peripheral blood monocytes and T cells	*DNMT3A*+ monocytes showed a proinflammatory gene signature (*IL6*, *CXCL2*, *IL1B*, *TNF*, *NLRP3*) and increased T cell interaction molecules *DNMT3A*+ T cells exhibited altered TCR repertoire
Svensson et al, 2022[129]	MACE (composite of nonfatal MI, nonfatal stroke, or cardiovascular death) in patients with previous MI and elevated CRP	3,946 patients in the CANTOS genomic sub-study 8.6% CHIP; 2.6% *TET2* CHIP	Targeted deep sequencing	Evaluate effect of Canakinumab, an IL-1β neutralizing antibody, on MACE risk conferred by CHIP	In patients that received Canakinumab, those with *TET2* CHIP showed a significant reduction in MACE (HR: 0.38; 95% CI: 0.15-0.96), whereas those without CHIP did not (HR: 0.93; 95% CI: 0.78-1.10)
Yu et al, 2023[175]	CVD events (a composite of MI, CAD, or revascularization, stroke, or death)	417,570 in UKB 6.2% CHIP	Whole exome sequencing	Evaluate the effect of predicted inflammatory expression scores on CHIP-associated CVD risk	In common driver mutations genetically determined increased IL1RAP signaling predicted CHIP-associated CVD risk Increased *AIM2* gene expression was found to predict heightened *JAK2*- and *ASXL1*-associated CVD risk
Shumliakivska et al, 2024[165]	Chronic HFrEF	10 HF patients: DNMT3A+ (n = 5), CHIP-negative (n = 4) Publicly available single-nuclei RNA-sequencing data of human heart tissue: healthy (n = 14), HFrEF (n = 3)	Deep targeted amplicon sequencing	Single-cell sequencing analysis of gene signatures in peripheral blood monocytes and how they interact with cardiac tissue	*DNMT3A*+ monocytes show greater interaction with cardiac fibroblasts through EGF signaling pathways
Vlasschaert et al, 2023[142]	CAD	451,180 individuals from UKB	Whole exome sequencing	Evaluate effect of IL-6R p.Asp358Ala variant, which results in genetically attenuated IL-6 signaling, on CAD risk conferred by CHIP	CHIP-mediated risk of CAD reduced by genetically attenuated IL-6 signaling, particularly for non-*DNMT3A*
Zuriaga et al, 2024[159]	Incident MI	37,181 individuals from MGBB and 437,236 individuals from UKB 13.9% and 6.8% CHIP, respectively	Whole exome sequencing	Evaluate effect of colchicine (broad-spectrum anti-inflammatory, including NLRP3 inhibition) on CHIP-associated incident MI risk	Colchicine use attenuated the association between *TET2* CHIP and incident MI, with no effect seen for other CHIP drivers

CANTOS = Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CRP = C-reactive protein; CXCL2 = CXC motif chemokine ligand 2; EGF = epidermal growth factor; HFrEF = heart failure with reduced ejection fraction; IL-6 = interleukin 6; TCR = T cell receptor; TNF = tumor necrosis factor; other abbreviations as in Tables 1 and 2.

progression. TI-CH also has been associated with inferior survival across a wide range of cancers (HR: 1.17; 95% CI: 1.06-1.29), particularly for NSCLC (HR: 2.01; 95% CI: 1.37-2.95).[68] A study in preprint form documented that *TET2*-mediated CH is associated with a poor survival in anaplastic thyroid cancer (HR: 2.68; 95% CI: 1.49-4.81).[67] Consistently, preoperative driver gene CH was associated with inferior survival in patients with NSCLC following surgical resection (HR: 1.56; 95% CI: 1.07-2.28).[69] Notably, CH led to worse overall survival in individuals who had stage IIb NSCLC who also received adjuvant therapy (HR: 1.19; 95% CI: 1.00-1.41), suggesting a possible interaction between CH and adjuvant therapy. Another study involving 1,677 patients with cancer noted an interaction between CH and survival following treatment with immune checkpoint inhibition (HR: 1.28; 95% CI: 1.07-1.53).[70] These findings perhaps suggest that CH has an impact on the efficacy of cancer treatment. Interestingly, the impact of CH on survival following colorectal cancer appears to differ between studies. One study involving 10,866 women aged 50 to 79 found that CHIP was associated with increased mortality from colorectal cancer (HR: 3.99; 95% CI: 2.41-6.62).[71] On the contrary, another study found that driver gene-mediated CH, particularly due to *DNMT3A* mutations, was associated with improved survival in patients with metastatic colorectal cancer (HR: 0.64; 95% CI: 0.46-0.89).[62] Other studies have reported negligible effects of CH on prognosis following solid cancer diagnosis. In a study of young female patients with breast cancer, it was

TABLE 4 CH and Incident Solid Cancer—Clinical Studies

First Author, Year	Disease Focus	Population and CH Prevalence	Sequencing Method	Findings
Kar et al, 2022[176]	Phenome-wide association study including solid tumors	200,453 UKB participants CH: 5.45%	Whole exome sequencing	Significant associations found between CH and incident following cancers: Any CH: non-hematological neoplasms (HR: 1.10), lung (HR: 1.46), and kidney cancer (HR: 1.31) *DNMT3A*: lung (HR: 1.61), kidney (HR: 1.43), stomach (HR: 1.64), and bladder cancer (HR:1.41) *TET2*: kidney cancer (HR: 1.47) *ASXL1*: lung cancer (HR: 2.12) *SRSF2*/*SF3B1*: colorectal (HR: 2.10) and head/neck cancer (HR: 6.23)
Kessler et al, 2022[177]	Multiple longitudinal phenotypes, including solid tumors	454,803 individuals from UKB and 173,585 individuals from GHS (replication cohort) CHIP: 6% (UKB) and 7.4% (GHS)	Whole exome sequencing	Significant associations found between CH and incident following cancers (for UKB unless otherwise stated): CHIP: lung (HR: 1.64; GHS HR: 1.51), prostate (HR: 1.18), and non-melanoma skin (HR: 1.14) *DNMT3A*: lung (HR: 1.53; GHS HR: 1.53), prostate (HR: 1.27), and breast (HR: 1.24) *TET2*: lung (HR: 1.55) *ASXL1*: lung (HR: 1.53) MR analyses found significant causal associations for CH and the following cancers: lung (OR_{IVW}: 1.55), melanoma (OR_{IVW}: 1.39), non-melanoma skin (OR_{IVW}: 1.26), prostate (OR_{IVW}:1.20), and breast (OR_{IVW}:1.17)
Tian et al, 2023[178]	Lung cancer	832 cases/3,951 controls from within UKB; CH: 12.5% cases vs 8.7% controls 141 cases/652 controls from within MGBB; CH: 15.6% cases vs 12.7% controls 2,279 lung cancer cases within MSK-IMPACT; CH: 22.5%	Whole exome sequencing	CH was associated with increased risk of incident lung cancer (UKB OR: 1.36; 95% CI: 1.06-1.74; UKB+MGBB OR: 1.35; 95% CI: 1.08-1.68), which was strongest for adenocarcinoma (HR: 1.68; 95% CI:1.23-2.29) and squamous cell carcinoma (HR: 1.59; 95% CI: 1.51-1.68) subtypes CH enriched in lung cancer cases
Wang et al, 2023[179]	Prostate cancer	2,118 cases and 67,384 controls within UKB; CHIP: 4.86% cases vs 4.11% controls 2,770 aggressive and 2,775 nonaggressive prostate cancer cases within WESP; CHIP: 7.15% aggressive vs 6.99% nonaggressive	Whole exome sequencing	No association between CHIP and risk of overall (HR: 0.93; 95% CI: 0.76-1.13) or aggressive prostate cancer (OR: 1.14; 95% CI: 0.92-1.41)
Desai et al, 2024[71]	Breast, lung, and colorectal cancers	10,866 WHI participants from TOPMed NHLBI cohort CHIP: 8.7% with incident cancer vs 8.2% without	Whole genome sequencing	CHIP was associated with higher risk of breast (HR:1.30; 95% CI: 1.03-1.64) but not colorectal (HR: 1.05; 95% CI: 0.74-1.50) or lung cancers (HR: 1.17; 95% CI: 0.86-1.60)
Xi et al, 2025[180]	Gastric cancer	1,070 gastric cancer cases and 401,183 controls within UKB CHIP: 6.54% cases vs 5.14% controls	Whole exome sequencing	CHIP was associated with increased risk of gastric cancer (OR: 1.29; 95% CI: 1.004-1.63) Gene-specific associations found for *DNMT3A* (OR: 1.81; 95% CI: 1.05-2.88) and *ASXL1* (OR: 2.43; 95% CI: 0.95-4.99)
Liu et al, 2025[181]	Colorectal cancer	5,310 cases and 26,550 noncancer controls within UKB CHIP: 5.63% cases vs 4.74% controls	Whole exome sequencing	CHIP was associated with increased risk of colorectal cancer (OR: 1.19; 95% CI:1.05-1.36) Risk was strongest for higher VAFs, females, individuals >60 years, and those with *TET2* or *ATM* mutations

GHS = Geisinger MyCode Community Health Initiative; MR = Mendelian randomization; MSK-IMPACT = Memorial Sloan Kettering - Integrated Mutation Profiling of Actionable Cancer Targets; NHLBI = National Heart, Lung, and Blood Institute; TOPMed = TransOmics for Precision Medicine; WESP = Whole-Exome Sequencing (WES) for Prostate Cancer; other abbreviations as in Tables 1 and 2.

found that the presence of CH at baseline did not affect breast cancer or non-breast cancer-related survival at 9 years' follow-up.[72] Nevertheless, this study cohort was young, specifically younger than ≤40 years at the time of diagnosis, and most individuals may have had clones that were too small to cause any detectable effect on clinical outcome. Another study reported similar findings in a cohort of 255 patients with solid cancer from the STING (Gustave Roussy Cancer Profiling program; NCT04932525) trial, in which the presence of CH had no effect on progression-free survival or overall survival.[60] Similarly, another study noted that CH had no effect on progression-free survival in a cohort of 633 patients with metastatic esophagogastric and colorectal cancer.[60] Additional studies are required to better understand the impact that CH has on solid cancer prognosis. Patients should be stratified by tumor type whenever feasible, as CH may exert divergent effects across different cancers, potentially resulting in differing outcomes. It would also be important to examine the effect of CH on response to treatment, as it is possible that CH may interact with certain cancer therapies, particularly those targeting the immune system.

CLINICAL STUDIES: mCAs. In addition to driver gene-mediated CH, mCAs also have been associated with various solid organ cancers, with prominent associations found for LOY. In 2012, a study by Jacobs et al[10] was the first to identify a link between

autosomal mCAs and solid organ tumors. By analyzing mCAs in 31,717 cancer cases and 26,136 cancer-free controls across 13 genome-wide association studies, the researchers found that mCAs were enriched in individuals with solid organ tumors and were associated with increased incidence of solid organ tumors (OR: 1.27; 95% CI: 1.05-1.52). Notable associations were found for lung (OR: 1.56; 95% CI: 1.18-2.08) and kidney cancers (OR: 1.98; 95% CI: 1.27-3.06). Interestingly, it was found that mCAs were more prevalent in individuals before or around the time of cancer diagnosis, and this appeared to decrease to a similar level as controls following treatment. Since this study, a few additional associations have been discovered between autosomal mCAs and solid organ cancers. Analysis of a large dataset comprising 127,179 individuals revealed an association between mCAs and solid organ cancers, specifically endometrial, kidney, liver, lung, and prostate cancers.[73] However, only lung cancer remained statistically significant after correction for multiple testing. It is important to note that the 2 aforementioned studies used both blood and buccal samples, and thus, it has been suggested that the association between mCAs and solid organ malignancy may be due to widespread genomic instability rather than a causal effect by mutant leukocytes. A study examining the relationship between mCAs and incident disease associations using data from the UKB reported a link between mCAs and a personal history of malignant neoplasm (HR: 1.2; 95% CI: 1.13-1.29);[74] however, the exact nature of these malignant neoplasms remains unclear. Further, the OncoArray study of INTEGRAL-ILCCO (Integrative Analysis of Lung Cancer Etiology and Risk project of the International Lung Cancer Consortium), including 18,221 lung cancer cases and 14,825 cancer-free controls, found an association between mCAs and increased risk of lung cancer (HR: 1.33; 95% CI: 1.17–1.52), which remained significant after adjusting for major risk factors. This association was primarily driven by copy-neutral loss of heterozygosity events and was linked to an increased risk of the lung cancer subtypes of lung adenocarcinoma and squamous cell carcinoma.[75] Another study using data from the TOPMed (TransOmics for Precision Medicine) cohort within the Women's Health Initiative found an association between expanded mCAs (cell fraction >5%) and an increased risk of breast cancer (HR: 1.39; 95% CI: 1.06-1.83). It was also found that expanded mCAs were associated with higher mortality due to colorectal cancer (HR: 2.19; 95% CI: 1.11-4.3), perhaps indicating that mCAs are associated with a poorer prognosis for this type of cancer.[71]

Several studies have reported links between hematopoietic LOY in the blood and solid cancers. In a cohort of 1,153 elderly men, LOY was reported to be associated with an increased risk of solid cancer diagnosis (HR: 2.68) and mortality (HR: 3.62).[13] In terms of cancer types, it has also been reported that LOY is enriched in the blood of men with colorectal, prostate, and pancreatic cancers[76,77] and associated with increased risk of prostate (OR: 1.35; 95% CI: 1.04-1.74), bladder (OR: 1.47; 95% CI: 1.09-1.99), and lung cancers (HR: 2.25; 95% CI: 1.36-3.71).[42,78] Nevertheless, after adjustment for smoking, a known risk factor for LOY, the association with lung cancer decreased, suggesting that smoking may be an important confounder in the association.[78] Further supporting the link between LOY and cancer, studies have found that T regulatory cells with LOY are enriched in the tumor microenvironment of men with colorectal cancer and liver metastases.[79] Given that T regulatory cells contribute to immune evasion in cancer,[80] this finding suggests a potential role for hematopoietic LOY in tumor progression.

As mentioned previously (Mosaic chromosomal alterations section), heritable loci have been associated with an increased risk of LOY. Using these loci, researchers can generate a genetic risk score to assess LOY susceptibility.[14,42,44] Many of these heritable loci overlap with cancer susceptibility genes.[14,42,44] Notably, genetic LOY susceptibility has been linked to an increased risk of various solid organ cancers, including prostate cancer, testicular germ cell cancer, glioma, renal carcinoma, lung cancer, and colorectal cancer.[14,81] Consequently, some researchers suggest that LOY may serve as a barometer of widespread genomic instability rather than playing a direct causal role in cancer. Consistently, studies have reported that LOY is more likely to occur in cells harboring mutations in *TP53* mutations,[82,83] a driver gene mutation linked to many human cancers.[84] Conversely, a recent study used Mendelian randomization to suggest that genetically determined LOY is a causal risk factor for prostate cancer (OR: 1.09; 95% CI: 1.05-1.13).[81] However, more work is needed to determine whether LOY is causal for solid organ malignancies.

EXPERIMENTAL STUDIES. Because both cancers and CH arise from somatic mutations, they could be consequences of widespread genomic instability rather than causally linked. Thus, experimental studies that interrogate the cause-effect relationship between CH and cancer are essential to better understand the direction of this relationship. A growing

TABLE 5 CH and Cancer—Experimental Studies

First Author, Year	Driver Gene	CH Model	Cancer Type(s) and Model	Main Phenotype	Mechanism
Feng et al, 2023[182]	*Dnmt3a*	Myeloablative BMT (*Dnmt3a*-hemizygous mutant and WT donor cells)	Colitis-associated colon cancer: administration of azoxymethane/dextran sodium sulfate to mice	High tumor penetrance and increased tumor burden	Enhanced angiogenesis
Pan et al, 2017[183]	*Tet2*	Lyz2-Cre × *Tet2*$^{flox/flox}$ mice	Melanoma: subcutaneous transplantation of YUMM1.7 melanoma cells and B16-OVA cells	Suppressed tumor growth	Increased proinflammatory macrophages, which enhance effector T cell antitumor activity
Nguyen et al, 2021[184]	*Tet2*	Mx1-Cre × *Tet2*$^{flox/flox}$ mice Lyz2-Cre × Tet2$^{flox/flox}$ mice	Lung cancer: subcutaneous transplantation of Lewis lung carcinoma cells	Larger tumor growth	*Tet2*$^{-/-}$ myeloid cells produce S100a8/S100a9, promoting VEGFa production and consequent angiogenesis within the tumor
Pich et al, 2025[68]	*Tet2*	Myeloablative competitive BMT (50% *Tet2*$^{-/-}$ donor cells) Myeloablative BMT (CRISPR-Cas9 *TET2*-deleted or WT human HSC donor cells)	Lung cancer: intravenous injection of Kras^{G12C} 3LL cells Human lung tumor organoids	*Tet2*$^{-/-}$ myeloid cells are enriched in orthotopically transplanted tumors Coculture of humanized Tet2$^{-/-}$ myeloid cells and human tumor organoids leads to larger and more numerous organoids	
Tiedje et al, Preprint[67]	*Tet2*	Myeloablative competitive BMT (*Tet2*$^{-/-}$, *Tet2*$^{+/-}$, or *Tet2*$^{+/+}$ donor cells)	Anaplastic thyroid cancer: orthotopic transplantation of TBP3743 cells	*Tet2*$^{-/-}$ macrophages are enriched in tumors Increased resistance to BRAF/MEK inhibition associated with greater tumor growth and inferior survival	Increased TGF-β signaling in *Tet2*$^{-/-}$ macrophages
Liu et al, 2022[185]	*Asxl1*	Vav-Cre × *Asxl1*-MT$^{flox/flox}$ Lyz2-Cre × *Asxl1*-MT$^{flox/flox}$ Lck-Cre × *Asxl1*-MT$^{flox/flox}$	Melanoma: subcutaneous transplantation of B16F10 cells Lung cancer: subcutaneous transplantation of Lewis lung carcinoma cells Colon adenocarcinoma: subcutaneous transplantation of MC38 cells Breast cancer: subcutaneous transplantation of Py8119 cells or mammary tumor susceptible, MMTV-PyMT mice	Subcutaneous transplant models: no phenotype in hematopoietic or myeloid-specific strains Increased tumor growth in T cell-specific Asxl1 mutant strains MMTV-PyMT mice: hematopoietic-specific Asxl1 mutants show increased tumor growth and numbers alongside poorer survival	T cell dysregulation and exhaustion creating a protumor environment
He et al, 2015[186]	*Trp53*	Lyz2-Cre × *Trp53*$^{flox/+}$ mice	Intestinal adenoma: Apc$^{Min/+}$ mice	Increased propensity for colon adenomas	Increased inflammation and higher numbers of tumor-associated M2 macrophages

BRAF = B-Raf; HSC = hematopoietic stem cell; Lck = tyrosine-protein kinase Lck; Lyz2 = lysozyme 2; MEK = mitogen-activated protein kinase kinase 1; MMTV-PyMT = mouse mammary tumor virus-polyoma middle tumor-antigen; Mx1 = myxovirus resistance protein 1; S100a8 = S100 calcium-binding protein A8; S100a9 = S100 calcium-binding protein A9; TGFβ = transforming growth factor β; VEGF = vascular endothelial growth factor; other abbreviations as in Tables 1 and 2.

number of experimental studies have examined whether mutations in CH driver genes may causally contribute to tumorigenesis in animal models (Table 5). These studies have also explored the possible underlying mechanisms by which mutant leukocytes contribute to this process. However, many of these studies have used lineage-restricted or total hematopoietic mutant models and, thus, may not truly represent the CH observed in humans, where the mutation is carried in all hematopoietic lineages, or a smaller proportion of leukocytes carry the mutation. Thus, future work in this area should be directed at using experimental models that more closely mimic the human condition of CH. As for mCAs, to the best of our knowledge, no experimental study has directly examined the contribution of mCAs to tumor progression. However, for LOY, studies suggest that this specific mutation can polarize cells toward an immunosuppressive phenotype, which could conceivably lead to immune evasion by tumor cells.[52,79,85] Additional studies directly examining whether hematopoietic LOY contributes to tumorigenesis are warranted to clarify whether the relationship with cancer is causal.

THERAPY-RELATED CH

Beyond age-related clonal hematopoiesis, is another type of CH that is commonly observed in cancer survivors, namely therapy-related clonal hematopoiesis (tCH) (Figure 2). This type of CH is associated with mutations in genes involved in the DNA damage response pathway, such as *TP53, PPM1D,* and *CHEK2*.[35,61,86,87] It is thought that these mutations

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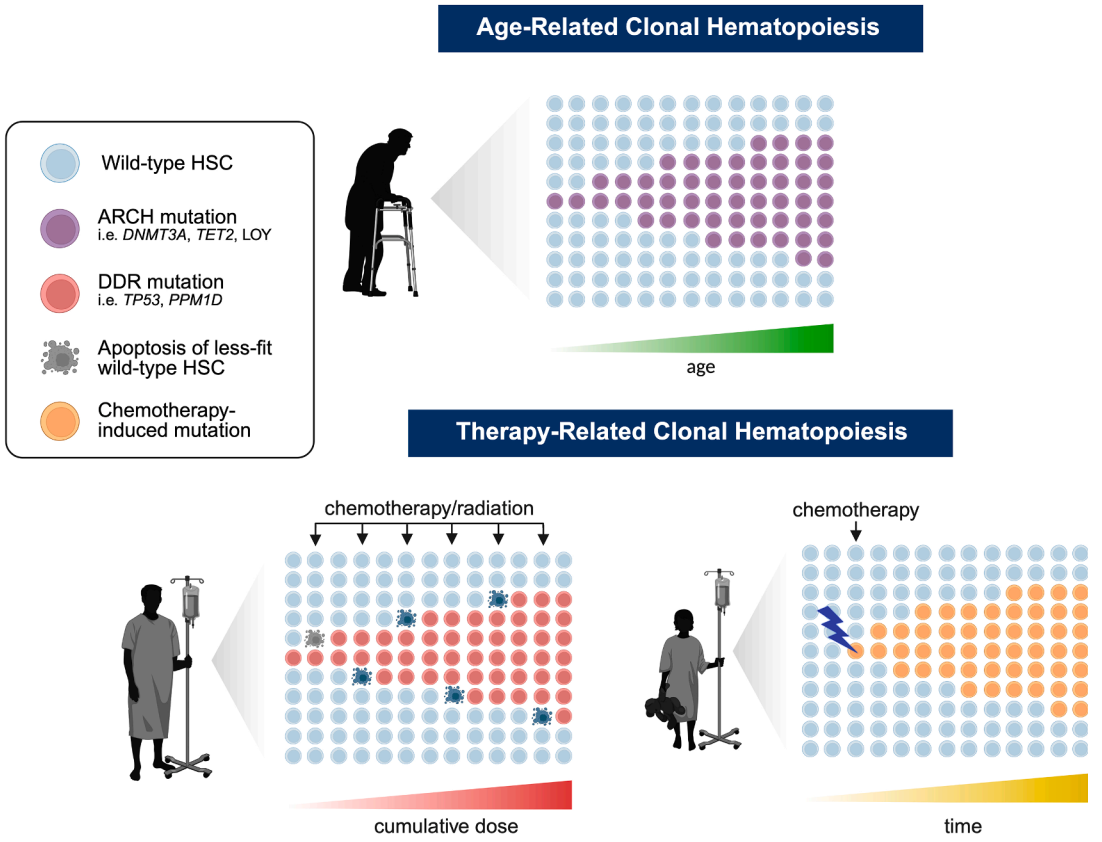
FIGURE 2 Comparison of Age-Related Clonal Hematopoiesis With Therapy-Related Clonal Hematopoiesis



(Top) Age-related hematopoietic mutations, such as those in *DNMT3A*, *TET2*, or LOY, are positively selected for during aging or in response to age-associated and lifestyle-related stressors, such as chronic inflammation and smoking. (Bottom left) Mutations in DNA damage response (DDR) genes such as *TP53*, *PPM1D*, or *CHEK2* confer a selective survival advantage under genotoxic stress, such as that induced by chemotherapy or radiation. Following such exposure, "less-fit" wild-type hematopoietic stem cells (HSCs) are more likely to undergo cell death, thereby reducing competition and allowing DDR-mutant clones to expand disproportionately. (Bottom right) Clonal hematopoiesis induced by cancer therapy, found exclusively in some pediatric cancer survivors. This occurs when the cancer therapy itself causes an HSPC mutation, which provides that cell with a competitive advantage and thereby allowing it to expand over time. *TET2* = ten eleven translocation 2; other abbreviations as in Figure 1. Created with BioRender.com, with permission.

confer a survival advantage to the mutant cell, allowing it to persist following exposure to genotoxic stress, such as that induced by specific cancer therapies.[88-91] Individuals with this form of CH are at increased risk of developing a therapy-related myeloid neoplasm (t-MN), particularly for those with *TP53* mutations.[92,93] t-MNs carry a substantially worse prognosis compared with primary myeloid neoplasms,[94] and thus, it has been of interest to study tCH, as it represents a precursor to this condition. Whether mCAs are implicated in this type of CH remains largely unknown;[95] however, their acquisition in preexisting mutant clones is known to be associated with the development of t-MNs.[94] The following section explores the current epidemiology of tCH, its mechanisms of evolution, and the specific cancer therapies with which it is associated.

One of the earliest indications of tCH originated from a 2013 study that sought to identify mutations that may increase susceptibility to breast and ovarian cancer. In a case-control study of 7,781 patients with cancer and 5,861 controls, it was noted that mosaic *PPM1D* mutations were more frequent in the lymphocytes of patients with cancer.[96] Other studies observed similar findings in other cohorts of patients with cancer, where *PPM1D* mutations were found to be present at a higher frequency in the white blood cells.[97,98] In 2016, 2 studies made the connection that the blood-borne *PPM1D* mutations were associated with prior chemotherapy exposure.[99,100] At a similar

time, an independent study noted a similar connection for hematopoietic *TP53* mutations that were selectively enriched following exposure to chemotherapy.[92] Although these studies did not explicitly define these observations as tCH, they suggested a possible link between prior chemotherapy exposure and the enrichment of *PPM1D* and *TP53* mutations in the blood.

Since this initial work, numerous studies have made similar connections by examining the prevalence of driver gene-mediated CH in cancer cohorts, leading to the definition of tCH.[35,61,86,87,93,101-104] Gibson et al[86] conducted a study to investigate the impact of preexisting CHIP on outcomes among 401 patients undergoing autologous stem cell transplantation for non-Hodgkin's lymphoma. The preconditioning regimen used to facilitate stem cell engraftment involves high-dose myeloablative chemotherapy and therefore the hematopoietic system is exposed to high amounts of genotoxic stress. In this cohort, it was noted that CHIP was present in 29.9% of patients before autologous stem cell transplantation, and relative to the general population, mutations in *PPM1D* and *TP53* occurred at a higher frequency. Another study by Coombs et al[35] involved a larger cohort of 8,810 patients with nonhematological cancers and reported similar findings. It was found that 25% of patients had CH and a history of chemotherapy was associated with mutations in *PPM1D* and *TP53*. Wong et al[87] used error-corrected sequencing to investigate the prevalence of CH, including small clones, in 119 lymphoma and myeloma patients, highlighting differences between those who had undergone chemotherapy and those who had not. Specifically, chemotherapy was associated with a higher incidence and number of mutant clones, particularly in the DNA damage response genes *PPM1D* and *TP53*. The incidence of CH and the number of mutant clones did not differ between the patients who did not receive chemotherapy and healthy controls, again supportive of the notion that chemotherapy selects for the growth of clones with mutations in DNA damage response genes. The largest study to date, involving a cohort of 24,146 patients with cancer, further validated these findings, identifying that *PPM1D*, *TP53,* and *CHEK2* driver mutations are associated with exposure to cancer therapies.[61] Of note, researchers of this study also performed sequential sampling on 525 patients with solid tumors (median: 23 months), 61% of whom underwent cytotoxic or external beam radiation therapy. This approach allowed for direct investigation into the effects of cancer therapies on the clonal dynamics of the different mutations over time. It was found that radiation or cytotoxic therapy was associated with the largest growth in DNA damage response genes, *TP53*, *PPM1D,* and *CHEK2*, and this occurred in a dose-dependent manner providing strong evidence that these therapies selectively promote expansion of clones carrying DNA damage response gene mutations.

Research has begun to interrogate this relationship more deeply, aiming to identify the specific classes of cancer therapies linked to the enrichment of mutant clones. In one study focusing on *PPM1D* mutations, it was noted that prior exposure to platinum-based agents, such as cisplatin, carboplatin, and oxaliplatin, as well as doxorubicin and etoposide, were associated with clone enrichment.[91] Similar findings were reported in an extensive study of 24,146 patients with cancer with diverse tumor types.[61] In particular, it was found that *PPM1D*, *TP53,* and *CHEK2* driver mutations were most strongly linked with exposure to specific cancer therapies. *PPM1D* mutations were associated with prior exposure to platinum agents, radionuclide therapy, topoisomerase I and II inhibitors, taxanes, and external beam radiation but not to antimetabolites or microtubule-damaging agents. *TP53* mutations were linked to exposure to platinum agents, radiation therapy, and taxanes, but not to topoisomerase I/II inhibitors, antimetabolites, or microtubule-damaging agents. *CHEK2* mutations were associated specifically with platinum and topoisomerase II inhibitors. In addition, a systematic review of 416 patients with therapy-related myeloid neoplasms revealed a significant association between *TP53* mutations and prior treatment with lenalidomide, a thalidomide analog.[88] Other studies have found that in individuals with prostate and ovarian cancer, treatment with poly (ADP-ribose) polymerase (PARP) inhibitors was associated with growth of *PPM1D* and *TP53* clones.[101,102] Among childhood cancer survivors, it has been reported that exposure to alkylating agents, radiation, and bleomycin are all associated with a higher prevalence of CH and both alkylating agents and radiation showed a dose-dependent relationship with the emergence of CH.[105] Collectively, this would suggest that the cancer therapy based enrichment of *PPM1D* and *TP53* clones is agent specific and, in many instances, reflects the ability of the agent to activate the DNA damage response pathway. Experimental studies have further supported this notion, showing that specific agents that activate the DNA damage response pathways, such as ionizing radiation, doxorubicin, and cisplatin, are responsible for the enrichment of *PPM1D* and/or *TP53* clones.[89-91,106,107]

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An alternative hypothesis for the emergence of tCH is that cancer therapies directly induce mutations in driver genes. Most chemotherapies act by damaging or inhibiting the synthesis of DNA of cancer cells, and if improperly repaired, it could lead to the acquisition of a mutation. Although this idea has been debated in the literature, the prevailing view is that it may depend on the timing of cancer therapy in an individual's life. In adults who have developed therapy-related myeloproliferative neoplasms (t-MNs), retrospective analysis has shown that mutations are present as very small clones (ie, below most sequencing detection limits), which subsequently become selected for following exposure to therapy.[92] On the contrary, studies using ultradeep sequencing on the blood of childhood cancer survivors have found no evidence of small clones before treatment for their primary malignancy.[108] Furthermore, analyses of childhood cancer survivors who later developed t-MNs have revealed that in some patients, mutational signatures are consistent with those induced by cytotoxic therapies, such as platinum-based drugs and thiopurines.[108,109] A recent study noted that in 9 pediatric cancer survivors treated with platinum-based drugs, an average of 500 platinum-induced clonal mutations were detected, where most expanded after cessation of therapy.[110] Notably, distinct driver mutations are predominant in pediatric cancer survivors who later develop t-MNs. Like adult cancer survivors, *TP53* mutations are common; however, mutations in other drivers, such as *STAT3*, *KRAS*, NF1, and *WT1*, have also been observed at higher frequencies.[105,108] Notwithstanding, pediatric cancer survivors also show a higher incidence of CH associated with common age-related drivers, such as *DNMT3A* and *TET2*, and this increases as a function of age.[104] Therefore, the mutational profile likely looks different depending on the age of cancer therapy exposure. Furthermore, it is plausible that the downstream consequences of tCH originating in pediatric cases may differ from those in adults.

CH AND CANCER THERAPY–RELATED CARDIOTOXICITY: IS THERE A CONNECTION?

Cancer survivors have an elevated risk of CVD compared with individuals of a comparable age.[3,111] A substantial portion of this elevated cardiovascular risk has been attributed to the effects of cancer therapies on the cardiovascular system. Although anthracyclines have traditionally been associated with cardiovascular damage and toxicity, several other classes of cancer therapies, including chest radiation, kinase inhibitors, immunotherapies, and certain targeted therapies, also have been implicated.[112] With advances in cancer treatment, the number of cancer survivors has substantially increased over the past decade. Consequently, a larger population may have therapy-related cardiovascular damage, highlighting the importance of better understanding the risk factors.

It has been of clinical interest to study the connection between CH and cardiotoxicity. A few key clinical observations have driven researchers to investigate this putative connection. First, CH has been linked to heart failure in elderly people,[18-20,33,34,113-115] and thus, there potentially could be mechanistic overlap in the pathogenesis with therapy-related cardiotoxicity (ie, elevated inflammation). Second, it has been observed that specific anticancer therapies, such as anthracyclines and radiation, can promote the expansion of hematopoietic clones carrying driver mutations,[89-91] thus expanded clones could potentially exacerbate cardiovascular damage in cancer survivors. This is important, as mutant clones appear to contribute to CVD in a dose-dependent manner.[34,50,116] Third, patients with cancer are often older and thus are more likely to have clones large enough to increase the risk of CVD. The following section provides an up-to-date review of the links between CH and cardiotoxicity, with a particular focus on the anthracyclines class of chemotherapeutics. Here, we discuss the clinical and experimental evidence supporting this connection.

Clinical: anthracycline-induced cardiotoxicity.

Anthracyclines are a common class of chemotherapeutic used to treat a range of malignancies, including breast cancer, ovarian cancer, sarcomas, and acute leukemias, as well as Hodgkin's and non-Hodgkin's lymphomas.[117] Anthracyclines are known to inhibit topoisomerase 2β, and although this is effective at killing cancer cells, it also causes cardiomyocyte injury through mechanisms involving oxidative stress, apoptosis, and inflammation.[118]

To date, a handful of clinical studies have examined the links between CH and anthracycline-induced cardiotoxicity (AIC). In a cohort of 110 lymphoma survivors who received anthracyclines as part of their initial treatment, *TET2*-mediated CH was found to be associated with AIC (OR: 5.15; 95% CI: 1.10-24.05).[119] Similarly, in a separate study of 100 cancer patients treated with doxorubicin there was an association between CH and an increased risk of AIC (OR: 8.58; 95% CI: 2.05-36.0).[120] Nevertheless, both of these studies had small sample sizes, and therefore, their findings should be considered exploratory. Since, a larger study has investigated the impact of CHIP on the risk of heart failure following autologous hematopoietic stem cell transplantation for

lymphoma.[121] The study included 861 patients with non-Hodgkin's lymphoma, 94.3% of whom received anthracyclines as part of their treatment. CHIP was detected in 27.6% of patients, which is a higher prevalence than in the general population. Notably, *PPM1D* mutations were more frequent in this cohort compared with the general population, suggesting a potential link to tCH. The incidence of heart failure was higher in patients with CHIP compared with those without (HR: 2.48; 95% CI: 1.32-4.68), with higher VAFs further increasing this risk. This risk appeared to be elevated in individuals with hypertension, and the strongest association was observed with *TET2* mutations. In addition, patients with CHIP had poorer 5-year survival (HR: 1.41; 95% CI: 1.02-1.95) and a higher incidence of non-relapse mortality (HR: 5.37; 95% CI: 2.34-12.35). Similarly, in a retrospective analysis of 623 patients with acute myeloid leukemia, the presence of any CHIP mutation was associated with a higher rate of cardiovascular events (HR: 1.74; 95% CI: 1.03-2.93) among intensively treated individuals (at least 1 induction with anthracyclines) but not in the overall cohort (HR: 1.26; 95% CI 0.81-1.97).[122] The strongest associations were found for patients with *TP53* (HR: 4.18; 95% CI: 2.07-8.47) and *ASXL1* mutations (HR: 2.37; 95% CI: 1.21-4.63). Despite this study focusing on acute myeloid leukemia, which often arises from the malignant transformation of CHIP, it suggests that there could be a relationship between CHIP mutations that may influence CVD development among those treated with anthracyclines. Another study investigated whether CHIP serves as a risk factor for the development of cardiomyopathy in a cohort of patients undergoing treatment for solid organ tumors.[123] Unlike the other studies, this was not limited to patients primarily receiving anthracycline treatment, with only 27.5% receiving this drug class. Other potential cardiotoxic therapies included human epidermal growth factor 2-targeting agents, chest radiation therapy, and immune checkpoint inhibitors. In this study, it was observed that 38% of patients had CHIP, with *DNMT3A* and *TET2* being the most frequently mutated drivers. With a median follow-up of 570 days, CHIP was identified as an independent predictor of cardiomyopathy, with CHIP-positive patients being more likely to develop the condition (HR: 2.01; 95% CI: 1.03-3.93). Collectively, these studies suggest that CH may contribute to an elevated risk of cardiotoxicity following treatment with anthracyclines and possibly other cancer treatments. Although further studies with larger sample sizes are needed to validate these findings, the presence of CH may serve as a useful biomarker to identify patients at elevated risk of AIC following cancer treatment.

Beyond driver gene CH, a recent study examined whether mCAs influence CVD development in cancer survivors.[124] In this study, a prospective cohort analysis was performed on 48,919 UKB participants with a cancer diagnosis. It was found that mCAs were associated with an increased risk of death due to coronary artery disease (CAD) (HR: 1.37; 95% CI: 1.09-1.71). This association was particularly prominent in individuals diagnosed with kidney and breast cancers. Furthermore, analysis of specific mCA subtypes revealed that autosomal mCAs were associated with an increased risk of death from all CVD causes (HR: 1.35; 95% CI: 1.04-1.75), whereas LOX was explicitly linked to a higher risk of death from CAD (HR: 2.01; 95% CI: 1.16-3.54). In contrast, LOY was associated only with an increased risk of death from any cause (HR: 1.08; 95% CI: 1.02-1.14). Interestingly, previous work has not identified a clear association between autosomal mCAs and CVD,[37] suggesting a potential synergistic effect of cancer in this relationship. Despite these initial findings, further studies involving well-characterized cohorts of cancer survivors are needed to assess whether mCAs serve as a risk factor for CVD in this population. Detailed documentation of chemotherapy exposures would be valuable in determining whether mCAs specifically contribute to cardiotoxicity.

Experimental studies. As previously discussed, mutant clones harboring mutations in DNA damage response genes, such as *TP53* and *PPM1D*, are prevalent among cancer survivors. These clones have a survival advantage on exposure to genotoxic stress induced by certain cancer therapies, resulting in their selective enrichment and expansion. Various cancer therapies, including anthracyclines, have been linked with selective enrichment of both *TP53* and *PPM1D* mutations. Considering this, it has been hypothesized that CH associated with mutations in *TP53* and *PPM1D* may be associated with cardiotoxicity and cardiovascular complications among cancer survivors. Experimental studies have examined the connection between *TP53* and *PPM1D*-mediated CH and CVD to test this hypothesis.[89,125,126] The first of these studies examined whether doxorubicin-induced expansion of *TP53* mutations contributed to the pathology of relatively acute AIC.[89] To investigate this potential connection, 2 nonmyeloablative mouse models of *TP53*-mediated CH were employed, avoiding the genotoxic effects of radiation typically used to establish mouse models of CH. One model used bone cells from heterozygous *Trp53*-deficient mice and the other used cells from $Trp53^{R270H}$ mutant

mice, as this mutation closely resembles the codon 273 hotspot *TP53* mutation frequently observed in humans with CH. It was observed that cyclic administration of doxorubicin led to the expansion of both heterozygous *Trp53*-deficient cells and *Trp53*^{R270H} mutant cells over a period of 9 weeks. The doxorubicin-induced clonal expansion of *Trp53* mutant cells was associated with significantly worse cardiotoxicity, characterized by poorer indexes of cardiac function, myocardial wall thinning, reduced capillary density, and elevated fibrosis and inflammation when compared with mice that were transplanted with wild-type cells. In terms of mechanism, it was found that neutrophil-mediated inflammation played a key role in the accelerated doxorubicin-induced cardiotoxicity in mice transplanted with *Trp53* mutant cells. Collectively, these findings may suggest that expanded *TP53* mutant clones can contribute to the risk of AIC in cancer survivors.

In addition to AIC, the contribution of *TP53*-mediated CH to the development of atherosclerosis also has been examined.[126] To do this, a competitive bone marrow transplant approach was taken to generate chimeric atherosclerosis-prone *Ldlr-/-* mice carrying 20% *Trp53*-deficient hematopoietic cells. It was found that *Trp53* deficient expanded over the 13-week study time course, which was associated with a 40% increase in atherosclerotic plaque size. By way of mechanism, it was found that Trp53-mutant macrophages within the plaque were more proliferative, and thus, plaques had an increased macrophage content. From these experimental data, it may suggest that *TP53* mutations in cancer survivors could contribute to atherosclerosis and its downstream cardiovascular consequences.

Another study investigated the effect of *PPM1D*-mediated CH on the development of heart failure induced by pressure overload.[125] Although this study did not examine AIC directly, as mentioned previously, *PPM1D* clones are enriched in cancer survivors and thus could conceivably contribute to chronic late-onset AIC. To investigate this connection, a CRISPR-Cas9 approach was taken to create a mutation in exon 6 of the *PPM1D* gene of lineage-negative bone marrow cells, mimicking the mutation commonly observed in humans with *PPM1D*-mediated CH. The *PPM1D* mutant bone marrow cells were then transplanted into lethally irradiated mice. To induce heart failure, mice were subjected to a continuous infusion of a supraphysiological dose of angiotensin II. Using this model, it was found that mice with hematopoietic mutations in *Ppm1d* displayed worse cardiac function and exacerbated cardiac remodeling following angiotensin II infusion. Mechanistically, the *PPM1D* mutation led to the generation of a population of mutant macrophages that were more proinflammatory, producing elevated levels of reactive oxygen species, interleukin (IL)-1β, and IL-18. Furthermore, inhibition of the NLRP3 inflammasome with MCC950 mitigated the worsened cardiac dysfunction and adverse cardiac remodeling observed in mice with *Ppm1d*-mutant HSPCs suggesting that NLRP3 contributes to the phenotype. Taken together, these findings suggest that *PPM1D* mutations associated with therapy-related CH may contribute to the delayed onset of heart failure observed in cancer survivors.

Although the experimental studies described previously are proof-of-concept that mutations associated with tCH could contribute to cardiotoxicity and vascular complications in cancer survivors, they require clinical validation. Notably, the clinical studies conducted so far have only been able to associate *TET2*-mediated CH with adverse cardiac events in cancer survivors.[119,121] Although CH associated with *TP53* mutations has been associated with poorer overall survival in cancer survivors, it remains unclear whether this reduced survival was related specifically to cardiotoxicity.[95] It also has been shown that both *TP53* and *PPM1D* mutations have been linked to CVD in human cohorts but not in the context of AIC.[19,126] Larger cohort studies are required to investigate the role of *TP53* and *PPM1D* mutations, which, although enriched in cancer survivors, may still occur less frequently than more common age-related driver mutations such as *DNMT3A* and *TET2*.[35,61] This is possibly because most cancer survivors are older and are thus more likely to have age-related CH. It is also possible that unique cancer survivor cohorts are required to investigate the connection between tCH and cardiotoxicity. For instance, in a cohort of 100 childhood cancer survivors, it was documented that *PPM1D* and *TP53* were the second and third most common driver gene mutations, respectively.[104] Of note, childhood cancer survivors have a 7-fold increase in risk of death due to cardiovascular causes. Thus, studies designed to longitudinally assess CH and health outcomes in childhood cancer survivors could be useful in determining whether *TP53* and *PPM1D* are linked with cardiotoxicity.

PERSPECTIVES, FUTURE WORK, AND CONCLUSIONS

Cancer and CVD, the leading causes of death worldwide, are increasingly recognized as being connected through shared biological mechanisms.[1,2] In addition

to predisposing individuals to CVD, CH also may play a role in cancer development and tumorigenesis. Therefore, CH may represent a previously unrecognized link between these conditions and is an emerging research area in cardio-oncology (**Central Illustration**). Chronic inflammation, such as that promoted by hematopoietic driver gene mutations, has been implicated in both CVD and tumor progression, suggesting a shared pathological pathway.[127] Conversely, elevated TGF-β1 signaling, such as that seen in conditions like LOY, has been associated with cardiac fibrosis and immune evasion by tumors.[128] This supports the idea that CH may drive both CVD and cancer through overlapping pathological mechanisms, such as inflammation and altered immune signaling. Related to this, recent clinical work, like the exploratory analysis of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) (**Table 3**), has shown that interventions targeting IL-1β pathways can specifically mitigate the cardiovascular risk associated with *TET2*-mediated CH.[129] Interestingly, another exploratory analysis of CANTOS observed that targeting IL-1β led to reduced incidence of lung cancer and lower lung cancer mortality in patients with a history of CVD.[130] These observations reinforce the idea that chronic inflammation driven by CH could potentially link CVD and cancer through shared pathways (**Central Illustration**). Furthermore, this raises the intriguing possibility that the same therapeutic approach could help reduce the risk of both CVD and cancer.

Recent clinical findings suggest that CH may contribute to cardiotoxicity in cancer survivors. It is unclear as to whether this association is driven by the expansion of mutant clones to a clinically significant level by cancer therapies[89-92] particularly as it has been found that larger clones are associated with a heightened risk of CVD.[34,50,117] An active area of research is to identify targetable pathways that limit clonal expansion,[131-135] and these could conceivably be useful in preventing mutant clones from reaching thresholds associated with increased cardiotoxicity risk. Another possibility is that CH contributes to the pathological processes underlying cardiotoxicity, such as by augmenting inflammation (**Central Illustration**). More experimental work in this area could prove useful and provide insight on whether CH-driven inflammation contributes to the development of cardiotoxicity. Overall, a better understanding of the relationship between CH and cardiotoxicity is warranted, as CH may serve as a risk factor for future cardiotoxicity or to guide treatment strategies for patients with cardiotoxicity.

Most research on cancer to date has relied on data from the low-risk UKB cohort. Although work stemming from this cohort has identified valuable associations, it lacks granularity, may oversimplify patient conditions, has limited ability to capture disease progression, and there is variability in International Classification of Diseases coding and CH variant calling. Moreover, recent work suggests that there are ancestral differences in both the frequency and subtypes of CH, alongside the presence of ancestry-specific genetic variants that determine CH susceptibility.[38,136] As UKB is primarily composed of individuals of European ancestry, overreliance on this cohort may limit our understanding of how CH contributes to disease risk, particularly for cancer. Additional studies using well-characterized, diverse patient cohorts are needed to clarify the relationship among CH, cancer risk, and outcomes. It also appears that different drivers may confer an increased risk for different tumors. Future clinical studies using large cohorts should perform mutation-specific analyses to better understand this relationship. In addition, experimental studies will be helpful in determining how specific hematopoietic mutations contribute to tumor development. Related to this, much of the experimental work in cancer has relied on cell-specific mutation models of CH. These models do not fully replicate the human condition of CH, where mutations are initially present in a small subset of leukocytes that expand over time. In addition, although lineage skewing is common in CH,[137,138] the mutation is often found across all lineages. This is an important consideration, as it is known that different immune cell subsets play different roles in tumorigenesis. Thus, experimental studies using mouse models that fully recapitulate CH are necessary to better understand the contribution of CH to solid organ cancer development and progression.

It is hoped that new opportunities for precision medicine may emerge by improving our understanding of CH and its link to CVD and cancer. This is already becoming evident in cardiology, where studies suggest that targeting IL-1β may be particularly beneficial for individuals with *TET2* mutations. Expanding this approach to oncology could not only aid in prevention but also improve survival and outcomes while helping to reduce complications such as cardiotoxicity.

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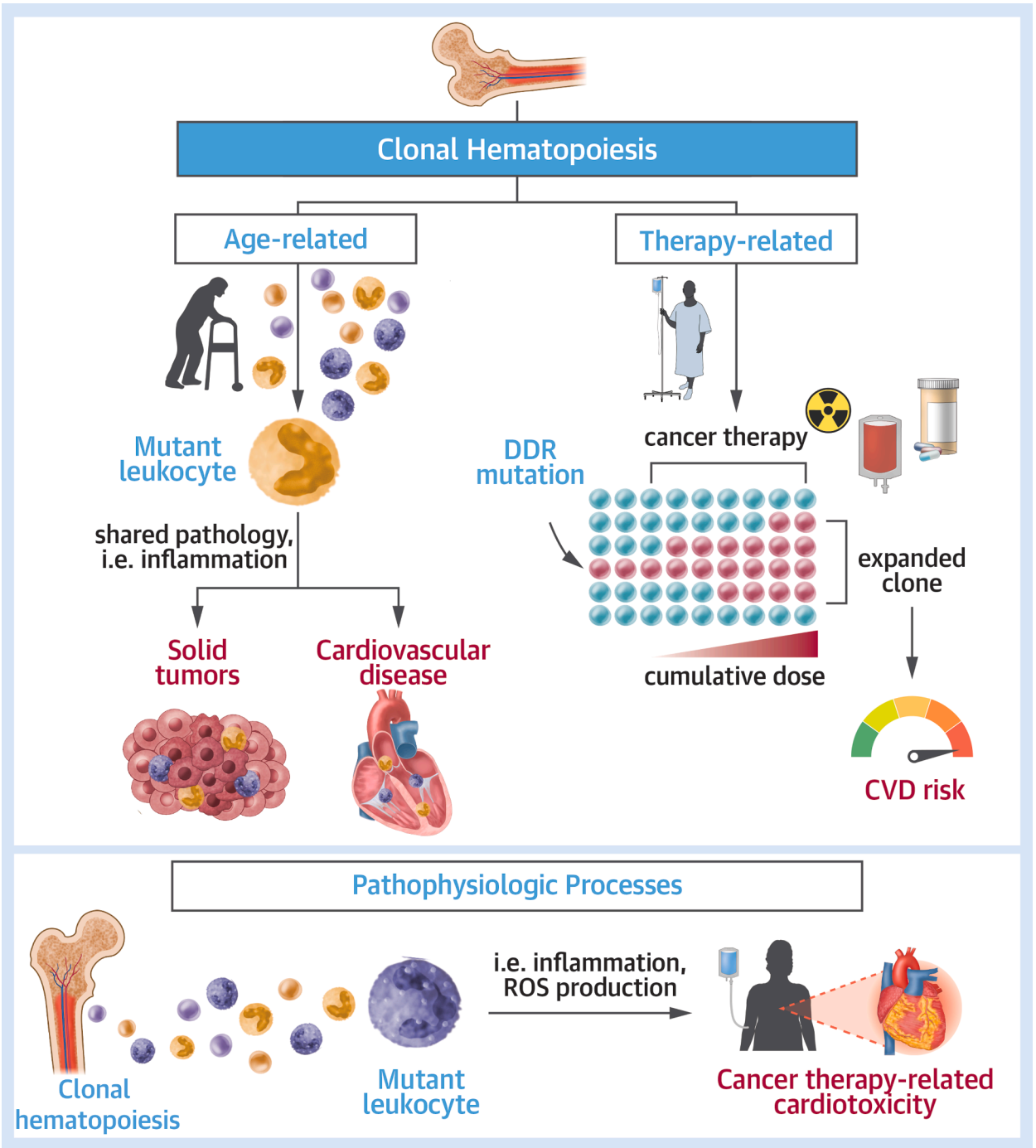
CENTRAL ILLUSTRATION **The Putative Links Among Clonal Hematopoiesis, Cardiovascular Disease, and Cancer**



Evans MA, et al. JACC CardioOncol. 2025;7(5):470–495.

Age-related clonal hematopoiesis may represent a mutual risk factor between solid tumors and cardiovascular disease (CVD) and contribute to disease via shared pathological mechanisms. Exposure to certain cancer therapies can lead to expansion of clones carrying mutations in DNA damage response (DDR) genes, such as *TP53*, *PPM1D*, or *CHEK2*. Large clones are associated with a further increased risk of CVD. Leukocytes with clonal hematopoiesis mutations may contribute to the pathological processes underlying cancer therapy-related cardiotoxicity, such as by promoting inflammation or the production of reactive oxygen species (ROS).

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