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CHIP ahoy: charting a decade of discovery in clonal hematopoiesis

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Authors' contributions

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Abstract

Clonal hematopoiesis (CH) involves the expansion of hematopoietic stem cells with age-acquired mutations linked to myeloid malignancy. Advances in next-generation and single-cell sequencing, along with computational modeling, have expanded our ability to detect both common and rare CH drivers, including single-nucleotide variants and mosaic chromosomal alterations, with increasing sensitivity. While sequencing methods differ in accuracy, cost, and ability to detect low-frequency variants, they have deepened our understanding of CH biology. A growing body of evidence has identified both somatic drivers, such as variants in *DNMT3A*, *TET2*, and *ASXL1*, and germline genetic variants that modify CH risk, highlighting the complex interplay between inherited and acquired factors. These collective discoveries are guiding the development of targeted therapies and interventions, particularly for individuals at risk of progression to myeloid neoplasms or cardiovascular disease. Additionally, CH is emerging as a clinically relevant factor in the treatment of solid tumors, where it may influence the tumour microenvironment, treatment response and the risk of therapy-related complications. Risk stratification models are facilitating earlier identification and monitoring of high-risk individuals, enabling personalized treatment decisions. The scope of CH management continues to expand, from surveillance to intervention, with ongoing trials testing preventive strategies in high-risk populations. Emerging trial frameworks emphasize risk stratification, age-appropriateness, inclusive recruitment, decentralized trial models, and the use of traditional clinical and novel endpoints. Together, these advances reflect a shift from passive observation to proactive intervention, charting a course for early detection, precision treatment, and prevention in CH care.

Introduction

In 2014, three studies uncovered a link between clonal hematopoiesis (CH), aging and blood cancer[1–3], sparking a surge of research investigating disease progression and somatic variation[4]. CH involves the expansion of hematopoietic stem cells (HSCs) following the acquisition of somatic mutations that confer a competitive fitness advantage. Improved sequencing methods have revealed that approximately 10–20% of individuals over 70 years old harbor clonal expansions meeting the criteria for clonal hematopoiesis of indeterminate potential (CHIP), defined by a variant allele fraction (VAF) of at least 2%[5]. Although the overall progression rate to overt malignancy remains relatively low at 0.5-1% per year, progression risk is modified by clone size, number of variants, and the specific genes affected[6]. These insights are crucial to developing targeted interventions and improving patient outcomes.

Beyond hematological cancer, CH is linked to non-malignant conditions including an increased risk of cardiovascular disease (CVD)[7] and kidney disease[8], among others, and intriguingly a protective effect in Alzheimer's disease[9] (as reviewed by Weeks *et al*.). The CVD risk conferred by CH is comparable to well-characterized risk factors such as smoking, cholesterol, and blood pressure[6]. These associations have heightened the urgency to identify high-risk populations, elucidate the mechanisms driving CH, and determine appropriate clinical actions upon detection[6]. This review outlines current knowledge of CH, including its recognized subtypes, associated conditions, detection strategies, clinical implications, emerging therapeutic approaches, and future directions for clinical management to set the sails for another decade of impactful research and translation.

Navigating the Diversity of CH Subtypes

CH is defined by the acquisition of somatic variants and mosaic chromosomal alterations (mCAs) in the hematopoietic system[10]. Common types of genetic variants include single-nucleotide variants (SNVs), small insertions or deletions, and broader chromosomal alterations collectively termed, copy number alterations (CNAs), which also include copy-neutral loss of heterozygosity[11]. The World Health Organization (WHO) defines CHIP as CH with variants in myeloid malignancy-associated genes, present in blood cells at a VAF ≥2% (≥4% of circulating blood cells carrying a heterozygous variant), in the absence of other diagnostic criteria for a hematologic neoplasm (Figure 1)[12]. When CH is accompanied with cytopenia, it is classified as clonal cytopenia of undetermined significance (CCUS)[13]. Although the distinction between CCUS and overt myeloid neoplasms remains ambiguous, it is well-established that individuals with a VAF >20% are at a significantly higher risk of progressing to myelodysplastic neoplasm (MDS) and acute myeloid leukemia (AML)[10]. It is important to note that the 2% VAF threshold for CHIP was originally established based on previous limitations of sequencing technologies. However, emerging data suggests this cutoff correlates with clinical outcomes, while the relevance of CH clones with VAF <2% is uncertain. Given the limitations associated with inconsistency in CHIP terminology, we advocate for more stringent definitions and yield to the broader, “CH” for the remainder of this review unless WHO criteria were explicitly met.

There is notable consistency among drivers associated with myeloid CH (M-CH), with most individuals exhibiting variants in *DNMT3A, TET2* and *ASXL1*[14]. In contrast, drivers linked to lymphoid clonal hematopoiesis (L-CH) are distributed across a broader array of genes[15]. While M-CH and L-CH are predictive of myeloid and lymphoid malignancies, respectively, the detection and characterization of L-CH remain nascent, highlighting the need to further identify recurrent L-CH drivers[16]. Given these circumstances, our discussion will primarily focus on M-CH and its associated subtypes.

Discovering the Drivers of CH

CH was first identified in cytogenetic studies in the 1960s and later confirmed in healthy adults during the 1990s using non-random X chromosome inactivation studies[17]. A major breakthrough came in 2012 with the discovery of recurrent *TET2* variants in otherwise healthy individuals[18]. Subsequent studies established a consistent, age-related association with CH driven by mCAs and mutations in a restricted set of genes, primarily those involved in DNA methylation (*DNMT3A*, *TET2*) and chromatin regulation (*ASXL1*)[6]. Collectively termed "DTA", these genes account for roughly two-thirds of CH-associated somatic variants[14]. Additional driver mutations have been identified in genes responsible for the DNA damage response (DDR; *TP53*, *PPM1D*, *CHEK2*), growth factor signaling (*JAK2*, *KRAS*, *CBL*), and RNA splicing (*SF3B1*, *U2AF1*, *SRSF2*), reflecting the diverse biological pathways that can initiate clonal expansion[31].

Among the best-characterized CH drivers are *DNMT3A*, *TET2*, and *ASXL1*, where CH variants promote clonal expansion by epigenetically reprogramming HSCs. LOF variants in *ASXL1* disrupt Polycomb repressive complexes, leading to loss of H3K27me3-mediated silencing at key developmental genes and enabling aberrant self-renewal[30]. Although *DNMT3A* and *TET2* occupy opposite ends of the DNA methylation cycle, loss of function (LOF) mutations in both genes converge on a common outcome: epigenetic derepression of self-renewal programs in HSCs[19]. *DNMT3A* normally deposits de novo CpG methylation to silence HOX-cluster and other progenitor-associated loci[20]. Without it, these loci remain hypomethylated and constitutively active, locking HSCs into a self-renewing state that encourages clonal outgrowth. This enables aberrant transcription of inflammasome components and cytokines such as NLRP3 and IL-1β[21]. Conversely, *TET2* catalyzes the oxidation of 5-methylcytosine to 5-

hydroxymethylcytosine (5hmC) at enhancer regions of differentiation and proinflammatory genes. *TET2* loss reduces 5hmC, leading to aberrant retention of methyl marks, which skew myelopoiesis and upregulate cytokine loci, including NLRP3 and IL-1β. This directly primes progeny for inflammasome activation[22]. Though both LOF mutations modify HSC differentiation and lead to clonal outgrowth, the link between *TET2* variants and inflammation is more attributable to inflammasome gene activation, while *DNMT3A* variants enable aberrant transcription of cytokines and inflammasome components through generalized hypomethylation.

Despite extensive characterization of recurrent mutations, whole genome sequencing (WGS) has shown that almost half of CH cases lack a known driver but are still associated with increased mortality. This observation suggests the presence of additional, unidentified somatic alterations and non-mutational mechanisms contributing to clonal expansion[23,24]. Cryptic somatic events include large chromosomal rearrangements or mutations in non-coding regions of the genome that are challenging to detect with standard sequencing approaches[25]. mCAs confer an independent risk of CH and can provide a selective advantage to HSCs[26]. mCAs may promote resistance to programmed cell death, supporting clonal persistence and expansion[27]. Individuals carrying both SNVs *and* mCAs exhibit increased genetic instability, driving progression towards overt hematological disease[28]. Structural alterations involving sex chromosomes, particularly the loss of the Y chromosome in males and the X chromosome in females, are the most prevalent somatic chromosomal events observed in blood-derived DNA, with their frequency rising steadily with age[28,29]. In contrast, autosomal mCAs appear less often and display substantial variability, frequently impacting genomic regions that encode regulators of hematopoietic proliferation and DNA repair, such as 9p (*JAK2*), 17p (*TP53*), 4q (*TET2*), 13q14, 1p (*MPL*), and 11q (*ATM*)[29]. These alterations not only drive clonal expansion but are also associated with an up to tenfold increased risk of hematologic malignancy, particularly

chronic lymphocytic leukemia (CLL) [30]. Individuals with mCA-driven CH also exhibit increased morbidity and mortality[31].

In parallel, several non-mutational mechanisms have emerged as contributors to CH, including stochastic neutral drift (random clonal expansion without selective advantage), epigenetic variability, and bone marrow niche–derived signals that influence HSC behavior[25]. Telomere length dynamics also appear relevant: both unusually short[32,33] and long telomeres[34] have been linked to increased CH incidence, likely by promoting genomic instability or delaying senescence, respectively[34]. Understanding how these diverse somatic and non-mutational factors shape clonal dynamics remains an important area of future research.

Germline Modifiers of CH

Germline genetic variation can shape somatic variation in HSCs and play a significant role in CH risk and progression[35]. Several germline loci, including *TERT*, *SMC4*, *KPNA4*/*TRIM59*, *IL12A*, *CD164*, and *ATM*, have been shown to influence both the rate of somatic mutation acquisition and the selection of CH drivers[36]. For example, the *TERT* locus, particularly the rs34002450 variant, is associated with increased CH risk and supports the hypothesis that CH may emerge as a compensatory response to compromised cellular fitness[37]. Germline variants can also interact differentially with distinct CH drivers. In a GWAS of 200,453 UK Biobank participants, variants in *TCL1A* and *CD164* were associated with CH in opposite directions: the *TCL1A* rs10131341 variant was protective against *DNMT3A*-mutant CH but conferred increased risk for *TET2*-associated CH, while *CD164* rs35452836 showed the reverse pattern[38]. Another variant at the *TCL1A* locus, rs2887399, was linked to differential HSC expansion depending on CH genotype; carriers exhibited reduced expansion of *TET2*, *ASXL1*, *SF3B1*, and *SRSF2* clones, but not those with *DNMT3A* mutations[39]. Importantly, germline

associations with CH vary across ancestries, reinforcing the need for large, diverse population datasets to fully understand inherited contributions to clonal expansion and disease progression[40].

Currents in Genetic Detection of CH

Technological innovation has been central to uncovering the genetic landscape of CH, but each sequencing and analytical approach presents trade-offs in sensitivity, resolution, and interpretability, especially when detecting low-VAF somatic variants.

Early studies of CH primarily relied on whole-exome sequencing (WES) and focused on canonical drivers of hematologic malignancy[1–3]. However, WES was limited in its sensitivity to detect low–VAF clones, constraining its utility in identifying early or minor clonal events. By the late 2010s, targeted sequencing panels gained traction for their ability to sensitively detect low-VAF mutations in predefined genes or regions, offering greater efficiency and cost-effectiveness in both research and clinical settings. More recently, WGS has been used to track somatic mutation "barcodes" acquired throughout life by HSCs and inherited by their clonal progeny[24]. Single-cell sequencing has further advanced the field by allowing high-resolution detection of rare clones that are often missed in bulk datasets[41]. In parallel, AI-powered models have been developed to predict novel and established CH drivers, highlighting the utility of machine learning in mining complex genomic datasets[42,43].

While each sequencing platform has enabled key discoveries, they differ substantially in performance characteristics. WES and WGS are well-suited for discovering novel CH-associated genes and for re-mining large existing datasets. However, their sensitivity is typically limited to clones with VAFs above 2–10%, making them less suitable for detecting early clonal events. In contrast, targeted panels can detect smaller clones but may miss driver mutations

outside predefined regions. Distinguishing true variants with VAF <2% from sequencing artifacts remains a challenge, especially in low-coverage settings[44]. Thus, study design must carefully weigh the trade-offs between sensitivity, specificity, cost, and throughput to ensure appropriate method selection for a given research or clinical objective.

Accurate somatic variant calling in CH is complicated by several technical limitations of next-generation sequencing (NGS). Certain genomic regions, such as mononucleotide and polynucleotide tandem repeats, are prone to polymerase slippage, leading to sequencing errors[45]. Homopolymer indels are especially problematic, as they are often misclassified as artifacts, despite potentially reflecting true LOF mutations relevant to CH[46]. Variant detection is further challenged when small variants or indels occur in close proximity, requiring highly precise alignment[45]. Traditional germline variant callers are poorly suited for CH analysis, as they assume VAFs of 50% or 100% and fail to accommodate the wide range of mutated allele frequencies seen in somatic variants[45].

To address these challenges, a range of somatic variant calling tools, such as GATK-MuTect2, VarScan, Strelka, and Shearwater, have been developed, each using distinct algorithms to identify somatic mutations[45]. However, accuracy varies across tools. For instance, a comparison of Torrent Variant Caller, MuTect2, and VarScan2 found extremely low concordance, with only 0.5% of SNVs and 0.02% of indels detected by all three[47,48]. These discrepancies underscore the value of consensus-based approaches that integrate results from multiple callers. SomaticCombiner, for example, uses a VAF-adaptive majority voting strategy to significantly improve sensitivity, particularly for low- and ultra-low-VAF variants that are frequently missed by individual tools[46].

CH as a Bearing for Clinical Intervention

CH, though often asymptomatic, is increasingly recognized as a premalignant state that can precede hematologic cancers and contribute to non-malignant morbidities. While the absolute risk of transformation to myeloid neoplasms remains relatively low for most individuals with CH[23], its association with aging, inflammation, and cardiovascular disease underscores the need for early detection and proactive management[23]. This has prompted a growing effort to translate our molecular understanding of CH into clinical strategies spanning targeted therapies, immunomodulation, and surveillance frameworks.

The development of precision approaches to managing CH – ranging from gene-specific targeted therapies and anti-inflammatory interventions to risk-adapted surveillance and optimized clinical trial designs – requires careful navigation of biological complexity and therapeutic risk.

Making Headway: Gene-Specific Targeted Treatments for CH

TET2 variants, prevalent in CH and myeloid malignancies, present an attractive therapeutic target. Vitamin C serves as an essential cofactor for TET2, binding to its catalytic domain and enhancing its activity. Given the high frequency of truncating and hypomorphic *TET2* variants in CH and CCUS, it is proposed that vitamin C may drive epigenetic modifications by boosting TET activity – primarily targeting the wild-type allele and leveraging functional redundancies in TET1 and TET3. This mechanism could help restore DNA methylation and potentially alleviate cytopenias[49]. A clinical trial investigating high-dose intravenous vitamin C in patients with *TET2*-mutant CCUS (NCT03418038) showed no clinical responses based on MDS criteria. However, the treatment was well tolerated and induced epigenetic changes consistent with increased TET2/TET3 activity in patients with stable disease[49]. On the other hand, a trial of oral vitamin C in patients with CCUS and low-risk myeloid malignancies (MDS and MDS/MPN)

demonstrated significantly longer overall survival in the vitamin C supplemented group compared to placebo group (NCT03682029). In an extended analysis, vitamin C modified concentrations of previously identified disease-related inflammatory cytokines, IL-6 ($p<0.001$), IL-10 ($p<0.001$), CXCL10 ($p=0.003$), M-CSF ($p<0.001$), G-CSF ($p<0.001$), and CCL5/RANTES ($p=0.023$), in a manner that was associated with better clinical outcomes[50].

Aside from vitamin C, other potential therapeutics targeting *TET2* variants are being investigated in preclinical models. Vitamin A and retinoic acid were found to enhance TET2 activity and supress clonal hematopoiesis in myeloid leukemia cells and *Tet2*$^{+/-}$ mice[51]. Eltrombopag, a thrombopoietin receptor (MPL) agonist, can inhibit the growth of malignant *TET2*-mutant clones while promoting the expansion of healthy cells[52] and this may relate to aberrant MPL signalling in *TET2*-mutant CH[53]. Nuclear export inhibitors selinexor and eltanexor have been shown to selectively kill *Tet2*-mutant HSPCs in zebrafish embryos[54]. Emerging research is demonstrating that eltanexor reduces aortic atherosclerotic plaque formation in *Tet2*-mutant mice, selectively reducing *Tet2*-mutant circulating monocytes and pro-inflammatory macrophages, thus inducing a decrease in IL-1β expression in a mouse model of atherosclerosis[55]. Colchicine, an anti-inflammatory drug, also inhibited the progression of accelerated atherosclerosis and suppressed overproduction of interleukin-1β in a mouse model of *TET2*-mutant CH[56].

Recent studies have provided greater insight about factors that influence *DNMT3A*-mutant clonal expansion and the potential for related interventions. For example, estrogen may contribute to the female bias observed in *DNMT3A*-mutant CH, including high-risk R882 variants. Mouse models suggest that prolonged estrogen exposure and activation of estrogen receptor alpha promote the expansion of *Dnmt3a*-mutant myeloid cells, highlighting sex hormones as a potentially targetable axis for blood cancer prevention[57]. Erythropoietin exposure promotes the clonal expansion of non-canonical *DNMT3A* variants, whereas interferon-gamma

preferentially supports the growth of *DNMT3A* R882-mutant clones. This presents a potential method of modulating specific *DNMT3A*-mutant populations[58]. Finally, three recent studies convergently revealed that *DNMT3A*-mutant HSCs depend on enhanced mitochondrial respiration for their competitive advantage, and provided preclinical rationale that mitochondrial-targeting agents, like metformin, with good safety profile may be worth investigating in future human trials[59–61].

While most therapeutic efforts have focused on *DNMT3A* and *TET2*, several emerging strategies are targeting less common CH drivers. In individuals with CCUS harboring *IDH1* or *IDH2* mutations, small-molecule inhibitors such as ivosidenib (NCT05030441) and enasidenib (NCT05102370) are under clinical investigation. Preclinical studies indicate that *TP53* mutations enhance EZH2 binding to chromatin, and inhibiting EZH2 impairs the repopulating potential of mutant hematopoietic cells. Small-molecule JAK inhibitors targeting the *JAK2 V617F* mutation, including ruxolitinib and fedratinib, have been approved for the treatment of myelofibrosis[62,63]. In contrast, CH driven by mutations in splicing factors remains therapeutically unaddressed, despite its association with a high risk of progression to myelodysplastic syndromes and leukemia. Whether aberrant splicing generates neoantigens suitable for immunotherapeutic targeting remains unknown, but may represent a promising future direction[64].

Calming the Storm: Targeting the Inflammatory Microenvironment in CH

The relationship between CH and inflammation appears to be mutually reinforcing, with CH both driving and being fueled by a pro-inflammatory environment (Figure 2). This hyperinflammatory environment created by CH, often amplified by external factors such as infection and related microbial metabolites[65], accelerates the development and expansion of CH clones, creating a cycle that worsens inflammation[66]. Chronic inflammation has been specifically

linked to the expansion of CH driven by *DNMT3A* and *TET2* variants[38]. In murine models, *DNMT3A*-null HSCs showed increased self-renewal and proliferation as well as downregulated differentiation factors, while *TET2* knockout models demonstrated upregulated inflammatory markers and enhanced myeloid differentiation, reflecting the role of TET2 in immune regulation[67]. Variants such as *DNMT3A* and *TET2* in CH have been linked to immunologic diseases[68] and low-grade inflammation[69], further establishing CH as a central factor in multiple health conditions. As such, clinical trials targeting inflammation are investigating statins (NCT05483010), metformin (NCT04741945) and curcumin (NCT06063486) in patients with CCUS and low-risk myeloid malignancies.

The interplay between CH and inflammation has garnered significant interest in the prevention of CVD. The epigenetic priming described, including hypomethylation of inflammatory enhancers in *DNMT3A*-LOF and loss of 5hmC (at NLRP3/IL1B loci) in *TET2*-LOF, directly feeds into NLRP3 inflammasome assembly and mature IL-1β secretion[70]. In *TET2*-LOF macrophages, reduced 5hmC at NLRP3 and IL-1β enhancers (Signal 1) primes these cells for rapid inflammasome assembly upon mitochondrial danger signals (Signal 2), culminating in caspase-1mediated maturation of IL-1β[71]. *DNMT3A*-deficient myeloid cells upregulate inflammatory markers such as NLRP-3, IL-1, and IL-6 in heart failure, emphasizing the role of CH variants in promoting and maintaining inflammation[72] CH-associated may broadly amplify inflammatory responses in the innate immune system, contributing to atherosclerosis[67,70,73] This CH-driven inflammation provides the mechanistic link connecting *DNMT3A* and *TET2* CH to cardiovascular outcomes[11] and also provides the rationale for targeting IL-1β to reduce cardiovascular risk associated with chronic inflammation.

Early evidence supporting this notion comes from the CANTOS trial, where the use of anti-IL-1β canakinumab, reduced major cardiovascular events in patients with *TET2* CH[74,75]. The ability of canakinumab to prevent leukemic progression is currently being evaluated in

patients with CCUS (NCT05641831). The CANTOS study also showed that patients with *TET2* variants treated with canakinumab also had the lowest incidence of non-hematological malignancies[76]. Further evidence from the UK Biobank showed that a genetic proxy for IL-6 receptor inhibition, the *IL6R D358A* variant, significantly lowered CVD risk in individuals with *DNMT3A* or *TET2* CH, returning their risk levels to those seen in CH-negative individuals[77]. Recently, a study involving 63,700 patients across five randomized trials tested established CVD treatments targeting PCSK9, SGLT2, P2Y12, and FXa proteins and found no significant difference in treatment effects between individuals with and without CH[78]. This suggests that the presence of CH does not indicate a greater benefit from commonly used CVD therapies and that we cannot treat CVD in isolation without concurrently considering CH and inflammation. Thus, further investigation on CH-targeted therapies to mitigate CH-associated CVD risk is still warranted.

Managing CH During Treatment of Solid Cancers

As our understanding of CH advances, it is becoming increasingly evident that its presence may impact the efficacy of cancer treatment and pose risks such as therapy-related myeloid neoplasms (tMN). Extensive research has explored the frequent role of CH as a precursor to tMNs[79], especially in patients receiving radio- or chemotherapy for solid tumors[80]. The risk of therapy-induced expansion is notably heightened in CH drivers involved in DDR, such as *TP53*, *PPM1D*, and *CHEK2*, and in individuals exposed to radiation, platinum, or topoisomerase II inhibitor therapy[80]. Specifically, chemotherapy can accelerate the expansion of age-related CH carrying *PPM1D* and *TP53* mutations[81,82]. Crucially, CH variants that ultimately progress to tMNs are often detectable before the initiation of cytotoxic therapy[80]. This suggests that the variants are not induced by therapy, but rather are selectively favored by therapeutic pressure. This insight raises the possibility of screening for CH before administering specific

genotoxic therapies, enabling the identification of high-risk patients and potential modification of clinical strategies to control the growth of clones and diminish the risk of tMN[83]. Beyond the risk of tMN, however, two recent studies have shown that the infiltration of CH myeloid cells into the solid tumour microenvironment increases inflammation and decreases survival[84,85]. These findings suggest the need for further studies to evaluate tailored treatment decisions in cancer patients with CH.

Risk Stratification for Earlier Detection and Monitoring of CH: View from the Crow's Nest

Presently, feature-defined clinical classifications of CH enable risk stratification based on the classifications of CCUS, MDS, and hematological malignancies. The implementation of risk stratification will be valuable for clinicians to enable the identification of high-risk patients for whom early intervention may be appropriate, while avoiding toxicities linked to overdiagnosis[44], unnecessary monitoring, and treatment in low-risk individuals[86]. Emerging research strives to stratify individuals by risk and identify high-priority groups to facilitate earlier detection and monitoring, and to inform medical decision-making.

Multiple studies have pinpointed CH characteristics linked to the progression to myeloid neoplasms including variants in high-risk genes, distinctive co-mutation patterns, larger clone sizes, and the presence of cytopenia[86]. Recently, several studies have developed tools aimed at recognizing healthy individuals with an elevated risk of developing overt disease before the onset of symptoms. These tools include risk prediction of AML[87], myeloid neoplasia[88], and myeloid malignancies[86]. The introduction of the Clonal Hematopoiesis Risk Score (CHRS), incorporating eight features, provides a prognostic framework for predicting the risk by stratifying CH/CCUS into low, intermediate, and high risk of progression to overt myeloid neoplasms[86]. Most notably, the CHRS highlights that individuals with high risk for progression to

myeloid neoplasms represent a small minority of individuals with CH/CCUS, identifying a focused group of individuals whom clinicians could feasibly monitor and potentially treat[86]. The CHRS was also found to be associated with increased risk for cardiovascular death and cardiovascular events, supporting the use of the CHRS to inform medical decision-making regarding cardiovascular evaluation and optimization of therapeutic treatments[89]. A Clonal Cytopenia Risk Score (CCRS) model, with 3-parameters including the presence of splicing variants, platelet count <100×109/L, and ≥2 variants, was devised specifically to predict risk of myeloid neoplasm in patients diagnosed with clonal cytopenia[90]. MN-Predict, developed by Gu *et al.*, provides further detail on the prediction of myeloid neoplasm risk by categorizing high-risk groups into the probability of developing AML, MDS, and MPN. While current tools have demonstrated effective and clinically validated risk stratification, structural aberrations/mCAs and germline genetics are not included in prediction models despite their modulatory effects on risk of CH[35,91]. Together, these innovative tools will offer strategies to identify high-priority groups and determine clinical trial eligibility, contributing to a more personalized and targeted approach to patient management.

Clinical Management of CH: All Hands on Deck

Recognizing the diverse clinical implications of CH and the absence of evidence-based interventional strategies and guidelines, several CH-focused clinics have emerged to provide interim management strategies for individuals with CH (Figure 3). For instance, Memorial Sloan Kettering (MSK) runs a multidisciplinary CH clinic involving specialists from various fields including hematology, oncology, cardiology, and pathology, where decisions regarding CH management are guided by factors such as mutational characteristics, patient prognosis and preferences, consideration of adjuvant therapy, and available laboratory results[30]. Patients with CH are offered consultations with cardiologists or primary care physicians to address their

increased CVD risk. Despite a lack of data and evidence-based recommendations specifically targeting CH-related CVD risk, individualized risk assessment and counseling are provided based on comprehensive assessments of traditional cardiovascular risk factors[92]. Finally, lifestyle recommendations regarding exercise and diet are provided. Ongoing research at MSK investigates how intensive exercise training could alter the course of CH and lower the occurrence of cardiovascular events (NCT01943695).

The CH clinic at Mayo Clinic emphasizes research protocols to support prospective follow-up, understand clonal selection pressures, and assess associated outcomes in cancer treatment scenarios[93]. CH screening and monitoring may be beneficial for cancer patients undergoing specific genotoxic therapies known to increase risk of tMN, autologous stem cell transplantation for multiple myeloma and non-Hodgkin's lymphoma, and chimeric antigen receptor T-cell therapies[93]. Although clonal monitoring in cancer patients is currently confined to the research setting, establishing its clinical relevance and safety may ultimately support the use of CH screening to inform treatment decisions and improve patient care. Beyond cancer-specific contexts, patients with high-risk CH features, such as mutations in *TP53*, *PPM1D*, or spliceosome genes (e.g., *SRSF2*, *U2AF1*), or with VAF ≥10% may also benefit from additional follow-up, genetic counseling, and hematologic monitoring[93]. In contrast, patients with age-related, low-risk CHIP variants (*DNMT3A* or *TET2* mutations, low VAF) may not require immediate further testing[93].

As CH becomes increasingly relevant for personalized risk-directed interventions and the occurrence of incidental findings rises, there is limited understanding of patient preferences regarding CH testing. Sella *et al.*[94] demonstrated that most young breast cancer survivors showed a preference for CH testing in a theoretical exercise, with their interest influenced by how risks were framed and whether actionable management strategies were provided. Considering that knowledge of CH and its associated risks could induce considerable anxiety,

the study highlighted the importance of healthcare provider awareness, specific care, and psychosocial support in discussing biomarkers for future cancer risk among survivors. In the future, it is possible consent forms may be revised to include the option to receive information about important health-related incidental findings, like CH, even where there is no possibility of prevention or treatment. With CH testing already underway and expected to be an integral part of future healthcare, respecting patient preferences regarding incidental findings and revising patient consent forms accordingly is essential (Figure 3).

Clinical Trials in CH Prevention on the Horizon

Despite the promise of early intervention, several barriers challenge the design and implementation of CH-directed treatments. Many CH-associated variants are LOF mutations, rendering conventional enzyme inhibition strategies ineffective[95]. Moreover, selective pressure from targeting one clone could inadvertently promote the expansion of other, potentially more aggressive subclones[95]. These risks raise important questions about the clinical benefit of treating CH in asymptomatic individuals, particularly given the need for interventions that are both safe and tolerable in this largely healthy population.

According to Haque *et al*., clinical trials aimed at preventing clonal hematopoiesis should be guided by risk assessment, tailored to age groups, and designed to minimize toxicity[96]. To identify individuals most likely to benefit from treatment, a key consideration in trial design is distinguishing between secondary and tertiary prevention. Tertiary prevention aims to reduce disease burden in symptomatic individuals (e.g. CCUS) by slowing disease progression and preventing complications, whereas secondary prevention focuses on high-risk but asymptomatic individuals (e.g. CH carriers with high VAF) to delay or prevent disease development. To maximize clinical impact, trials should prioritize patients at increased risk for disease

progression, including individuals with high-risk genetic variants (e.g., *TP53*, *IDH1/2*, *DNMT3A R882* mutations), clinically significant cytopenias, high cardiovascular risk, undergoing chemotherapy and, in future trials, older individuals and those with immune disorders associated with high rates of CH.

Creating referral networks across disciplines will be essential to improving enrollment of eligible patients. While CCUS patients are typically identified by hematologists, asymptomatic CH carriers may be identified by oncologists, geneticists, primary care doctors, and cardiologists. Efforts should be made to recruit underrepresented groups, such as Hispanic populations, who have lower observed CH rates compared to individuals with European ancestry[40]. To comprehensively understand CH dynamics and its implications, it will be crucial to collect data on individual CH status over time for effective surveillance and risk monitoring. The electronic medical record may be an invaluable tool in this endeavor, facilitating enhanced communication among primary care providers. In the absence of longitudinal monitoring of CH dynamics, pioneering efforts by Weinstock *et al.* have already provided methods to infer clonal expansion rate from a single time point[39]. The emergence of decentralized clinical trials, which allow trial activities to occur outside of academic clinical settings, will be essential for studying specific CH drivers, especially in rare and small patient populations who may find it difficult to travel to centralized trial locations. This decentralized approach, which allows for remote subject participation, has already facilitated the ongoing pilot study of ivosidenib for adults with CCUS carrying an R132 *IDH1* mutation (NCT05030441).

While overall survival is a valuable outcome, its use in CH trials is limited by the slow progression of CH-related conditions and the presence of other age-related health risks that may affect survival measurements. To improve the feasibility of CH trials, endpoints may be adjusted to focus on measurable outcomes within a shorter timeframe, such as progression to cytopenias or early myeloid neoplasia[97], improvement in clinically significant cytopenias, or

reduction in major cardiovascular events, as seen in the CANTOS trial. Surrogate or novel biomarkers may also be used as early indicators of treatment effectiveness, including reduction in VAF, incidence of cytopenia, lower levels of inflammatory markers (e.g., IL-1β, IL-6, IL-18, CRP), genotype-specific markers (e.g., GDF15 in *TP53*-mutated CH, 2-hydroxyglutarate in *IDH1/2*-mutated CH), reduction in pyroptosis markers, or changes in gene expression immune profiles[97]. Surrogate biomarkers are advantageous as they are easier to observe in a shorter time frame; however, the clinical relevance of these surrogate endpoints is unknown. Overall, a balance between clinically meaningful and feasible outcomes is required to design effective therapeutic trials.

Charting a New Course for CH Detection and Treatment

Historically, the ≥2% VAF threshold for defining CH was established due to the technical limitations of early sequencing platforms such as targeted NGS and ddPCR[12]. This cutoff, along with a focus on variants in canonical myeloid driver genes, was reinforced by the WHO criteria for CHIP. Today, the choice of VAF threshold depends on context: in clinical settings, thresholds like ≥2% ensure reproducibility across platforms and association with known clinical outcomes, while in research, deeper sequencing technologies and machine learning methods allow for the detection of rare or low-VAF variants. The establishment of harmonized standards by CH research consortia, including aligned VAF thresholds, gene panels, and calling pipelines, will further facilitate consistent data sharing and genomic interpretation across studies. Although the discovery of novel or rare CH variants can yield valuable biological insights, their clinical translation is often limited by their low prevalence and the difficulty of validating their relevance in prospective studies. Thus, a guiding principle in the field is that clinical relevance is not defined solely by the presence of CH, but rather by the specific driver gene involved and the size of the clone.

Realizing the clinical potential of CH will require a cultural shift in both trial design and care delivery. Early-phase CH studies should adopt pragmatic, biomarker-driven endpoints, such as reduction in VAF, improvement in cytopenias, attenuation of inflammatory markers, or prevention of disease progression, to enable more efficient assessment of candidate therapies. As CH is increasingly recognized as a contributor to a broad spectrum of non-malignant conditions, a multidisciplinary clinical framework will be essential. This includes the development of specialized CH clinics that integrate hematology, oncology, cardiology, pathology and other disciplines to provide coordinated care, risk stratification, and access to clinical trials. With incidental CH detection expected to rise, clinical workflows will need to incorporate updated consent procedures, risk communication strategies, and clear guidelines for follow-up. Risk prediction tools will also be critical for prioritizing patients most likely to benefit from surveillance or intervention. Together, these efforts will help transform CH from a poorly understood biomarker into a modifiable clinical target with implications across multiple disciplines, positioning the field to sail into the next transformative decade.

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Figure 1. Healthy aging compared to clonal hematopoiesis.

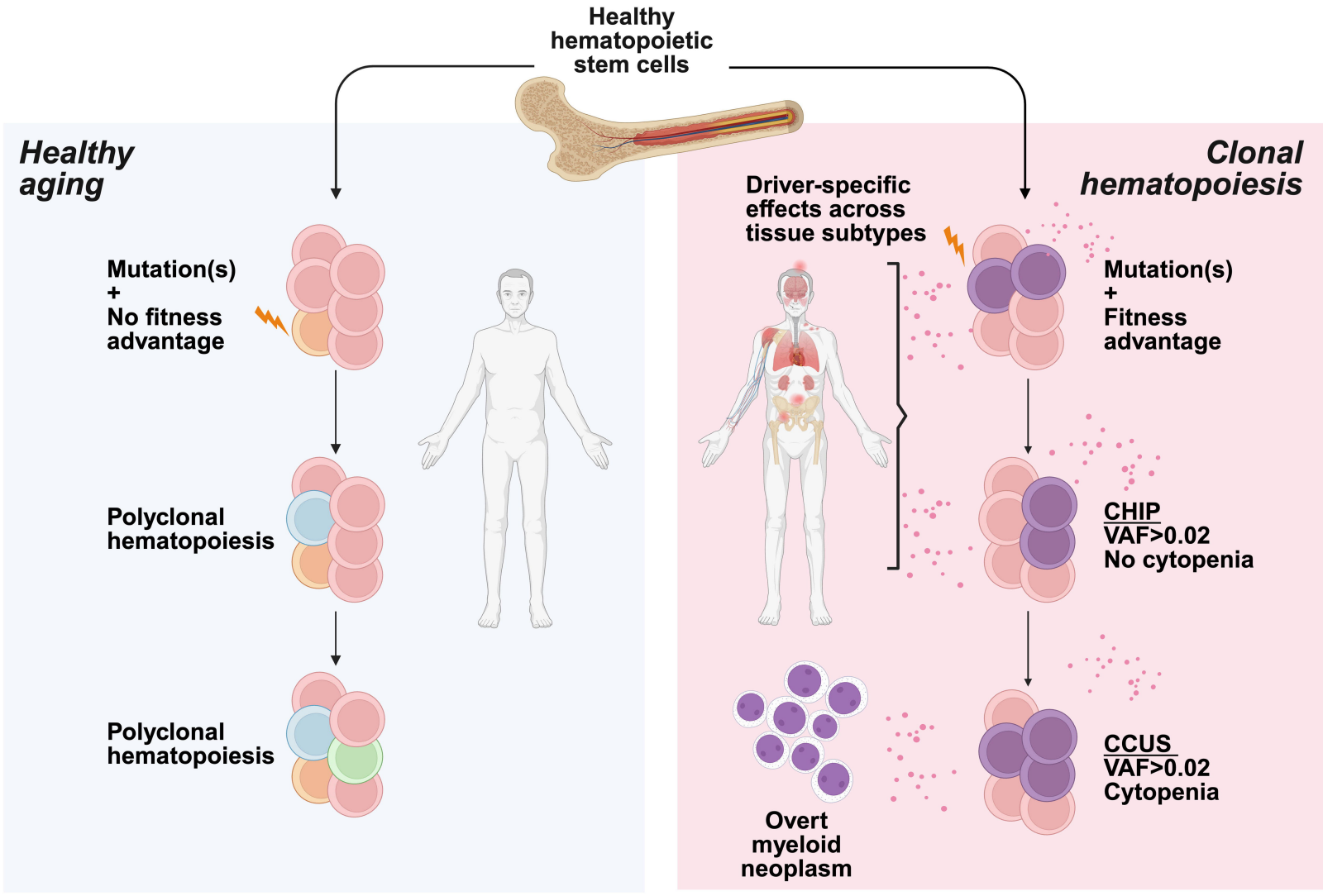
Somatic variants occur in hematopoietic stem cells with age. When they occur in driver genes associated with myeloid neoplasms, they impart a fitness advantage and lead to expansion of their progeny. Clonal hematopoiesis of indeterminate potential (CHIP) is defined when clones occupy at least 4% of the total proportion of blood cells (with variant allele fraction, VAF, of at least 0.02 or 2%) in the absence of cytopenia, and clonal cytopenia of undetermined significance (CCUS) when they are present. CH clones disrupt homeostasis, altering the risk of disease in surrounding tissues, and increasing the risk of hematopoietic neoplasms. Improved technology and expertise have increased the capacity to characterize mechanisms of expansion and recognize when to intervene. Created in BioRender.

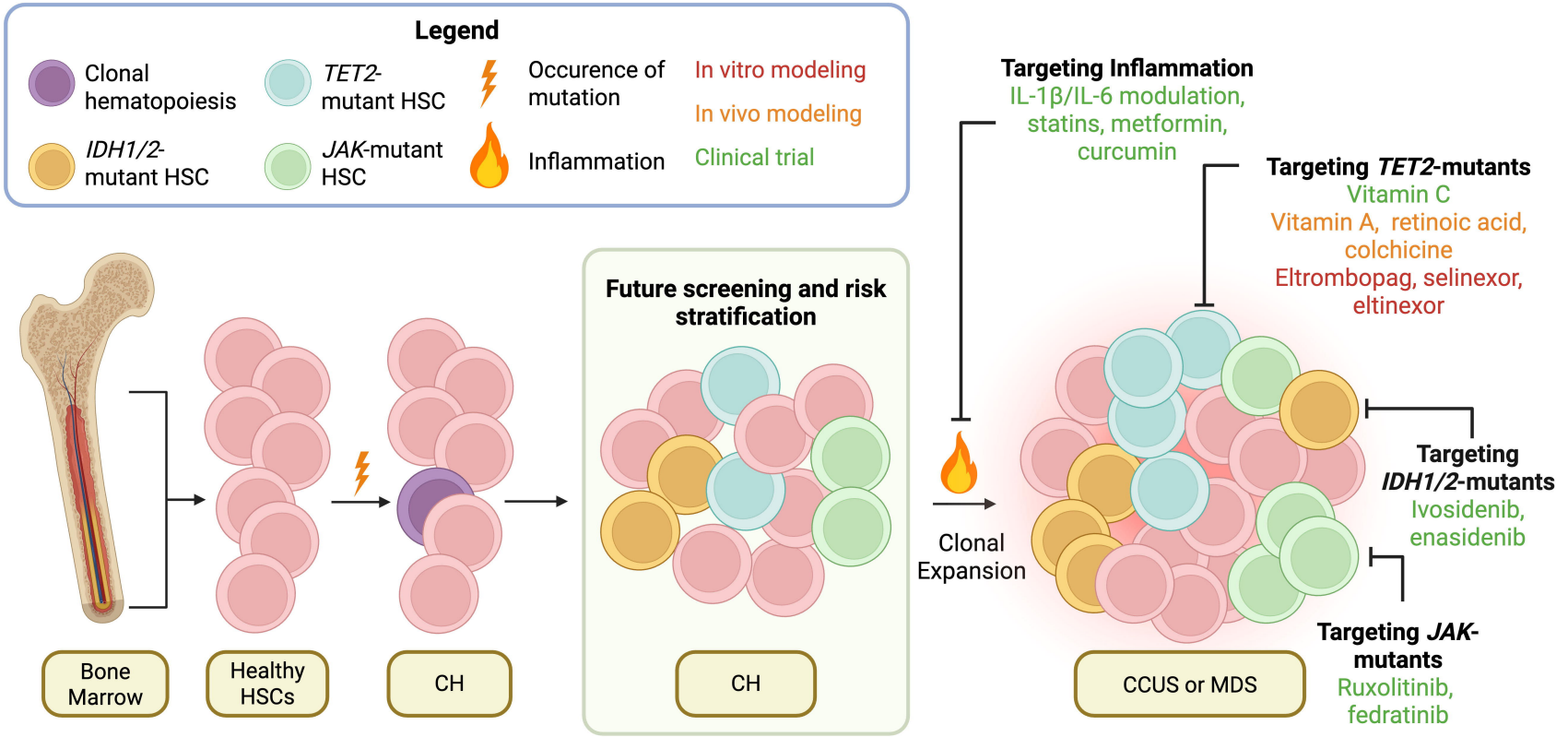
Figure 2. Potential mutant-specific and inflammation-targeting treatments for clonal hematopoiesis.

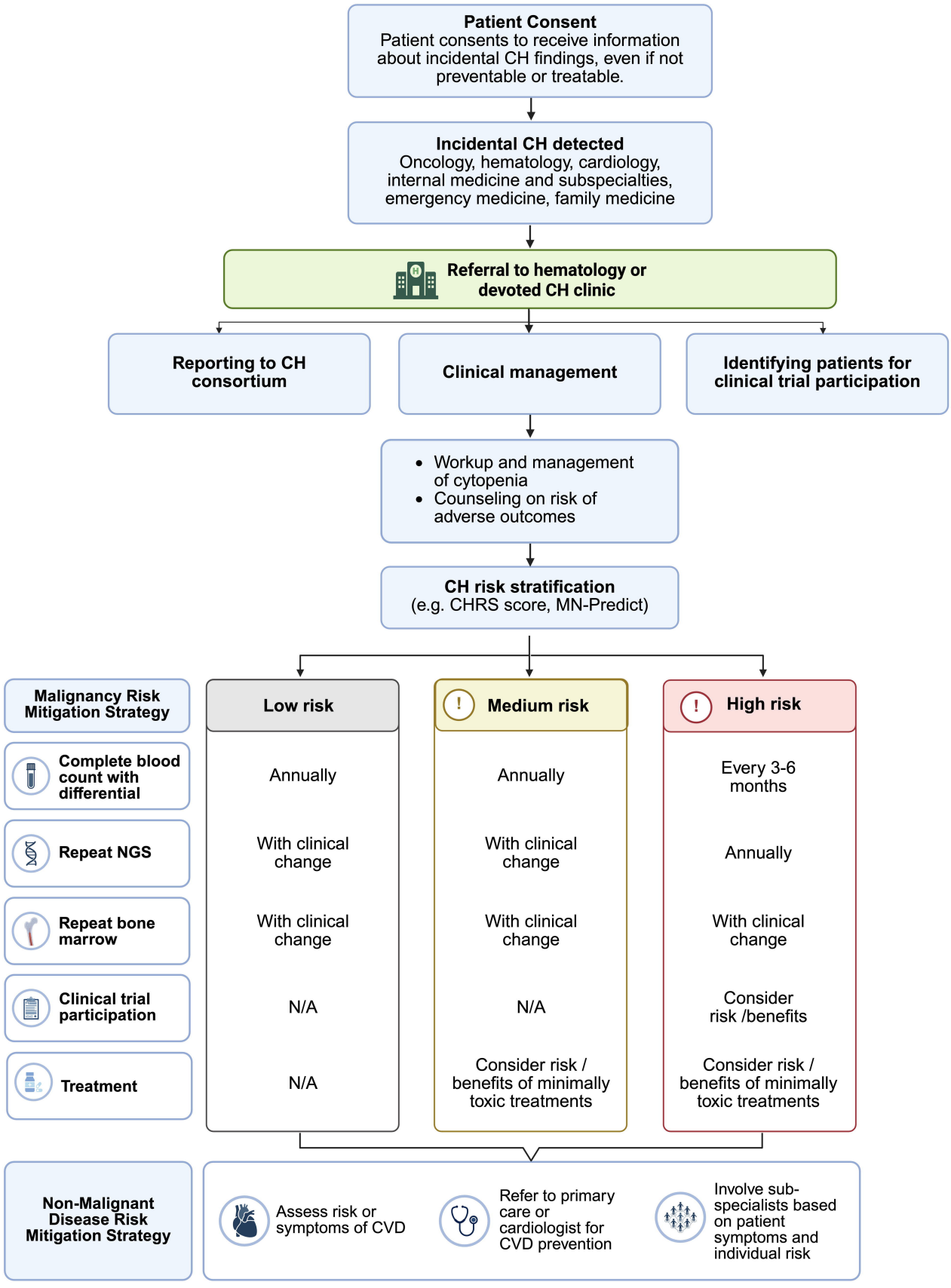
In a phenomenon termed CH, a somatic mutation conferring a fitness advantage to an HSC can lead to the clonal expansion of HSCs and progeny with the same mutation. Inflammation can provide an environment that further promotes the clonal expansion of CH mutants. Treatments targeting clones with specific CH variants have emerged, with ongoing clinical trials in MDS or CCUS patients targeting *TET2*-, *IDH1/2*- and *JAK*-mutants. Anti-inflammatory treatments, including IL-1β**/**IL-6 axis modulation by canakinumab, have been assessed in clinical trials with the goal of preventing cardiovascular events in patients with CH. Future research focused on screening and risk stratification of CH in patients with CH will be essential in early detection of MDS/CCUS and identification of high-risk patients. CCUS: clonal cytopenia of unknown significance; CH: clonal hematopoiesis; HSC: hematopoietic stem cell; IL-1β: interleukin 1β; IL-6: interleukin 6; MDS: myelodysplastic syndrome. Created in BioRender.

Figure 3. Clinical management of clonal hematopoiesis.

Currently, most cases of CH are incidentally detected in patients being investigated for unexplained cytopenias, such as CCUS, in hematology. Meanwhile, in oncology, CH is incidentally detected from paired tumour/blood sequencing, germline genetic studies with blood cells as the substrate, and the increasing use of cell-free DNA. In the future, we expect CH to be detected across internal medicinal and subspecialities such as cardiology, nephrology, critical care, infectious disease, respirology, and hepatology, and emergency and family medicine. Following referral to hematology or a specialized CH clinic, patients can be stratified by their risk of malignant transformation, offered targeted risk mitigation strategies for both malignant and non-malignant conditions, and considered for enrollment in relevant clinical trials. Created in BioRender.


Healthy hematopoietic stem cells
Healthy aging
Mutation(s) + No fitness advantage
Polyclonal hematopoiesis
Polyclonal hematopoiesis
Clonal hematopoiesis
Driver-specific effects across tissue subtypes
Mutation(s) + Fitness advantage
CHIP VAF>0.02 No cytopenia
CCUS VAF>0.02 Cytopenia
Overt myeloid neoplasm


Legend
Clonal hematopoiesis
TET2-mutant HSC
Occurence of mutation
In vitro modeling
IDH1/2-mutant HSC
JAK-mutant HSC
Inflammation
In vivo modeling
Clinical trial
Bone Marrow
Healthy HSCs
CH
Future screening and risk stratification
CH
Clonal Expansion
CCUS or MDS
Targeting Inflammation
IL-1β/IL-6 modulation, statins, metformin, curcumin
Targeting TET2-mutants
Vitamin C
Vitamin A, retinoic acid, colchicine
Eltrombopag, selinexor, eltinexor
Targeting IDH1/2-mutants
Ivosidenib, enasidenib
Targeting JAK-mutants
Ruxolitinib, fedratinib


Patient Consent
Patient consents to receive information about incidental CH findings, even if not preventable or treatable.
Incidental CH detected
Oncology, hematology, cardiology, internal medicine and subspecialties, emergency medicine, family medicine
Referral to hematology or devoted CH clinic
Reporting to CH consortium
Clinical management
Identifying patients for clinical trial participation
Workup and management of cytopenia
Counseling on risk of adverse outcomes
CH risk stratification
(e.g. CHRS score, MN-Predict)
Malignancy Risk Mitigation Strategy
Low risk
Medium risk
High risk
Complete blood count with differential
Annually
Annually
Every 3-6 months
Repeat NGS
With clinical change
With clinical change
Annually
Repeat bone marrow
With clinical change
With clinical change
With clinical change
Clinical trial participation
N/A
N/A
Consider risk /benefits
Treatment
N/A
Consider risk / benefits of minimally toxic treatments
Consider risk / benefits of minimally toxic treatments
Non-Malignant Disease Risk Mitigation Strategy
Assess risk or symptoms of CVD
Refer to primary care or cardiologist for CVD prevention
Involve sub-specialists based on patient symptoms and individual risk