REVIEW SERIES

Clonal hematopoiesis and its progression to myeloid neoplasms: insights into risk, biology, and therapeutic strategies

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Abstract

Clonal hematopoiesis (CH) is defined by the clonal expansion of hematopoietic stem and progenitor cells harboring somatic mutations that confer a fitness advantage. CH is common with advancing age and becomes nearly ubiquitous in middle age. Although typically asymptomatic, CH is associated with an increased risk of hematologic malignancies particularly myeloid neoplasms (MN), diverse non-malignant conditions, and all-cause mortality. Over the past decade, research has provided major insights into the origins of CH. In addition to aging, CH is promoted by environmental exposures, inherited genetic predisposition, and acquired conditions. Large-scale population and longitudinal sequencing studies have identified determinants of clonal behavior. Characterization of the natural history of CH has enabled the development of risk stratification models to identify individuals with CH at high risk of progression to MN, thereby providing a rationale for selecting patient populations best suited for therapeutic intervention trials. Emerging strategies include targeting mutation-specific vulnerabilities, modulating inflammatory pathways, reducing genotoxic therapy-induced clonal selection, and repurposing agents with efficacy in MN. In this review, we summarize current knowledge of the risk factors underlying CH development, highlight recent advances in understanding the determinants of clonal behavior including progression to MN, and discuss emerging therapeutic approaches for preventing malignant transformation and clinical trial design considerations.

Introduction

Clonal hematopoiesis (CH) is characterized by the clonal expansion of hematopoietic stem and progenitor cells (HSPC). These clones arise through the acquisition of somatic DNA alterations, which confer a selective advantage and enable clonal outgrowth. The process of normal stem cells acquiring somatic mutations that modify fitness is pervasive across human tissues and increases with advancing age.[1-3] A variety of DNA alterations can drive CH including point mutations, insertions-deletions (indels), and large-scale chromosomal changes (gains, losses, and copy-neutral loss of heterozygosity); the latter of which are termed mosaic chromosomal alterations.[4,5] Most cases of CH are caused by point mutations in a small number of genes that are recurrently mutated in myeloid neoplasms (MN).[6-8] These include genes involved in epigenetic modification (*DNMT3A, TET2, ASXL1*), DNA damage response (DDR; *TP53* and *PPM1D*), RNA splicing (*SRSF2, SF3B1, U2AF1*), and signal transduction (*JAK2*). CH is ubiquitous with aging and while typically clinically silent, is associated with an increased risk of progression to hematologic malignancies, including MN, as well as a variety of non-malignant adverse health outcomes which collectively result in increased all-cause mortality.[6,7] CH is a premalignant state, analogous to monoclonal gammopathy of undetermined significance, which offers a model for understanding the early stages of carcinogenesis in humans. Importantly, CH provides unique opportunities to study clonal dynamics and somatic mutation acquisition in humans since the peripheral blood allows for non-invasive sampling of the entire hematopoietic stem cell pool, which is not possible for other organ systems. This review summarizes current insights into the causes of CH, discusses the factors that drive progression of myeloid CH to MN, and highlights potential therapeutic approaches to prevent progression to MN. It focuses primarily on myeloid CH (commonly referred to as simply CH) driven by somatic

mutations, as our understanding of how mosaic chromosomal alterations – which typically involve multiple genes – contribute to progression to MN remains limited. Because the molecular mechanisms underlying many common myeloid CH mutations have been thoroughly reviewed recently,[9] this review briefly summarizes the most relevant pathways to contextualize the clinically important features of CH.

Key concepts and nomenclature of clonal hematopoiesis

The nosology of CH was comprehensively summarized in a recent excellent review by Weeks and Ebert.[10] Herein, we summarize the key concepts and definitions related to CH nosology that are fundamental to understanding the role of CH in hematologic malignancies.

Humans have an estimated 20,000 to 200,000 HSPC that contribute to hematopoiesis.[11] With clonal expansion, the proportion of peripheral blood cells arising from a single HSPC increases and can be quantified by measuring the variant allele fraction (VAF) of the somatic alterations harbored by the clone. CH mutations with a higher VAF are associated with an increased risk of hematologic malignancies and other adverse health outcomes. A minimum peripheral blood VAF threshold of 2% was used to define CH in early studies, a cutoff based on the sequencing error rate of traditional (non-error corrected) Illumina exome sequencing data.[6,7] This definition ultimately led to the term clonal hematopoiesis of indeterminate potential (CHIP), which is defined as CH with a somatic mutation in a MN driver gene with a VAF ≥2% in an individual without hematologic cancer or blood count abnormalities. While CH can now be detected at a VAF of ≥0.001 (0.1%) using error-corrected sequencing methodologies,[12-15] our understanding of the biological relevance of alterations with VAF <2%, termed micro-CH by some,[16] is limited even today.

CH can be driven by diverse alterations with specific genetic drivers influencing both CH biology and outcomes. For example, CH driven by alterations in known myeloid driver genes (which is referred to as myeloid CH) is associated more strongly with an increased risk of MN.[6,7] Conversely, CH driven by alterations in lymphoid drivers (referred to as lymphoid CH) is more strongly associated with risk of lymphoid neoplasms.[17] Myeloid CH is clearly more common than lymphoid CH largely due to highly recurrent mutations in *DNMT3A, TET2*, and *ASXL1*.[17-19] The distinction between these classes of CH is complicated by the fact that somatic mutations in many genes can drive both myeloid and lymphoid neoplasms (e.g., *TP53, TET2, RUNX1, SF3B1*, *IDH2*).[20] We found that 6.2% of individuals in the UK Biobank had somatic mutations in hematologic malignancy driver genes, with 4.6% occurring in myeloid only, 0.4% in lymphoid only, and 1.5% in both myeloid and lymphoid genes.[21] Like hematologic cancer, multiple classes of somatic events can drive CH. This includes single nucleotide variants, indels, and large-scale copy number events including mosaic chromosomal alterations. Attributing mosaic chromosomal alterations, which typically involve multiple genes, to a binary myeloid *versus* lymphoid classification is challenging. In aggregate, the prevalence of autosomal mosaic chromosomal alterations was lower than that of somatic CH mutations (3.2 *vs*. 6.2%) among individuals in the UK Biobank.[21] Furthermore, estimating the true prevalence of somatic copy number events is challenging, as the sensitivity for detecting even moderately sized copy number alterations is substantially lower than for single nucleotide variants at comparable sequencing depth and remains limited when using single nucleotide polymorphism arrays. The extent to which complex re-arrangements and fusion events (which are common drivers of hematologic cancer) might also drive CH is unclear due to difficulty in detecting these classes of events at a low VAF.

The evolution of myeloid CH to MN is summarized in Figure 1. Numerous features have been identified that contribute to the risk of CH progression (e.g. high-risk mutations, increased mutation number and VAF, ineffective erythropoiesis, cytopenias) and have been used to develop MN prediction models.[22,23] These are covered in detail later in this review. Myeloid CH with a persistent explained cytopenia and without dysplastic features meeting criteria for myelodysplastic syndrome (MDS) is termed clonal cytopenia of undetermined significance (CCUS).[24,25] Individuals with CCUS have a significantly elevated risk of progression to MN compared to those with CH without cytopenias or idiopathic cytopenia of undetermined significance.[26]

It is common to detect CH without identifying a somatic mutation or chromosomal alteration in a recognized hematologic malignancy driver gene.[6,11,27] Using distinct analytical approaches and large cohorts, Genovese *et al*.[6] and Zink *et al*.[27] found that 39% and 59% of CH cases, respectively, lacked a known driver. Importantly, CH without a known driver carried a risk of hematologic malignancy comparable to CH with an established driver.[6,27] Mitchell *et al*.[11] further confirmed the commonness of CH without a driver using an orthogonal approach, whole-genome sequencing of 3,579 single cell-derived HSPC colonies from ten donors across the human lifespan. Similar observations have been made in MDS, in which ~6% of patients lack genomic alterations in established MDS driver genes.[28] Potential explanations for CH with unknown drivers include the presence of novel driver genes (which would likely be relatively uncommon), mutations in non-coding regions (e.g., enhancers), mutations difficult to detect at a low VAF (e.g., complex rearrangements), genetic drift (i.e., random chance), and technical artifacts. Together, these findings highlight the need to better understand the biological underpinnings of CH lacking a known driver and its relationship with the progressive hematopoietic oligoclonality that is pervasive with aging.

Causes of clonal hematopoiesis

The modern concept of carcinogenesis, originally developed through the seminal work of Carl Nordling, Peter Armitage, and Richard Doll in the 1950s,[29,30] posits that cancer arises through the stepwise acquisition of genetic alterations in cells over time. Elucidation of the molecular events underlying carcinogenesis was first demonstrated in colon cancer by Fearon and Vogelstein in 1990 through analysis of biopsies obtained during colonoscopy, with publication of the "Vogelgram" model outlining specific genetic alterations associated with progression of normal colonic epithelium to adenoma and eventual carcinoma.[31] Subsequent studies using massively parallel sequencing have since characterized the genomic landscape of numerous cancer types, providing insight into the genetic alterations driving specific tumor subtypes.[32] The discovery of CH provided critical insights into the earliest stages of hematologic malignancies in humans through analysis of easily accessible peripheral blood samples. Furthermore, the presence of pre-existing large biobanks with linked genetic and longitudinal health data, such as the UK Biobank,[33] has fueled the rapid acquisition of knowledge on factors that influence the initiation and progression of hematologic malignancies, particularly MN.

Intrinsic factors

Age is the strongest risk factor for the development of CH,[6,7] reflecting the fact that age is the principal driver of accumulation of somatic mutations across human tissues.[1,34,35] The rate of somatic mutation acquisition is enhanced in

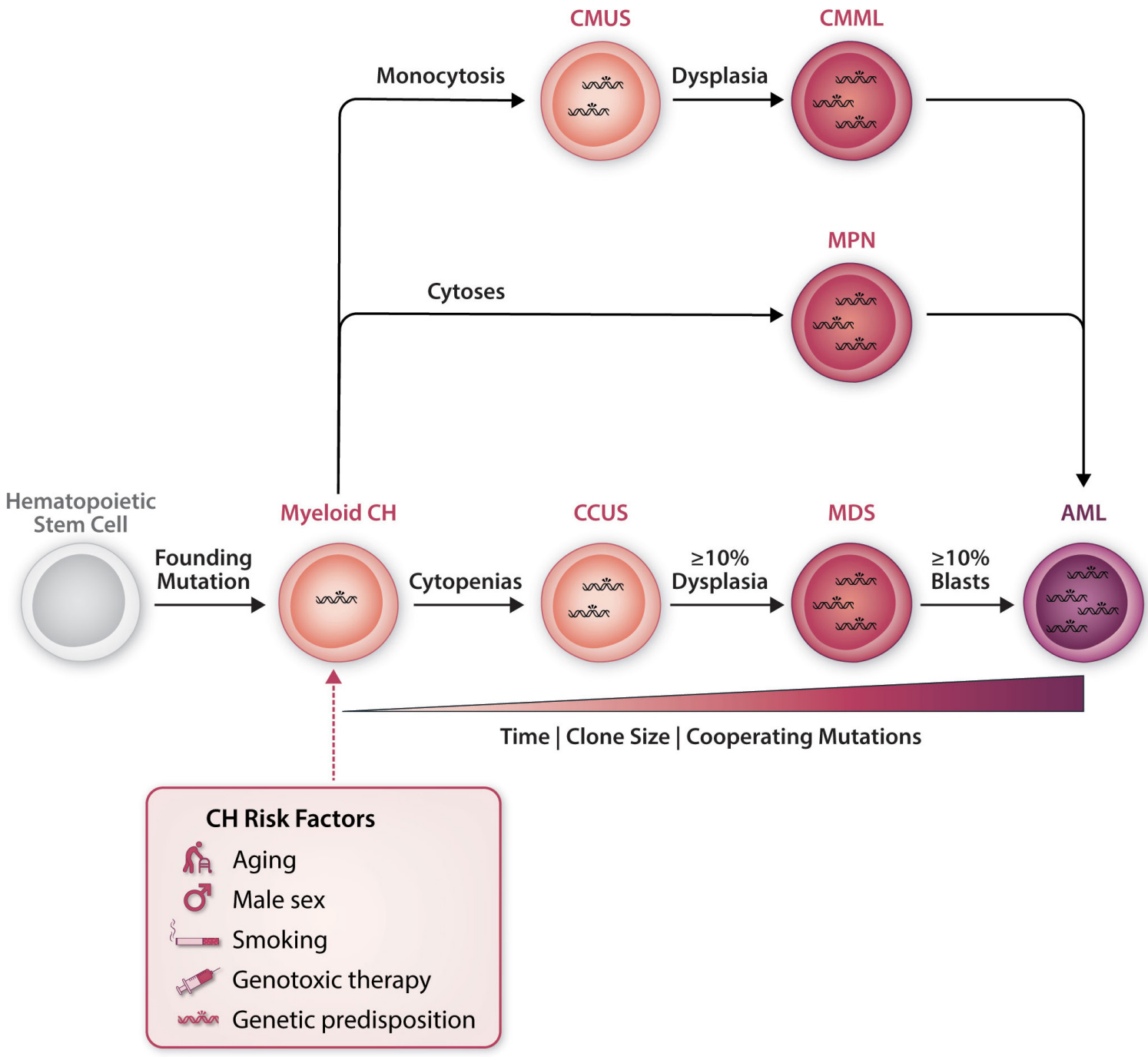

Figure 1. Evolution of clonal hematopoiesis to myeloid neoplasms. Hematopoietic stem cells acquire somatic mutations throughout life. Infrequently, these mutations confer a selective growth advantage, resulting in clonal expansion, which is termed clonal hematopoiesis (CH). Several risk factors for CH have been identified, many of which preferentially select for specific mutations. Common routes of progression from CH to specific myeloid neoplasms are shown and are driven by the acquisition of additional cooperating mutations. CMUS: clonal monocytosis of undetermined significance; CMML: chronic myelomonocytic leukemia; MPN: myeloproliferative neoplasm; CCUS: clonal cytopenia of undetermined significance; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia.

highly proliferative tissues such as the human bone marrow, which produces approximately 200 billion red blood cells and 100 billion neutrophils daily to maintain blood homeostasis.[36,37] With each cell division, somatic mutations are inevitably introduced despite the high fidelity of human DNA replication due to the inherent challenge of correctly copying a 3.2 billion base-pair genome. Somatic mutations can serve as a biological clock, marking the passage of time and the accumulation of genetic changes within HSPC. By age 60 years CH is common, with approximately 10% of individuals having CH detectable at a VAF ≥2% and 75% at a VAF ≥0.1%.[38] The somatic mutations that drive CH can occur early in life, including *in utero*, and typically take decades to manifest clinically.[39,40]

While the overall prevalence of CH is similar between males and females, sex influences the frequency of CH driven by alterations in specific genes. Males are more likely to have mutations in splicing factor genes (e.g., *SRSF2, SF3B1, U2AF1*) and *ASXL1*; and less likely to have *DNMT3A* mutations.[41-43] Additionally, males are more prone to mosaic loss of the Y chromosome than females are to mosaic loss of the X chromosome (20% *vs*. 5% in the UK Biobank), and do not develop mosaic loss of the X chromosome.[44] These sex-based differences persist after controlling for basic potential confounders (e.g., smoking rates). The CH mutational spectrum observed in males is over-represented for genes that confer an elevated risk of MN, consistent with the increased incidence of hematologic malignancies observed in males across ages.[45,46] Our understanding of the mechanisms underlying the sex-based differences in CH and hematologic malignancies are poorly understood. Potential contributors to increased risk of hematologic malignancy in males include differential carcinogen exposure, presence of tumor suppressor genes on the X chromosome that can escape X-inactivation,[47] and hormonal impacts on HSPC biology and leukemic potential.[48] These data collectively highlight an important and understudied biological role of sex on MN pathogenesis beyond differential environmental exposures, which warrants further investigation.

Environmental exposures

While smoking is moderately associated with multiple individual CH genes, including *SRSF2, SF3B1,* and *DNMT3A*, it is strongly associated with *ASXL1* mutations.[41,49] The mechanism underlying the association between *ASXL1* mutations and smoking is not understood. Most *ASXL1* mutations in CH and MN are caused by heterozygous truncating (frameshift indels and nonsense) mutations in the C-terminus, which allows for escape from nonsense-mediated decay.[50] Mutational signature analysis can identify characteristic patterns of somatic mutations induced by distinct mutational processes (e.g., tobacco carcinogens, ultraviolet light) through characterization of base substitution subtypes and their trinucleotide context (bases 5' and 3' of the mutated base). This has been used to show that smoking is associated with increased base substitutions and indels in tissues with and without direct exposure to tobacco smoke.[52] However, the trinucleotide context of CH drivers occurring in smokers and non-smokers is largely similar and predominantly driven by the age-related mutation signatures (e.g., SBS1).[53] It is unclear whether carcinogens in tobacco preferentially induce *ASXL1* mutations, or whether smoking simply confers a fitness advantage to HSPC with *ASXL1* mutations.

Genotoxic therapies, including cytotoxic chemotherapy and radiation therapy, are associated with CH. These therapies induce DNA damage in HSPC and create a selection pressure for clones with genetic alterations in DDR genes including *TP53, PPM1D,* and *CHEK2*.[49] This process is likely mostly driven by selection for pre-existing clones with DDR mutations, rather than generation of *de novo* mutations by genotoxic therapy, but distinguishing between these two possibilities is challenging.[54] However, some CH mutations may be induced by genotoxic therapy. A study of CH in long-term survivors of pediatric cancers (median follow up 32 years since diagnosis) identified recurrent *STAT3* mutations only among individuals with a history of Hodgkin lymphoma.[55] Single-cell whole-genome sequencing on peripheral blood from three individuals with *STAT3* mutations revealed that *STAT3*-mutant hematopoietic cells (and not wild-type cells) contained an ~3.5 fold increased mutation burden, and were strongly enriched for the mutational signature COSMIC SBS25, which occurs due to exposure to procarbazine, an alkylating drug used in Hodgkin lymphoma.[55] Cytotoxic chemotherapy regimens containing topoisomerase II inhibitors, platinum agents, alkylating agents, and bleomycin are most strongly associated with DDR CH,[49,55] consistent with the known risk of these agents for secondary MN. Higher radiation therapy doses are associated with increased risk of CH, with a stronger effect observed for DDR CH.[56] DDR CH was significantly associated with specific anatomic sites of radiation therapy delivery, including the head and neck, pelvis, brain, and thorax.[56] Interestingly, these sites account for ~65% of active bone marrow tissue in adults,[57] suggesting that radiation-induced CH expansion may be linked to the total dose applied to the hematopoietic compartment.

Genetic predisposition

Inherited genetic variation has a well-established role in predisposing individuals to CH and modifying clonal behavior. Inherited bone marrow failure syndromes (IBMFS) and familial acute myeloid leukemia and/or myelodysplastic syndromes (AML/MDS) are caused by rare pathogenic germline variants in genes with critical roles in hematopoiesis and have been identified as strong contributors to inherited CH risk at early ages, in addition to their well-established roles in MN predisposition.[58] While the pathophysiology of IBMFS is variable, these syndromes are united by ineffective hematopoiesis due to impaired HSPC function, which creates a unique selection pressure for somatic clones

with a relative fitness advantage to relieve the germline fitness constraints of the specific IBMFS. In these settings, CH arises through two principal mechanisms: (i) somatic normalization – adaptive mutations that compensate for the defect by reversion (the germline defect is corrected directly) or compensation (the germline defect is corrected indirectly), while leaving tumor-suppressor pathways intact; and (ii) somatic transformation – maladaptive mutations that subvert tumor-suppressor pathways, conferring an elevated risk of malignant transformation.[58] For example, in Shwachman-Diamond syndrome, which involves defects in ribosomal assembly due to loss-of-function mutations in *SBDS*, somatic normalization results from alterations that partially restore ribosome function through *EIF6* disruption (via inactivating mutations or deletion 20q) or partially correct the *SBDS* mutation (via isochromosome 7q).[59] In contrast, somatic transformation occurs as a consequence of *TP53* inactivation, resulting in uncoupling of ribosomal stress from activation of cellular senescence pathways (without correction of the ribosome function defect) and ultimately increased risk of transformation to MN. In dyskeratosis congenita, which is caused by loss-of-function mutations in genes that regulate telomere maintenance (e.g., *TERT*), mechanisms of somatic normalization include direct reversion, mutation of the unaffected wild-type *TERT* promoter (thereby leading to increased telomerase activity), and *POT1* loss-of-function mutations (facilitating telomere elongation).[60] *TP53* inactivation and chromosome 7 loss are the major causes of somatic transformation in dyskeratosis congenita.[61]

Similar to IBMFS, the unique selection pressures introduced by familial AML/MDS disorder result in the development of specific profiles of CH mutations. Individuals with germline pathogenic variants (without a hematologic malignancy) in *RUNX1* and *GATA2* had high rates of CH (35% and 22%, respectively) at all ages, whereas individuals with pathogenic *DDX41* germline variants had a low CH prevalence (3%).[62] In addition, *RUNX1* germline variant carriers had a unique CH mutational spectrum with a high frequency (42%) of *BCOR* variants. These findings collectively underscore the importance of integrating germline genetics into our understanding of CH biology. Such integration may improve risk stratification, inform surveillance strategies for individuals with hereditary predisposition to hematologic malignancies, and provide opportunities for mechanistic studies that explore how inherited variation shapes the evolutionary landscape of somatic hematopoietic clones.

Genome-wide association studies using large biobanks with linked phenotypic data have identified several common germline loci that increase susceptibility to CH, both overall and in specific genes. Most of the genes associated with CH globally have known roles in telomere biology, DDR, hematologic malignances (e.g., *TET2, SETB1, RUNX1, ETV6, GATA2, PTPN11A, MPL*), or HSPC biology (e.g., *CD164, LY75, SMC4*).[19,21,63,64] Among these, variants at the *TERT* locus associated with increased telomerase activity and telomere length consistently show the strongest association with overall CH risk.[27,64] Mendelian randomization analysis supports a causal role of increased telomere length on CH risk.[41] In line with this, a small family-based study found that germline heterozygous loss-of-function mutations in *POT1*, a telomere maintenance gene, confer a high risk of increased telomere length and CH risk, as well as a diverse spectrum of benign and malignant neoplasms.[65] Rare variants in *CTC1*, another important regulator of telomeres which has been implicated in dyskeratosis congenita, have been associated with global CH risk.[63] These findings collectively demonstrate a critical role for telomere biology in CH pathogenesis, suggesting that reduction of normal telomere shortening with aging promotes the development of CH.

Common germline variants in several DDR genes also predispose individuals to CH overall, including genes associated with well-established cancer predisposition syndromes (e.g., *CHEK2, ATM, PARP1, TP53*).[41,63] In addition, our group recently identified 22 new CH predisposition genes (20 CH gene-specific),[21] 14 of which have recognized roles in the DDR (*ATR, RAD51D, FANCI, NBN, RTEL1, ERCC1, ERCC2, ERCC3, ERCC4, MUTYH, NTHL1, LIG4, ERCC6L2, PRDM9*).

Previous studies have also identified common germline variants that drive CH in specific genes.[19,63,64,66] Most notably, a promoter variant at *TCL1A* associated with decreased *TCL1A* expression predisposes to *DNMT3A* CH, but is protective from CH driven by other genes including *TET2, ASXL1, SF3B1,* and *SRSF2*.[41] This difference was driven by the differential impact of the allele on CH expansion rate, resulting in slower growth of non-*DNMT3A* CH.[67] In addition, functional studies showed that *TCL1A* drives HSPC clonal expansion and that its expression is induced by introduction of mutations in *TET2* or *ASXL1*, but not *DNMT3A*. The results implicate *TCL1A* as a key mediator of the fitness advantage of many commonly mutated CH genes. Similarly, a variant in the *CD164* locus, which is involved in HSPC migration, is associated with *DNMT3A* and *ASXL1* CH, but not *TET2* CH for reasons that remain unclear.[41,63]

Overall, the link between germline variants and gene-specific CH predisposition appears to be driven primarily by the influence of germline variants on clonal fitness rather than direct mutagenesis, as mutational signatures were largely comparable between carriers and non-carriers, and dominated by the age-related SBS1 signature.[21] However, longitudinal studies comparing CH evolution in germline carriers and non-carriers would be needed to clarify the relative contribution of mutational acquisition *versus* expansion.

Acquired disorders

Aplastic anemia is a bone marrow failure disorder characterized by pancytopenia and bone marrow aplasia. Acquired forms of the disorder are usually caused by autoimmune

destruction of HSPC and associated with CH in approximately 50% of patients.[68] The genes most frequently involved with somatic mutations in acquired aplastic anemia include *DNMT3A, PIGA, ASXL1, BCOR,* and *BCORL1*. The unique enrichment of *PIGA, BCOR*, and *BCORL1* somatic mutations in acquired aplastic anemia may support their role in escape from immune-mediated destruction, although the mechanisms are not well characterized.

Drivers of progression of clonal hematopoiesis to myeloid neoplasms

Clonal evolution

Over the past 5 years our understanding of the determinants of clonal behavior and their influence on progression to MN has advanced substantially. Studies have employed diverse approaches to characterize clonal dynamics including serial measurement of CH through longitudinal aging studies,[69] phylogenetic analysis through sequencing of individual HSPC clones,[11,69] and clonal growth estimation from single timepoint data using passenger mutation analysis.[67] These complementary methodologies have yielded several broad insights across CH driver mutations. CH clones generally expand at an accelerated rate earlier in life, followed by a slower, steady exponential rate during older age (at least 55 years old).[69] Growth rates vary considerably between different CH mutations, with some mutations exhibiting age-dependent variability in growth.[69] Larger CH clone size, higher clonal growth rates, and a greater number of CH mutations are all associated with an increased risk of progression to MN.[7,69] Finally, CH mutations are typically acquired decades before manifesting clinically.[11]

Specific CH driver mutation genes play a central role in dictating clonal behavior, including both the risk and type of progression to MN. *DNMT3A* CH generally has a low clonal growth rate (~5% per year), though there is marked growth variation by age; faster at younger ages and slower at older ones.[69] The risk of progression to MN with *DNMT3A* mutations is relatively low and is driven primarily by an increased risk of AML.[41] In contrast, *TET2* mutations exhibit an intermediate clonal growth rate (~10% per year) which is stable across all ages, with one study suggesting *TET2* overtakes *DNMT3A* as the most common CH mutation in individuals over 75 years old.[69] *TET2* CH confers an intermediate risk of progression to MN, particularly MDS and chronic myelomonocytic leukemia.[41] Despite having opposite effects on DNA methylation, loss-of-function mutations in *TET2* and *DNMT3A* both drive CH clonal expansion. *ASXL1* mutations also demonstrate intermediate growth rates and are strongly associated with progression to AML and MDS risk.[41,69] Mutations in *IDH1* and *IDH2* are less common, have an intermediate-to-high growth rate (which is stable over time), and are strongly associated with risk of progression to AML.[22,69] In addition, *IDH1/2* mutations are largely mutually exclusive with each other and *TET2* mutations in MN (reflecting a shared pathogenic mechanism discussed later in this review),[70] which has been validated using single-cell DNA-sequencing approaches to reconstruct phylogenetic trees of the major driver clones in AML cases.[71,72]

Mutations in splicing factor genes (including *SRSF2, SF3B1*, and *U2AF1*) are rare before the age of 50 years old, but when present at older ages are associated with rapid clonal growth rates (15-20% per year).[69] The reasons for their late onset are incompletely understood, but likely reflect age-related changes in selection pressures, rather than a unique restriction of these mutations to older individuals. Recent work has shown that splicing factor mutations promote CH expansion in part by mitigating telomere shortening in HSPC with aging.[73] Investigating the molecular basis of this phenomenon has been difficult because current *in vitro* and *in vivo* models of splicing factor mutations often show reduced clonal fitness, the opposite of what is observed in humans.[74] Splicing factor mutations are typically mutually exclusive because their co-expression results in synthetic lethality.[75] Splicing factor-driven CH has a high risk of progression to all MN subtypes.[41] Interestingly, *SF3B1* CH is associated with a favorable prognosis upon progression to MDS,[76] but an adverse prognosis upon progression to AML,[77] highlighting the context-dependent effects of specific splicing factor mutations.

While CH clones harboring the *JAK2* V617F hotspot mutation generally have intermediate growth rates, they are unique in demonstrating unpredictable growth dynamics at older ages.[69] In contrast, mutations in other MPN drivers (*CALR* and *MPL*) are less frequently observed in CH, consistent with their lower prevalence in MPN.[41] The canonical MPN driver mutations (*JAK2, CALR, MPL*) are mutually exclusive and exert strong influence on the risk of developing specific MPN subtypes. *JAK2* V617F mutations are associated with all MPN types including polycythemia vera, primary myelofibrosis, and essential thrombocythemia, whereas *CALR* mutations are restricted to essential thrombocythemia and primary myelofibrosis, and *MPL* mutations to essential thrombocythemia. *JAK2* V617F VAF significantly influences MPN subtype distribution: higher VAF (>50%), often reflecting homozygous mutations due to copy-neutral loss of heterozygosity, are strongly associated with polycythemia vera and myelofibrosis, whereas lower VAF, consistent with heterozygous mutations, are more commonly observed in essential thrombocythemia.[78] The factors that influence the progression of MPN driver mutant CH to specific MPN subtypes remain poorly understood.

The growth of DDR-mutated CH is generally modest in the absence of genotoxic therapy-induced selective pressure. *TP53* mutations are typically associated with a low clonal growth rate, which further decelerates with aging, whereas *PPM1D*-mutant CH demonstrates an intermediate growth rate.[69] Both *TP53*- and *PPM1D*-mutant clones are linked with

a relatively average risk of progression to MN. This may help to explain why MN uncommonly occur in patients with Li Fraumeni syndrome (pathogenic germline *TP53* variants) in the absence of prior genotoxic therapy.[22,23,79,80] In contrast, exposure to cytotoxic chemotherapy or radiation therapy drives expansion of *TP53*- and *PPM1D*-mutant CH clones and increases the risk of MN.[49,54,81] The selection advantage provided by somatic *TP53* mutations is not restricted to genotoxic therapies, but is also observed with lenalidomide[82] and MDM2 inhibitors.[83]

Although *NPM1* and *FLT3* are common driver mutations in *de novo* AML, they are rarely detected in CH. In the UK Biobank cohort, only two out of ~200,000 individuals were found to have a *NPM1* driver mutation with normal blood counts.[84] Both individuals developed AML within 6 months of the sample collection. The near lack of *FLT3* and *NPM1* mutations in CH studies may reflect a rapid progression to *de novo* AML.

Factors other than CH mutations play an important role in governing clone behavior and include both cell-intrinsic and extrinsic factors. The relevance of non-mutational factors is highlighted by several observations. Low frequency CH mutations (micro-CH) are ubiquitous with aging (>95% after 50 years old), however only a small minority of these clones expand to meet criteria for CHIP (VAF of 2%).[13] Parallel observations have been made in other somatic tissues including the skin and esophagus, which have frequent oncogenic mutations, but low overall rates of progression to carcinoma.[2,3] The same driver mutations have variable growth rates between different clones.[67,69] Expanded clones lacking known drivers are not uncommon, particularly at advanced ages.[27] While acquisition of somatic alterations is typically involved in driving progression to MN, a large proportion of *JAK2* CH that progresses to MPN[85] and a subset of *SF3B1* CH to MDS[86] without the acquisition of new somatic alterations.

Cell-intrinsic factors that govern clonal behavior beyond individual CH mutations are diverse, and several examples are highlighted below. Clinical markers of ineffective erythropoiesis, such as increased mean corpuscular volume and red cell distribution width, as well as the presence of cytopenias, are associated with an elevated risk of MN even after accounting for specific CH mutations.[41] Germline genetic variation also plays a substantial role. In the UK Biobank cohort, 14 out of 98 CH predisposition genes were associated with increased risk of hematologic malignancy, eight of which were linked with CH overall.[21] Moreover, CH carriers with germline variants in these 14 CH predisposition genes had a higher risk of developing a hematologic malignancy compared with CH carriers lacking the variants.[21] The previously discussed *TCL1A* promoter variant, which confers gene-specific effects on CH predisposition, is also associated with slower expansion of non-*DNMT3A* CH.[67] In addition, germline pathogenic variants in *DDX41* exhibit a markedly higher penetrance of MN in men compared to women for unknown reasons.[87] Down syndrome (trisomy 21) is frequently associated with hematologic abnormalities, including neonatal transient abnormal myelopoiesis (TAM). TAM is a preleukemic syndrome unique to Down syndrome, which typically presents with circulating blasts that originate from the fetal liver and harbor somatic *GATA1* mutations, and resolves spontaneously within a few months.[88] Notably, approximately 20% of neonates with Down syndrome have detectable somatic *GATA1* mutations in the absence of hematologic features of TAM.[89]

Beyond selection of DDR mutations with genotoxic therapy, the extent to which cell-extrinsic factors influence CH progression to MN is less well established. Multiple preclinical models have demonstrated that systemic inflammation can promote the expansion of specific CH clones, particularly those with *TET2*- and *DNMT3A*-mutations.[90] However, there are limited data supporting this in humans. We recently identified a number of plasma proteins associated with CH (N=34) and subsequent risk of progression to MN (N=115) in the UK Biobank cohort.[91] The proteins associated with MN risk were enriched for involvement in regulation of the innate and adaptive immune system, and improved risk prediction beyond clinical and CH-related features.[91] Longitudinal studies in humans are needed to further characterize the extent to which inflammatory stress might influence CH evolution.

Risk stratification of clonal hematopoiesis

CH is ubiquitous with aging, but progression to MN only occurs in a small subset of patients (<1% per year among those with CHIP). As knowledge of the factors driving progression of CH to MN increases, there has been growing interest in developing models to predict risk of progression. Such models are essential for consideration of interventional trials to prevent malignant transformation, given that the overall risk of MN in unselected CH populations is low, and therefore the potential harms of preventative approaches could outweigh their benefits. Recently, two groups developed models for predicting MN risk that have gained prominence in the CH field.[22,23] Both efforts used the UK Biobank, which is uniquely suited for this purpose due to its in-depth genetic (including CH mutation profiling) and longitudinal (>10 years) health information on over 450,000 individuals.

Weeks *et al.*[23] employed a decision tree-based machine-learning model to identify demographic factors, CH clone characteristics, and laboratory values predictive of incident MN. From this, they created the Clonal Hematopoiesis Risk Score (CHRS), which stratifies individuals with CHIP and CCUS into three risk groups. The estimated 10-year probability of incident MN was 52% in the high-risk group (1% of individuals), 8% in intermediate-risk group (10%), and <1% in low-risk group (89%). The CHRS model incorporates the following binary features, listed in order of decreasing

risk contribution: presence of high-risk mutation, mean corpuscular volume ≥100 fL, red cell distribution width ≥15, VAF ≥0.2, ≥2 CH mutations, presence of cytopenia, age ≥65 years, and presence of a single *DNMT3A* mutation. Gu *et al.*[22] used Cox regression to develop MN-predict, a set of models that estimate the risk of progression to MPN, MDS, or AML separately. These models rely on features similar to those in CHRS, but also allow for utilization of optional parameters such as body mass index and clinical laboratory values, which can improve prediction accuracy.

However, it is important to note that both CHRS and MN-predict were developed using data from the UK Biobank, a cohort enriched for healthy volunteers predominantly of European ancestry, which limits their generalizability to other patient populations.[33] This cohort also lacks longitudinal blood count data to assess persistence of cytopenias and bone marrow biopsies were not performed to exclude MN including MDS, both of which are required to meet diagnostic criteria for CCUS. To address these limitations, Xie *et al.*[92] developed the Clonal Cytopenia Risk Score (CCRS) using real-world data from patients evaluated at tertiary referral centers who met diagnostic criteria for CCUS (and underwent bone marrow biopsy). The CCRS model stratifies individuals with CCUS into three risk groups based on three binary variables, listed in order of decreasing risk contribution: presence of ≥2 mutations, platelet count <100x10^9/L, and presence of a splicing factor mutation. The estimated 2-year probability of incident MN was 37% in the high-risk group (10% of individuals), 14% in the intermediate-risk group (39%), and 6% in the low-risk group (51%). Notably, the incidence of MN observed in this real-world cohort was substantially higher than that observed among healthy participants in the UK Biobank cohort (~1%).[23] Further refinement of CH/CCUS risk prediction models in real-world patient populations will be critical to guide future therapeutic intervention trials.

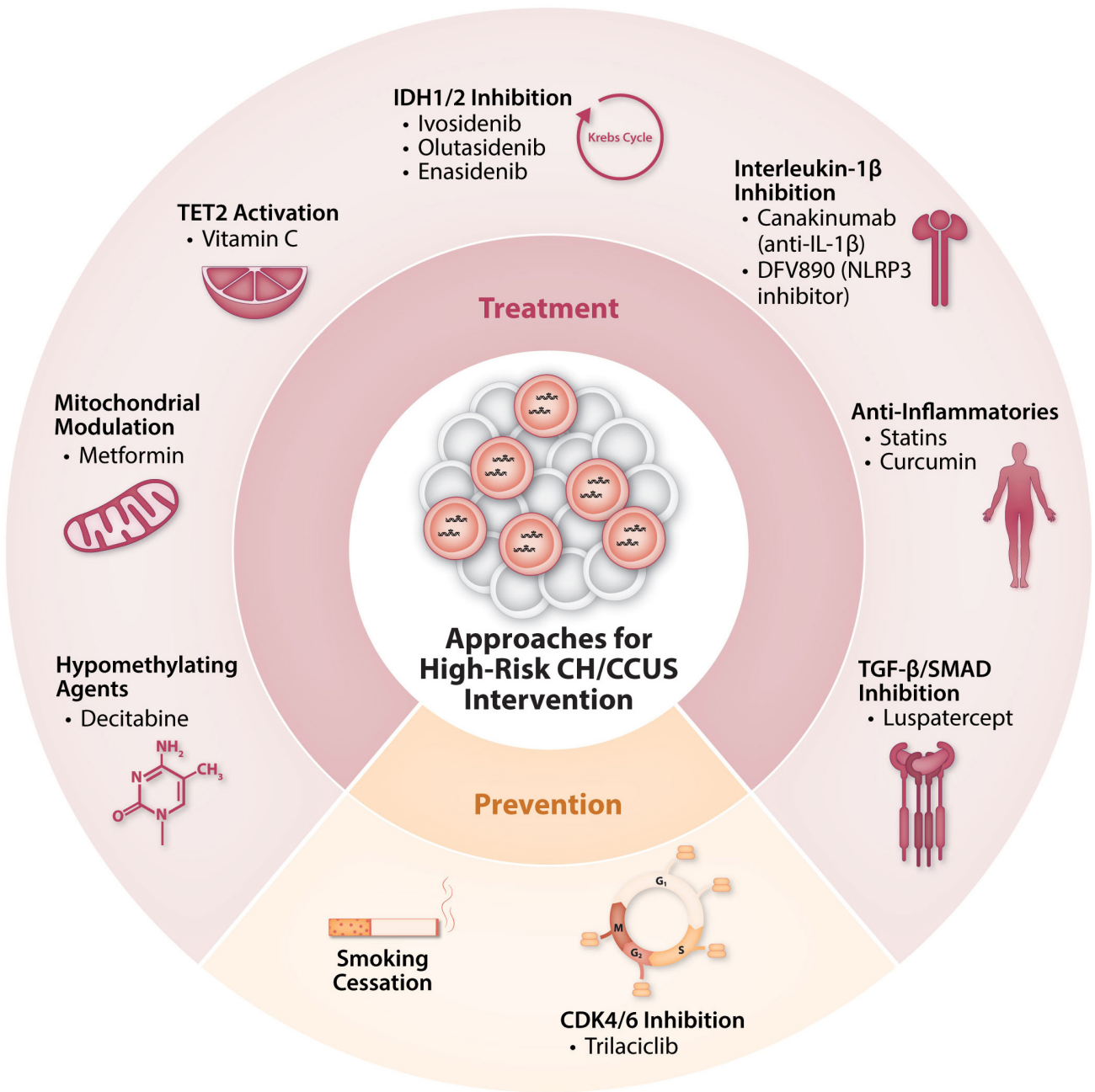

Figure 2. Summary of the intervention approaches to mitigate malignant transformation in high-risk clonal hematopoiesis and clonal cytopenia of undetermined significance. CH: clonal hematopoiesis; CCUS: clonal cytopenia of undetermined significance; IDH1/2: isocitrate dehydrogenase 1 and 2; TET2: tet methylcytosine dioxygenase 2; IL-1β: interleukin-1 beta; NLRP3: NLR family pyrin domain containing 3; TGF-β: transforming growth factor beta; SMAD: SMAD family member 2; CDK4/6: cyclin-dependent kinase 4 and 6.

Interventional studies in high-risk clonal hematopoiesis

Advances in CH risk stratification have identified populations at significant risk of progression to MN based on clinical and molecular features,[22,23] thereby creating opportunities for therapeutic intervention trials. The increasing use of next-generation sequencing in oncology, both for detecting circulating tumor DNA and assessing for hereditary cancer syndromes, has also led to more frequent detection of CH as part of routine clinical care. Together, these developments have provided strong impetus to investigate targeted approaches to mitigate malignant transformation, particularly in individuals with high-risk clonal profiles. Several such approaches are now being investigated in clinical trials, which are summarized in Figure 2 and Table 1.

Ascorbic acid (vitamin C)

TET family methylcytosine dioxygenases, including TET2, catalyze the oxidation of methylated DNA, thereby promoting DNA demethylation, which has key roles in the regulation of gene expression.[93] Loss-of-function mutations in *TET2* are very common in CH (second after only *DNMT3A* CH) and confer a fitness advantage to HSPC by impairing DNA demethylation, ultimately resulting in enhanced self-renewal and impaired differentiation. Preclinical studies demonstrated that treatment with ascorbate (vitamin C), which is a cofactor for TET2, can restore TET2 activity in the setting of *TET2* haploinsufficiency, resulting in increased DNA demethylation, normalization of HSPC function, and impaired leukemogenesis.[94,95] This compelling preclinical work led to the initiation of two clinical trials studying vitamin C in CCUS. The phase II trial of single-agent high-dose intravenous ascorbic acid in *TET2*-mutant CCUS (NCT03418038) has readout and did not identify any clinical responses at 20 weeks by International Working Group MDS criteria (out of 8 patients eligible for response assessment) or significant changes in *TET2* VAF.[96] Results from a phase II study of oral vitamin C in low-risk MN including CCUS (NCT03682029) are pending.

IDH1/2 inhibition

Mutations in *IDH1* (R132) and *IDH2* (R140 or R172) are associated with high-risk CH and represent common early clonal leukemogenic events in MN. Isocitrate dehydrogenase (IDH) enzymes normally catalyze the conversion of isocitrate to alpha-ketoglutarate (αKG). These missense IDH mutations result in production of the oncometabolite

Table 1. Overview of the interventional clinical trials in clonal hematopoiesis and clonal cytopenia of undetermined significance.

Study ID	Phase	Intervention	Mechanism	Population	Target enrollment	Primary endpoint(s)
NCT03418038	II	Vitamin C (IV)	Enhance TET2 activity	*TET2* CCUS	10	Hematologic response rate
NCT03682029	II	Vitamin C (oral)	Enhance TET2 activity	CCUS & low-risk MN	109	Δ VAF at 12 months
NCT05030441	II	Ivosidenib	IDH1 inhibitor	*IDH1* CCUS	20	Hematologic improvement rate
NCT06566742	II	Olutasidenib	IDH1 inhibitor	*IDH1* CCUS & low-risk MN	15	Safety
NCT06240754	II	Enasidenib	IDH2 inhibitor	*IDH2* CCUS	15	Best hematologic response
NCT05641831	II	Canakinumab	Anti-IL-1β	CCUS	110	Time to MN
NCT05552469	I	DFV890	NLRP3 inhibitor	CCUS & low-risk MN	105	Safety
NCT06097663	II	DFV890 or	NLRP3 inhibitor	*TET2* & *DNMT3A* CHIP with CHD	31	Δ IL-6 & IL-18
		MAS825	IL-1β x IL-18 BsAb			Δ IL-6
NCT06788691	II	Luspatercept	TGF-β superfamily ligand trap	CCUS	50	Hematologic improvement rate
NCT06802146	I	Decitabine/ cedazuridine	DNA hypomethylating agent	CCUS	108	Feasibility failure rate
NCT04741945	II	Metformin	Mitochondrial modulation	CCUS & low-risk MDS	40	Safety & feasibility
NCT05483010	II	High-intensity statin	Anti-inflammatory	CCUS & low-risk MDS	16	Δ CRP
NCT06063486	II	Curcumin	Anti-inflammatory	CCUS & low-risk MN	30	Δ cytokines & symptoms

ID: identity; IV: intravenous; *TET2*: tet methylcytosine dioxygenase 2; CCUS: clonal cytopenia of undetermined significance; MN: myeloid neoplasm; Δ: change in; *IDH1*: isocitrate dehydrogenase 1; *IDH2*: isocitrate dehydrogenase 2; IL-1β: interleukin-1 beta; NLRP3: NLR family pyrin domain containing 3; IL-6: interleukin-6; IL-18: interleukin-18; BsAb: bispecific antibody; DNMT3A: DNA methyltransferase 3 alpha; CHIP: clonal hematopoiesis of indeterminate potential; CHD: coronary heart disease; TGF-β: transforming growth factor beta; MDS: myelodysplastic syndrome; CRP: C-reactive protein.

2-hydroxyglutarate, which competitively inhibits αKG-dependent enzymes (including *TET2*), resulting in broad effects including altered metabolism, aberrant DNA and histone methylation, and differentiation blocks.[70] Mutant-specific small molecule inhibitors of these enzymes are already approved for *IDH*-mutated AML, including ivosidenib and olutasidenib (*IDH1*), as well as enasidenib (*IDH2*). Given that *IDH* mutations are early clonal events in the natural history of MN and that IDH inhibitors have a reasonably good safety profile, IDH inhibition is an ideal target for initial CH intervention studies. Our group is leading two early phase clinical trials studying enasidenib in *IDH2*-mutant (NCT06240754) and ivosidenib in *IDH1*-mutant CCUS (NCT05030441). There is also an active trial (NCT06566742) assessing olutasidenib in *IDH1*-mutant CCUS and low-risk MN. Initial results from our *IDH1*-mutant CCUS trial (median follow-up of 16 months) demonstrated that ivosidenib was well tolerated and induced high rates of hematologic response (>80%) and *IDH1* mutation clearance (>40%).[97]

Interleukin-1β inhibition

The relationship between CH, aging, and inflammation is complex and likely involves bidirectional causality between the three. This has been thoroughly reviewed in detail elsewhere.[98,99] In brief, both CH (particularly *TET2* mutant) and aging are associated with elevated levels of proinflammatory cytokines, which can provide a selection pressure for expansion of specific CH clones with a relative fitness advantage in the context of systemic inflammation (*TET2* and *DNMT3A* CH).[90] Preclinical studies in mice have shown that *TET2* loss in hematopoietic cells results in accelerated atherosclerosis and increased proinflammatory cytokines (including interleukin [IL]-1β and IL-6) secretion by macrophages.[100,101] Furthermore, IL-1 (which increases with aging) induces expansion of *Tet2*$^{+/-}$ HSPC in mouse models of *Tet2*$^{+/-}$ driven CH, whereas genetic and pharmacological inhibition of IL-1 signaling impairs expansion of *Tet2*$^{+/-}$ clones.[102] These findings collectively provide a strong biological rationale for the therapeutic targeting of IL-1β in CH and CCUS, which has fueled subsequent clinical investigation in this space.

Canakinumab is an anti-IL-1β monoclonal antibody that inhibits IL-1β from binding to and activating the IL-1 receptor. The large phase III CANTOS trial assessed whether treatment with canakinumab reduces major adverse cardiovascular events in patients with prior myocardial infarction and an elevated baseline C-reactive protein level.[103] The trial found that treatment with canakinumab (compared to placebo) resulted in an ~15% relative risk reduction in major adverse cardiovascular events, increased incidence of fatal infections, and no difference in overall survival. Subsequent exploratory analyses of CANTOS showed that: CH mutations in *TET2* were more common than in *DNMT3A* (which could be related to the inclusion criteria requirement of an elevated C-reactive protein level); patients with *TET2* CH who were treated with canakinumab had a decreased risk of major adverse cardiovascular events (compared to those given a placebo); and canakinumab treatment was associated with decreased risk of incident anemia and improved hemoglobin response (particularly among patients with concurrent CH mutations and anemia).[104,105] A randomized placebo-controlled clinical trial (NCT05641831) of canakinumab in patients with CCUS is currently underway and aims to determine whether canakinumab IL-1β inhibition can prevent or delay MN development (primary endpoint of time to MN). A recent small single-arm trial of canakinumab in lower-risk MDS demonstrated a modest 17% overall response rate, with all responders (N=4) having an IPSS-M score <0.[106]

The NLRP3 inflammasome pathway is aberrantly activated in many MN, leading to caspase-1-dependent secretion of the pro-inflammatory cytokines IL-1β and IL-18, which drive inflammation and ineffective hematopoiesis.[107] The small molecule NLRP3 inhibitor DFV890 is currently under investigation in low-risk MN including high-risk CCUS (NCT05552469) as well as *TET2*- and *DNMT3A*-mutant CHIP with coronary heart disease (NCT06097663).

Transforming growth factor-β/SMAD Inhibition

Luspatercept is a recombinant fusion protein composed of the extracellular domain of the activin receptor type IIB and the Fc domain of immunoglobulin G1 that is approved by the United States Food and Drug Administration for treating anemia in patients with low-risk MDS and β-thalassemia. It binds to multiple transforming growth factor-beta (TGF-β) superfamily ligands, resulting in inhibition of SMAD2 and SMAD3 signaling, which promotes effective maturation of erythroid progenitor cells.[108] Luspatercept is particularly efficacious for treating anemia due to MDS with *SF3B1* mutations and/or ring sideroblasts,[109] which is characterized by pronounced ineffective erythropoiesis and an indolent clinical course.[110] Interestingly, no change in the VAF of *SF3B1* or other somatic mutations has been observed in luspatercept responders compared with non-responders.[111] Additional clinical trials will be required to determine whether luspatercept has disease-modifying activity in MDS or CCUS. A clinical trial (NCT06788691) of luspatercept in patients with CCUS is ongoing.

CDK4/6 inhibition

Cyclin-dependent kinases 4 and 6 (CDK4/6) play a key role in cell cycle regulation, promoting progression through the G1/S checkpoint by phosphorylating retinoblastoma protein. CDK4/6 inhibitors are used widely in combination with endocrine therapy to treat hormone receptor-positive breast cancers, which are sensitive to the inhibitors due to intact retinoblastoma protein function and reliance on CDK4/6 signaling for cell cycle progression.[112] HSPC are also reliant on CDK4/6 activity for cell cycle progression and undergo transient G1 arrest after CDK4/6 inhibition.[113] Trilaciclib is a CDK4/6 inhibitor that was developed to protect HSPC from DNA damaging agent-induced myelosuppression by

inducing G1 arrest prior to administration of DNA damaging agents.[114] It is now FDA-approved for the prevention of chemotherapy-induced myelosuppression in patients with extensive-stage small cell lung cancer, a malignancy intrinsically resistant to CDK4/6 inhibition due to loss of retinoblastoma protein function, thereby explaining why trilaciclib does not compromise the antitumor efficacy of chemotherapy. Given the myeloprotective effects of trilaciclib, our group recently investigated the effect of trilaciclib on chemotherapy-related expansion of CH clones with DDR mutations (e.g., *TP53, PPM1D, CHEK2*). We found that trilaciclib reduced expansion of DDR CH by 32% when given prior to cytotoxic chemotherapy in four randomized clinical trials and in a *TP53*-mutant CH mouse model.[115]

Given the poor outcomes associated with therapy-related MN, strategies to mitigate cytotoxic chemotherapy-driven expansion of DDR CH, particularly *TP53*-mutant clones, are warranted and may reduce progression to therapy-related MN. A pragmatic approach is to quantify MN risk using validated clinical prediction models that integrate CH mutational data with routine laboratory parameters,[22,23,92] and to incorporate these individualized estimates when weighing the absolute benefit of adjuvant chemotherapy, whose survival advantage in some early-stage settings is modest, against long-term risk of therapy-related MN. CH status could also be determined from cell-free DNA assays already obtained as part of standard oncological care. Modeling analyses suggest that a subset of patients with early-stage breast cancer have a predicted MN risk that exceeds the expected absolute survival benefit from adjuvant chemotherapy (which frequently includes doxorubicin, a therapy associated with a high risk of MN), highlighting the potential utility of CH-based risk stratification to inform adjuvant treatment decisions.[49]

Hypomethylating agents

Hypomethylating agents such as decitabine have demonstrated efficacy in most MN, while maintaining a favorable safety profile. A clinical trial (NCT06802146) evaluating decitabine/cedazuridine (an oral formulation of decitabine) in patients with high-risk CCUS is ongoing.

Metformin

Metformin is widely used due to it being the first-line treatment for type 2 diabetes mellitus. It has a complex and incompletely understood mechanism of action that involves inhibition of hepatic gluconeogenesis and mitochondrial respiration.[89] A pair of preclinical studies from earlier this year demonstrated that the competitive advantage of murine *Dnmt3a* R878H HSPC is dependent on increased mitochondrial respiration and can be reduced by treatment with metformin.[116,117] Functional studies revealed that metformin treatment normalized the aberrant DNA methylation and gene expression profiles driven by *Dnmt3a* R878H. In addition, analysis of the UK Biobank showed that metformin use was associated with a lower prevalence of *DNMT3A* R882 CH. A small phase II clinical trial (NCT04741945) investigating metformin in patients with CCUS and low-risk MDS is ongoing.

Miscellaneous

Preclinical studies have demonstrated that statins can exert anti-cancer effects *in vitro*.[118] Statins also possess anti-inflammatory effects in addition to their lipid-lowering properties.[119] Observational data in MDS indicate that statin use is associated with improved overall survival and a reduced risk of progression to acute leukemia, as shown in a large retrospective database analysis employing propensity score matching.[120] These findings provided the impetus for a prospective clinical trial (NCT05483010), which is currently evaluating high-intensity statin therapy in patients with CCUS and low-risk MDS.

Curcumin, the active ingredient in turmeric, is a polyphenol with antioxidant and anti-inflammatory properties. It is currently being evaluated in a placebo-controlled clinical trial (NCT06063486) of patients with low-risk MN including CCUS. The primary endpoint of the study is the change in inflammatory cytokine levels and inflammation-related symptomatology.

Considerations on clinical trial design

Designing interventional trials for CH presents significant challenges. Because CH is a premalignant condition, potential interventions must be risk-informed and have a favorable toxicity profile. Trials should have clinically meaningful endpoints and avoid the overmedicalization of otherwise healthy individuals with low-risk CH features. To date, CH trials have largely focused on patients with CCUS; accordingly, the following discussion of clinical trial design considerations centers on this population. CCUS is particularly appropriate for interventional trials, as the risk of progression to MN among individuals with CH appears to reside almost entirely in those who develop a preceding cytopenia.[121]

Most CH trials have modeled their key endpoints from those used in low-risk MDS, such as hematologic improvement (Table 1). However, reductions in transfusion burden or infections are the only cytopenia-related outcomes recognized as clinically meaningful by the FDA in hematologic malignancies. Thus, studies that show improvement in neutropenia, for example, may not be considered “clinically meaningful”. The clinical relevance of currently accepted endpoints in studies of low-risk MDS remains under debate. For example, while there are multiple FDA-approved therapies for low-risk MDS that result in reduced transfusion burden, none has been prospectively shown to alter the natural history of the disease, such as improvement of overall survival.[122] Thus, it would be prudent for the CH field to learn from the persistent challenges faced in drug development for low-risk MDS[123] and design feasible studies that can demonstrate improvement in quality of life and the potential for disease modification.

Randomized, placebo-controlled trials with disease-free survival as the primary endpoint are the gold-standard for chemoprevention trials. However, this endpoint is limited by the natural history of CH, in which progression typically occurs over many years. Among healthy individuals in the UK Biobank, the 10-year risk of MN is approximately 52% for those with high-risk CH, a group that represents only 1% of individuals with CHIP/CCUS.[23] Intermediate-risk CH is more common (~10% of CHIP/CCUS), but only 8% of carriers progress to MN over a 10-year period.[23] Progression rates are higher among patients with CCUS evaluated at tertiary referral centers, but vary widely between studies ranging from ~20% at 4 years[92] to 95% at 10 years.[26] In addition, the absence of standard-of-care interventions may make participation in long-term placebo-controlled studies undesirable for some patients.[124]

Surrogate endpoints may enable more feasible trial designs but must be chosen carefully to ensure clinical relevance. Given that CH expansion is well-recognized to be part of the natural history of CH progression to MN, interventions that reduce the burden of high-risk CH clones (as reflected by VAF) should reduce MN development. However, the direct impact of a reduction in CH VAF on MN risk has not been measured in prospective trials. Furthermore, reductions in CH mutant VAF can be confounded by the variable distribution of CH-mutant cells across hematopoietic lineages, which in turn can fluctuate with clinical context (e.g., active infection).[125] However, the achievement of measurable residual disease negativity in hematologic malignancies is clearly associated with improved clinical outcomes across a variety of malignancies including chronic phase chronic myeloid leukemia, AML, acute lymphocytic leukemia, and multiple myeloma.[126] Thus, we believe that achievement of measurable residual disease negativity for high-risk CH clones represents a valid potential surrogate endpoint for MN prevention. This outcome is feasible for potent targeted therapies directed against high-risk CH mutations.

Finally, the inherent rarity of high-risk CHIP/CCUS, especially specific biological/molecular subtypes, poses significant challenges in recruiting study participants. Currently, screening for CH is not part of standard clinical practice. While targeted sequencing to identify somatic mutations in myeloid driver genes is increasingly common in the work-up of unexplained cytopenias, it is not uniformly applied. Thus, identification of individuals with high-risk forms of CH is challenging. Disease rarity combined with inefficiencies within the current clinical trial infrastructure and difficulties in securing interest from pharmaceutical industry partners for rare diseases make high-risk, gene-specific CH trials challenging to conduct. Decentralized clinical trials may represent an attractive approach for uncommon diseases. These trials are clinical studies in which some or all trial-related activities are conducted remotely using digital health technologies (e.g., telemedicine visits), instead of at a traditional centralized clinical research site (e.g., office visit at an academic medical center).[127] This model can reduce barriers to clinical trial participation including geographic distance, time toxicity, and financial burden. Hybrid versions can also be used which incorporate traditional design features (e.g. sample collection at local laboratories). Decentralized clinical trials are best suited for well-characterized therapies with good safety profiles used in relatively healthy patient populations with a low rate of serious adverse events.

In summary, to fully realize the potential of CH interventional studies to prevent MN, innovative and flexible clinical trial designs are needed. Rare diseases are subject to similar unique investigational and regulatory approaches.[128] High-risk CH should be included under this umbrella. Adoption of the rare disease regulatory paradigm including flexible evidence standards, and consideration of alternative data sources (including historic controls) will be needed to facilitate development and approval of therapies for individuals with high-risk CH. Encouragingly, the FDA has recognized the need to evolve its regulatory strategies for personalized therapies in rare diseases and recently announced plans for new drug development processes in this space, including the Plausible Mechanism Pathway and the Rare Disease Evidence Principles program.[129]

Conclusions

The CH field has made remarkable progress in the short time since the seminal studies by Jaiswal *et al.*[7] and Genovese *et al.*[6] were published in 2014. These investigations provided an unprecedented window into the earliest stages of carcinogenesis, elucidating how intrinsic, environmental, genetic, and acquired factors – often in a mutation-specific manner – govern CH initiation, clonal dynamics, and risk of progression to MN. Much of this progress has been driven by large-scale population (e.g., UK Biobank) and longitudinal sequencing studies, which are only feasible due to the unique ability to sample the hematopoietic system through peripheral blood draws. In turn, these discoveries have enabled the development of risk stratification models to identify individuals with CH at high risk of progression to MN, thereby opening the door for therapeutic intervention trials, which are now actively enrolling patients.

Despite these advances, significant unanswered questions remain. Key priorities for the field include defining the cell-intrinsic and -extrinsic mechanisms underlying the distinct clonal behaviors of specific driver mutations over time (particularly splicing factor mutations); elucidating the basis of hematopoietic oligoclonality that emerges with aging and its frequent association with CH lacking a known driver; and determining whether therapeutic intervention can alter the natural history of CH.

Moving forward, translating insights from CH biology into effective invention approaches will require careful balancing of the risk and benefits of intervention, as the absolute risk

of progression to MN is modest even among individuals with high-risk CH. Ultimately, these efforts will be essential for determining optimal clinical management of CH, which is increasingly being identified in clinical practice, and will deepen our understanding of early carcinogenesis in humans, regardless of the trial outcomes.

Disclosures

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Contributions

JSB, MJW and KLB conceived and wrote the manuscript.

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References

1. Yizhak K, Aguet F, Kim J, et al. RNA sequence analysis reveals macroscopic somatic clonal expansion across normal tissues. Science. 2019;364(6444):eaaw0726.
2. Martincorena I, Roshan A, Gerstung M, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 2015;348(6237):880-886.
3. Martincorena I, Fowler JC, Wabik A, et al. Somatic mutant clones colonize the human esophagus with age. Science. 2018;362(6417):911-917.
4. Laurie CC, Laurie CA, Rice K, et al. Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nat Genet. 2012;44(6):642-650.
5. Jacobs KB, Yeager M, Zhou W, et al. Detectable clonal mosaicism and its relationship to aging and cancer. Nat Genet. 2012;44(6):651-658.
6. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477-2487.
7. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488-2498.
8. Beeler JS, Bick AG, Bolton KL. Genetic causes and cardiovascular consequences of clonal hematopoiesis in the UK Biobank. Nat Cardiovasc Res. 2023;2(1):13-15.
9. Dunn WG, McLoughlin MA, Vassiliou GS. Clonal hematopoiesis and hematological malignancy. J Clin Invest. 2024;134(19):e180065.
10. Weeks LD, Ebert BL. Causes and consequences of clonal hematopoiesis. Blood. 2023;142(26):2235-2246.
11. Mitchell E, Spencer Chapman M, Williams N, et al. Clonal dynamics of haematopoiesis across the human lifespan. Nature. 2022;606(7913):343-350.
12. Kinde I, Wu J, Papadopoulos N, Kinzler KW, Vogelstein B. Detection and quantification of rare mutations with massively parallel sequencing. Proc Natl Acad Sci USA. 2011;108(23):9530-9535.
13. Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016;7(1):12484.
14. Young AL, Wong TN, Hughes AEO, et al. Quantifying ultra-rare pre-leukemic clones via targeted error-corrected sequencing. Leukemia. 2015;29(7):1608-1611.
15. Beeler JS, Bolton KL. How low can you go?: Methodologic considerations in clonal hematopoiesis variant calling. Leuk Res. 2023;135:107419.
16. Spira A, Yurgelun MB, Alexandrov L, et al. Precancer atlas to drive precision prevention trials. Cancer Res. 2017;77(7):1510-1541.
17. Niroula A, Sekar A, Murakami MA, et al. Distinction of lymphoid and myeloid clonal hematopoiesis. Nat Med. 2021;27(11):1921-1927.
18. Takahashi K, Wang F, Kantarjian H, et al. Copy number alterations detected as clonal hematopoiesis of indeterminate potential. Blood Adv. 2017;1(15):1031-1036.
19. Loh P-R, Genovese G, Handsaker RE, et al. Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations. Nature. 2018;559(7714):350-355.
20. Saygin C, Zhang P, Stauber J, et al. Acute lymphoblastic leukemia with myeloid mutations is a high-risk disease associated with clonal hematopoiesis. Blood Cancer Discov. 2024;5(3):164-179.
21. Liu J, Tran D, Xue L, et al. Germline genetic variation impacts clonal hematopoiesis landscape and progression to malignancy. Nat Genet. 2025;57(8):1872-1880.
22. Gu M, Kovilakam SC, Dunn WG, et al. Multiparameter prediction of myeloid neoplasia risk. Nat Genet. 2023;55(9):1523-1530.
23. Weeks LD, Niroula A, Neuberg D, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid. 2023;2(5):10.1056/evidoa2200310.
24. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
25. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
26. Malcovati L, Gallì A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371-3378.
27. Zink F, Stacey SN, Norddahl GL, et al. Clonal hematopoiesis, with and without candidate driver mutations, is common in the elderly. Blood. 2017;130(6):742-752.
28. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
29. Nordling CO. A new theory on cancer-inducing mechanism. Br J Cancer. 1953;7(1):68-72.
30. Armitage P, Doll R. The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer. 1954;8(1):1-12.
31. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-767.
32. Cancer Genome Atlas Research Network; Weinstein JN, Collisson EA, Mills GB, et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013;45(10):1113-1120.
33. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.

34. Hoang ML, Kinde I, Tomasetti C, et al. Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing. Proc Natl Acad Sci U S A. 2016;113(35):9846-9851.
35. Blokzijl F, de Ligt J, Jager M, et al. Tissue-specific mutation accumulation in human adult stem cells during life. Nature. 2016;538(7624):260-264.
36. Dzierzak E, Philipsen S. Erythropoiesis: development and differentiation. Cold Spring Harb Perspect Med. 2013;3(4):a011601.
37. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol. 2010;31(8):318-324.
38. Watson CJ, Papula AL, Poon GYP, et al. The evolutionary dynamics and fitness landscape of clonal hematopoiesis. Science. 2020;367(6485):1449-1454.
39. Williams N, Lee J, Mitchell E, et al. Life histories of myeloproliferative neoplasms inferred from phylogenies. Nature. 2022;602(7895):162-168.
40. Van Egeren D, Escabi J, Nguyen M, et al. Reconstructing the lineage histories and differentiation trajectories of individual cancer cells in myeloproliferative neoplasms. Cell Stem Cell. 2021;28(3):514-523.e9.
41. Kar SP, Quiros PM, Gu M, et al. Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis. Nat Genet. 2022;54(8):1155-1166.
42. Uddin MM, Saadatagah S, Niroula A, et al. Long-term longitudinal analysis of 4,187 participants reveals insights into determinants of clonal hematopoiesis. Nat Commun. 2024;15(1):7858.
43. Kamphuis P, van Zeventer IA, de Graaf AO, et al. Sex differences in the spectrum of clonal hematopoiesis. Hemasphere. 2023;7(2):e832.
44. Lin S-H, Brown DW, Rose B, et al. Incident disease associations with mosaic chromosomal alterations on autosomes, X and Y chromosomes: insights from a phenome-wide association study in the UK Biobank. Cell Biosci. 2021;11(1):143.
45. Valcarcel B, Schonfeld SJ, Jackson SS, Dores GM, Linet MS, Morton LM. Changes in sex-specific incidence of lymphoid neoplasms across the lifespan. Haematologica. 2024;109(10):3408-3413.
46. Daltveit DS, Morgan E, Colombet M, et al. Global patterns of leukemia by subtype, age, and sex in 185 countries in 2022. Leukemia. 2025;39(2):412-419.
47. Dunford A, Weinstock DM, Savova V, et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat Genet. 2017;49(1):10-16.
48. Zhang C, Hao T, Bortoluzzi A, et al. Sex-dependent differences in hematopoietic stem cell aging and leukemogenic potential. Oncogene. 2025;44(2):64-78.
49. Bolton KL, Ptashkin RN, Gao T, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 2020;52(11):1219-1226.
50. Gelsi-Boyer V, Trouplin V, Adélaïde J, et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. Br J Haematol. 2009;145(6):788-800.
51. Alexandrov LB, Nik-Zainal S, Wedge DC, Campbell PJ, Stratton MR. Deciphering signatures of mutational processes operative in human cancer. Cell Rep. 2013;3(1):246-259.
52. Alexandrov LB, Ju YS, Haase K, et al. Mutational signatures associated with tobacco smoking in human cancer. Science. 2016;354(6312):618-622.
53. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21(3):374-382.e4.
54. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. 2015;518(7540):552-555.
55. Hagiwara K, Natarajan S, Wang Z, et al. Dynamics of age- versus therapy-related clonal hematopoiesis in long-term survivors of pediatric cancer. Cancer Discov. 2023;13(4):844-857.
56. Goglia AG, Mustion G, Modlin LA, Levine RL, Bolton KL, Braunstein LZ. Impact of radiotherapy site, modality, and dose on subsequent clonal hematopoiesis. Blood Adv. 2025;9(21):5564-5567.
57. Vande Berg BC, Malghem J, Lecouvet FE, Maldague B. Magnetic resonance imaging of the normal bone marrow. Skeletal Radiol. 1998;27(9):471-483.
58. Tsai FD, Lindsley RC. Clonal hematopoiesis in the inherited bone marrow failure syndromes. Blood. 2020;136(14):1615-1622.
59. Kennedy AL, Myers KC, Bowman J, et al. Distinct genetic pathways define pre-malignant versus compensatory clonal hematopoiesis in Shwachman-Diamond syndrome. Nat Commun. 2021;12(1):1334.
60. Schratz KE, Gaysinskaya V, Cosner ZL, et al. Somatic reversion impacts myelodysplastic syndromes and acute myeloid leukemia evolution in the short telomere disorders. J Clin Invest. 2021;131(18):e147598.
61. Schratz KE. Clonal evolution in inherited marrow failure syndromes predicts disease progression. Hematology Am Soc Hematol Educ Program. 2023;2023(1):125-134.
62. Homan CC, Drazer MW, Yu K, et al. Somatic mutational landscape of hereditary hematopoietic malignancies caused by germline variants in RUNX1, GATA2, and DDX41. Blood Adv. 2023;7(20):6092-6107.
63. Kessler MD, Damask A, O'Keeffe S, et al. Common and rare variant associations with clonal haematopoiesis phenotypes. Nature. 2022;612(7939):301-309.
64. Bick AG, Weinstock JS, Nandakumar SK, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature. 2020;586(7831):763-768.
65. DeBoy EA, Tassia MG, Schratz KE, et al. Familial clonal hematopoiesis in a long telomere syndrome. N Engl J Med. 2023;388(26):2422-2433.
66. Liu J, Osman AEG, Bolton K, Godley LA. Germline predisposition to clonal hematopoiesis. Leuk Res. 2023;132:107344.
67. Weinstock JS, Gopakumar J, Burugula BB, et al. Aberrant activation of TCL1A promotes stem cell expansion in clonal haematopoiesis. Nature. 2023;616(7958):755-763.
68. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic mutations and clonal hematopoiesis in aplastic anemia. N Engl J Med. 2015;373(1):35-47.
69. Fabre MA, de Almeida JG, Fiorillo E, et al. The longitudinal dynamics and natural history of clonal haematopoiesis. Nature. 2022;606(7913):335-342.
70. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell. 2010;18(6):553-567.
71. Morita K, Wang F, Jahn K, et al. Clonal evolution of acute myeloid leukemia revealed by high-throughput single-cell genomics. Nat Commun. 2020;11(1):5327.
72. Poon G, Vedi A, Sanders M, Laurenti E, Valk P, Blundell JR.

Single-cell DNA sequencing reveals pervasive positive selection throughout preleukemic evolution. Cell Genom. 2025;5(2):100744.
73. McLoughlin MA, Cheloor Kovilakam S, Dunn WG, et al. Telomere attrition becomes an instrument for clonal selection in aging hematopoiesis and leukemogenesis. Nat Genet. 2025;57(9):2215-2225.
74. Saez B, Walter MJ, Graubert TA. Splicing factor gene mutations in hematologic malignancies. Blood. 2017;129(10):1260-1269.
75. Lee SC-W, North K, Kim E, et al. Synthetic lethal and convergent biological effects of cancer-associated spliceosomal gene mutations. Cancer Cell. 2018;34(2):225-241.e8.
76. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. Blood. 2020;136(2):157-170.
77. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
78. Grinfeld J, Nangalia J, Baxter EJ, et al. Classification and personalized prognosis in myeloproliferative neoplasms. N Engl J Med. 2018;379(15):1416-1430.
79. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016;122(23):3673-3681.
80. Vagher J, Zakas A, Donovan L, et al. Hematologic malignancy frequency, phenotypes, and outcomes in Li-Fraumeni syndrome. JCO Precis Oncol. 2025;9:e2400860.
81. Hsu JI, Dayaram T, Tovy A, et al. PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. Cell Stem Cell. 2018;23(5):700-713.e6.
82. Sperling AS, Guerra VA, Kennedy JA, et al. Lenalidomide promotes the development of TP53-mutated therapy-related myeloid neoplasms. Blood. 2022;140(16):1753-1763.
83. Marcellino BK, Farnoud N, Cassinat B, et al. Transient expansion of TP53 mutated clones in polycythemia vera patients treated with idasanutlin. Blood Adv. 2020;4(22):5735-5744.
84. Quiros PM, Gu M, Barcena C, Iyer V, Vassiliou GS. NPM1 gene mutations can be confidently identified in blood DNA months before de novo AML onset. Blood Adv. 2022;6(7):2409-2413.
85. Luque Paz D, Kralovics R, Skoda RC. Genetic basis and molecular profiling in myeloproliferative neoplasms. Blood. 2023;141(16):1909-1921.
86. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616-3627; quiz 3699.
87. Makishima H, Saiki R, Nannya Y, et al. Germ line DDX41 mutations define a unique subtype of myeloid neoplasms. Blood. 2023;141(5):534-549.
88. Verma A, Lupo PJ, Shah NN, Hitzler J, Rabin KR. Management of Down syndrome-associated leukemias: a review. JAMA Oncol. 2023;9(9):1283-1290.
89. Roberts I, Alford K, Hall G, et al. GATA1-mutant clones are frequent and often unsuspected in babies with Down syndrome: identification of a population at risk of leukemia. Blood. 2013;122(24):3908-3917.
90. Florez MA, Tran BT, Wathan TK, DeGregori J, Pietras EM, King KY. Clonal hematopoiesis: mutation-specific adaptation to environmental change. Cell Stem Cell. 2022;29(6):882-904.
91. Tran D, Beeler JS, Liu J, et al. Plasma proteomic signature predicts myeloid neoplasm risk. Clin Cancer Res. 2024;30(15):3220-3228.
92. Xie Z, Komrokji R, Al Ali N, et al. Risk prediction for clonal cytopenia: multicenter real-world evidence. Blood. 2024;144(19):2033-2044.
93. Tahiliani M, Koh KP, Shen Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science. 2009;324(5929):930-935.
94. Cimmino L, Dolgalev I, Wang Y, et al. Restoration of TET2 function blocks aberrant self-renewal and leukemia progression. Cell. 2017;170(6):1079-1095.e20.
95. Agathocleous M, Meacham CE, Burgess RJ, et al. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature. 2017;549(7673):476-481.
96. Xie Z, Fernandez J, Lasho T, et al. High-dose IV ascorbic acid therapy for patients with CCUS with TET2 mutations. Blood. 2024;144(23):2456-2461.
97. Bolton KL, Madanat Y, Chandhok N, et al. Ivosidenib leads to durable responses in IDH1 mutated clonal cytopenias of undetermined significance: a phase II decentralized clinical trial. Blood. 2025;146(Supplement 1):635.
98. Avagyan S, Zon LI. Clonal hematopoiesis and inflammation - the perpetual cycle. Trends Cell Biol. 2023;33(8):695-707.
99. Villaume MT, Savona MR. Pathogenesis and inflammaging in myelodysplastic syndrome. Haematologica. 2025;110(2):283-299.
100. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842-847.
101. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111-121.
102. Caiado F, Kovtonyuk LV, Gonullu NG, Fullin J, Boettcher S, Manz MG. Aging drives Tet2+/- clonal hematopoiesis via IL-1 signaling. Blood. 2023;141(8):886-903.
103. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-1131.
104. Svensson EC, Madar A, Campbell CD, et al. TET2-driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial. JAMA Cardiol. 2022;7(5):521-528.
105. Woo J, Lu D, Lewandowski A, et al. Effects of IL-1β inhibition on anemia and clonal hematopoiesis in the randomized CANTOS trial. Blood Adv. 2023;7(24):7471-7484.
106. Rodriguez-Sevilla JJ, Adema V, Chien KS, et al. The IL-1β inhibitor canakinumab in previously treated lower-risk myelodysplastic syndromes: a phase 2 clinical trial. Nat Commun. 2024;15(1):9840.
107. Basiorka AA, McGraw KL, Eksioglu EA, et al. The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. Blood. 2016;128(25):2960-2975.
108. Suragani RNVS, Cadena SM, Cawley SM, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014;20(4):408-414.
109. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017;18(10):1338-1347.
110. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. Blood.

2020;136(2):157-170. Erratum: Blood 2021;137(21):3003.
111. Kubasch AS, Fenaux P, Platzbecker U. Development of luspatercept to treat ineffective erythropoiesis. Blood Adv. 2021;5(5):1565-1575.
112. Morrison L, Loibl S, Turner NC. The CDK4/6 inhibitor revolution - a game-changing era for breast cancer treatment. Nat Rev Clin Oncol. 2024;21(2):89-105.
113. Johnson SM, Torrice CD, Bell JF, et al. Mitigation of hematologic radiation toxicity in mice through pharmacological quiescence induced by CDK4/6 inhibition. J Clin Invest. 2010;120(7):2528-2536.
114. Bisi JE, Sorrentino JA, Roberts PJ, Tavares FX, Strum JC. Preclinical characterization of G1T28: a novel CDK4/6 inhibitor for reduction of chemotherapy-induced myelosuppression. Mol Cancer Ther. 2016;15(5):783-793.
115. Chan I, Zhang P, Pan X, et al. CDK4/6 inhibition mitigates chemotherapy-induced expansion of TP53-mutant clonal hematopoiesis. Blood. 2025;146(Supplement 1):4.
116. Gozdecka M, Dudek M, Wen S, et al. Mitochondrial metabolism sustains DNMT3A-R882-mutant clonal haematopoiesis. Nature. 2025;642(8067):431-441.
117. Hosseini M, Voisin V, Chegini A, et al. Metformin reduces the competitive advantage of Dnmt3aR878H HSPCs. Nature. 2025;642(8067):421-430.
118. Brendolan A, Russo V. Targeting cholesterol homeostasis in hematopoietic malignancies. Blood. 2022;139(2):165-176.
119. Weitz-Schmidt G. Statins as anti-inflammatory agents. Trends Pharmacol Sci. 2002;23(10):482-486.
120. Afzal A, Fiala MA, Jacoby MA, Walter MJ. Statin use in myelodysplastic syndromes is associated with a better survival and decreased progression to leukemia. Blood Adv. 2023;7(15):3838-3841.
121. Brogan J, Kishtagari A, Corty RW, et al. Incident cytopenia and risk of subsequent myeloid neoplasm in age-related clonal hematopoiesis: a multi-biobank case-control study. EClinicalMedicine. 2025;84:103283.
122. Sekeres MA, Taylor J. Diagnosis and treatment of myelodysplastic syndromes: a review. JAMA. 2022;328(9):872-880.
123. Mina A, McGraw KL, Cunningham L, et al. Advancing drug development in myelodysplastic syndromes. Blood Adv. 2025;9(5):1095-1104.
124. Johnston K, Bolding S, Carlson C, Wentworth K, Merikle E. PCR127 a targeted literature review of patient perspectives of placebo use in clinical trials: how can the patient voice help drug developers in trial design, recruitment, and retention? Value in Health. 2025;28(6):S333-S334.
125. Parker AC, Van Amburg JC, Heimlich JB, et al. Methylation sequencing enhances interpretation of clonal hematopoiesis dynamics. Blood. 2025;145(9):988-992.
126. Chandhok NS, Sekeres MA. Measurable residual disease in hematologic malignancies: a biomarker in search of a standard. EClinicalMedicine. 2025;86:103348.
127. Underhill C, Freeman J, Dixon J, et al. Decentralized clinical trials as a new paradigm of trial delivery to improve equity of access. JAMA Oncol. 2024;10(4):526-530.
128. Subbiah V, Curigliano G, Sicklick JK, et al. Cancer treatment paradigms in the precision medicine era. Nat Med. 2025;31(11):3609-3611.
129. Prasad V, Makary MA. FDA's new plausible mechanism pathway. N Engl J Med. 2025;393(23):2365-2367.