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Clinical decisions in clonal hematopoiesis: a contemporary review for clinicians

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Author Contributions

A.B. conceptualized the study and wrote the original draft of the manuscript. R.V., A.G.X.Z., R.H.K., and S.C. critically reviewed the manuscript and provided significant intellectual input. All authors approved the final revised version of the manuscript.

Abstract

Clonal hematopoiesis (CH) has emerged as a critical mediator of age-associated diseases, with far-reaching implications for hematologic malignancies, cardiovascular diseases, cancer therapy, autoimmune disorders, and other health conditions. This review synthesizes the current evidence supporting the integration of CH testing and monitoring into clinical practice, with a focus on translating scientific discoveries into actionable diagnostic and therapeutic strategies. We present a systematic framework for establishing and operating a dedicated CH program, drawing on institutional experience and evolving best practices. Our analysis encompasses risk stratification approaches, surveillance protocols, and intervention timing for various CH-associated conditions. Special attention is given to the challenges and opportunities in implementing CH screening within existing clinical workflows, including considerations for genetic counseling, interdisciplinary coordination, and patient education. By providing practical insights and evidence-based recommendations, this review aims to serve as a roadmap for healthcare institutions looking to develop comprehensive CH management programs that bridge the gap between molecular discoveries and clinical care delivery.

Keywords: Clonal hematopoiesis, CHIP, CCUS, myeloid neoplasms, inflammation, aging, cardiovascular disease, risk prediction, clinical workflow

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Introduction to Clonal Hematopoiesis and its Various Forms

Case Vignette #1: Incidental Finding and Initial Classification
A 78-year-old male, with a history of prostate cancer in remission, underwent comprehensive genetic sequencing as part of a clinical trial for germline cancer predisposition. Unexpectedly, the results showed a somatic mutation in *DNMT3A* with a Variant Allele Frequency (VAF) of 2.8%. His complete blood counts (CBC) are within normal limits. The referring oncologist is unsure how to interpret this finding and whether it requires specific follow-up. This case highlights the increasing prevalence of incidental CH findings, particularly in an aging population and those undergoing broad genetic screening, posing a challenge for initial classification and risk assessment.

CH Definition

Clonal hematopoiesis (CH) is defined as the proliferation of hematopoietic stem and progenitor cells (HSPCs) with *somatic* mutations in the absence of overt hematologic malignancy[1]. CH is an age-related phenomenon, its prevalence increasing markedly with age, affecting up to 60% of people aged ≥ 80 years[2] and up to 40% of healthy volunteers ≥ 50 years[3]. The variability in the reported prevalence of CH is mainly explained by the use of different sequencing platforms and variant call criteria. CH has now been shown to have biologically plausible and clinically important implications in solid and hematologic malignancies, cardiovascular diseases, autostructural disorders, thrombosis, osteoporosis, pulmonary hypertension, structural dysregulation, impaired tissue regeneration, and overall mortality[4–8]. The increasing detection of CH through comprehensive genetic tests in both oncology and non-oncology scenarios poses a formidable challenge for the clinical management of CH in the absence of approved therapeutic interventions. This review will address bench-to-bedside applications of current evidence for the management of CH and clonal cytopenia of unknown significance (CCUS).

CH Detection and Classification

Clinical decision-making for CH patients is fundamentally dependent on detection and quantification using VAF- the proportion of mutated DNA sequence reads compared to total reads. Variant detection and confidence depends on the sequencing modality applied and source of DNA tested. Different bioinformatics protocols can produce discordant results from the same data, with up to a 30% variability[9]. Standard sequencing tools used for germline or high-VAF tumors often lack sensitivity for low-frequency CH variants[10]. Clinical screening for CH should therefore employ purpose-built next-generation sequencing (NGS) panels—such as those based on single-molecule molecular inversion probes (smMIPs)[11]—that incorporate validated strategies including unique molecular identifiers, error-corrected sequencing, and integration with reference datasets, in order to enhance sensitivity, reduce false positives, and ensure reliable detection and annotation of low-frequency CH variants (Table 1). These should be adaptable to expand target genes and chromosomal regions as our knowledge of CH grows. The interpretation of CH in the context of targeted panel versus whole-exome/genome sequencing also requires specific consideration. Panel-based techniques may fail to detect significant mutations that lie beyond the targeted regions, while more expansive sequencing methods are challenged by increased computational demands and a higher likelihood of false-positive findings, and higher likelihood of false negatives due to lower sequencing depth[12]. Consequently, the selection of a sequencing strategy should be consistent with the evidence base and clinical objectives, taking into account the balance between comprehensive coverage and analytical precision.

Classification of CH is important for prognostication and standardization for clinical trial enrollment. Current classification is based on VAF and blood count indices, encompassing several distinct forms:

- Clonal Hematopoiesis of Indeterminate Potential (CHIP): Defined by the presence of a somatic mutation in a hematological malignancy-associated driver gene (historically with a VAF ≥ 2%) in individuals without abnormal blood cell counts or overt hematologic disease[1, 13]. It is important to emphasize that CHIP is condition and not yet a "disease", as its definition excludes persistent cytopenia and overt pathology associated with the somatic lesion[13].

- Age-Related Clonal Hematopoiesis (ARCH): This term describes the presence of any detectable CH associated with aging, irrespective of VAF, and encompasses clones with VAF below 2%[13].

- micro-CH (or micro-CHIP): Although not formally recognized, the term “micro-CH” is occasionally employed to describe low-abundance clones identified through highly sensitive sequencing methods, typically with VAFs below the conventional 2% threshold used for CHIP[14]. While these clones are subsumed under the ARCH category, the term “micro-CH” specifically emphasizes their low abundance and the advanced detection techniques necessary for their identification. Despite their small size, such clones may hold clinical significance due to their potential for expansion or association with disease risk[15].

- Myeloid Clonal Hematopoiesis of Indeterminate Potential (M-CHIP): Specifically refers to CHIP with somatic mutations in myeloid neoplasm driver genes (e.g., *DNMT3A, TET2, ASXL1, JAK2, TP53*), which primarily increase the risk of myeloid malignancies[16].

- Lymphoid Clonal Hematopoiesis of Indeterminate Potential (L-CHIP): Defined by recurrent somatic mutations that increase the risk of lymphoid malignancy[16]. L-CHIP is often associated with mutations in genes such *PAX5, IKZF1, ID3*, and *NOTCH1*. While some of these mutations are distinct to L-CHIP, mutations common in M-CHIP—like those in *DNMT3A* and *TET2* —may also appear in the lymphoid lineage and impact its pathogenesis[16]. Overall, driver mutations influencing CH and lymphoid biology span a wide range of genes, including those involved in transcriptional regulation and signaling pathways relevant to lymphoid cells.

- Clonal Cytopenia(s) of Undetermined Significance (CCUS): Diagnosed when CH driver mutation is identified alongside one or more persistent (≥ 4 months) cytopenias that are otherwise unexplained by hematologic or non-hematologic conditions, and do not meet diagnostic criteria for defined myeloid neoplasms (MNs)[17]. The definition of cytopenia is as per ICC criteria: any one of the following lasting for ≥ 4 months- hemoglobin (Hb) <13 g/dL in males and <12 g/dL in females, absolute neutrophil count (ANC) of $<1.8 \times 10^9$/L, and platelets of $<150 \times 10^9$/L[17].

- Therapy-Related Clonal Cytopenia(s) of Undetermined Significance (t-CCUS): This term describes CCUS that develops in patients with CH following cancer therapies including chemotherapy, external radiation therapy, radioligand therapy, immunotherapy or cellular therapy. where CH clones tend to expand under therapeutic pressure and inflammatory conditions.

- Mosaic Chromosomal Alterations (mCAs): These are large structural somatic mutations (greater than 1 megabase) involving gains (+), losses (-), or copy-neutral losses of heterozygosity (=) that cause CH[18]. mCAs are a common type of clonal hematopoiesis[18]. They can predispose to lymphoid malignancies such as chronic lymphocytic leukemia (CLL) and myeloid neoplasms. mCAs often occur in conjunction with CH driver mutations, frequently causing bi-allelic alterations in the driver gene. Individuals with mCAs have a twofold increase in all-cause mortality[18].

- Loss of X (LoX) and Loss of Y (LoY) Chromosomes: These are specific types of sex chromosome mCAs, representing common forms of mCAs, and have been well-characterized and most frequently detected copy number alterations. In particular, mLoY is associated with significantly worse overall survival and higher risk both of hematologic and solid cancers[18]. Often considered an alteration, mLoY has also been associated with an increased risk of Alzheimer’s disease (AD)[19].

The VAF thresholds used for classifying CH are without biological demarcation[20]. Pathogenic implications are observable across varying VAF ranges with most correlations increasing in severity and significance with increasing VAF. The ≥ 2% VAF threshold for CH reflects the limits of detection of exome sequencing technologies used in landmark studies[1, 4] and a subjective clinically relevant mutant blood cell fraction of at least 4%, assuming a copy number neutral variant on a somatic chromosome. Pathogenic implications are observable across varying VAF ranges, with a strong dose responsiveness, as risk of hematological malignancy and negative non-hematological outcomes are significantly greater beyond mutant VAF >10%[21].

Resolution of Vignette #1: This finding would be classified as M-CHIP given the VAF (> 2%) and absence of cytopenias. However, given this was incidentally detected on a hereditary predisposition panel, the patient should ideally undergo CH screening using pupose-built NGS panels such as smMIP to evaluate for presence of additional CH variants. If no further variants were identified, then given the low risk of an isolated *DNMT3A* driver mutation, ongoing surveillance for this form of CH is not currently indicated.

Mitigating Factors Impacting CH VAF Calculations during Clinical Consults for CH

Case Vignette #2: Interpreting Ambiguous VAF in a Patient with Suspected Myelodysplastic Syndrome A 68-year-old male is undergoing workup for progressive macrocytic anemia and mild thrombocytopenia, raising suspicion for myelodysplastic syndrome (MDS). Initial targeted NGS of his peripheral blood reveals a *TET2* mutation with a VAF of 45%. This unusually high VAF coupled with his cytopenias, prompts concern for potential myeloid neoplasm with loss of heterozygosity (LOH) or a germline variant. The clinical challenge is to accurately interpret this VAF: does it reflect a large malignant clone, or is it inflated by a complicating genomic event, or is it a constitutional finding? The true challenge for clinicians is to determine the true clonal burden in the context of technical or biological factors that impact VAF calculations

Loss of Heterozygosity and Copy Number Variations

VAF's relationship to actual clone size should follow basic genetic principle, where in a heterozygous mutation with a VAF of 1% typically indicates approximately 2% cells harbor the CH mutation[22]. Yet, this relationship extends beyond the simple heterozygous model as several genetic and technical factors significantly impact VAF interpretation. LOH events can lead to overestimation of VAF values as the wild-type allele is lost in cells affected with CH[23]. For instance, if the observed VAF for a CH mutation is 50%, this could reflect a heterozygous mutation present in 100% of cells, or it could be a CH mutation with concurrent LOH present in 50% of cells. Similarly, in Copy number variations (CNV), amplification of the mutant CH allele increases VAF disproportionately to clone size, while deletion events may artificially lower VAF readings[24].

Resolution of Vignette #2: A *TET2* VAF of 45% presents a specific diagnostic triage. While the standard heterozygous model suggests a large dominant clone involving ≈ 90% of nucleated cells ($VAF \times 2$), accurate interpretation requires ruling out two critical 'mimics' that alter the VAF-to-clone-size relationship:

1. Step 1: Rule out Germline variant: A VAF approaching 50% is the hallmark of germline inheritance. Therefore, germline databases such as GnomAD and ClinVar should be queried to determine the variant's population allele frequency and established pathogenicity. Previously documented germline variants, and or those established as non-pathogenic, are more likely to be of germline origin. While *TET2* mutations are predominantly somatic, a germline variant and potential constitutional

syndrome can be excluded by analyzing DNA extracted from non-hematopoietic tissue such as fingernail clippings, cultured fibroblasts, or hair follicles.

2. Step 2: Genomic context (LOH/CNV): Order chromosomal microarray (SNP-array) or karyotype to assess chromosome 4q

    - Copy-Neutral LOH: If acquired uniparental disomy occurs at 4q24, cells become homozygous for the mutation. In this scenario, a 45% VAF reflects a 45% clone (homozygous) rather than a 90% clone (heterozygous).
    - Deletion: Deletion of the wild-type allele (e.g., del(4q)) artificially inflates VAF readings relative to the actual disease burden.

    If this work-up confirms germline variant, investigate for other causes of cytopenias. If this is somatic variant with LOH, proceed with bone marrow studies to categorize this as CCUS or MDS.

Germline variants, Somatic Mosaicism

Case Vignette #3: Distinguishing a *TP53* Variant in a Young Adult
A 38-year-old female undergoes genomic profiling due to a diagnosis of early-breast cancer, with a strong family history of early-onset cancers. Initial sequencing of her peripheral blood reveals a *TP53* variant at a VAF of 32%. This finding is immediately concerning due to the known association of *germline TP53* mutations with Li-Fraumeni Syndrome. However, the intermediate VAF raises questions: Is this a true germline mutation? Could it be a high-level somatic mosaicism event originating *early* in development? Or is a CH clone in a younger individual? The clinical challenge lies in accurately distinguishing between these possibilities, as the implications for her, and potentially her family, differ significantly, necessitating further exploration of the variant's origin.

Germline variants are present in the egg or sperm prior to fertilization, or arise in the zygote, and thus affect all of an individual's cells. They appear at VAFs of approximately 50% (heterozygous) or 100% (homozygous) across all tissues. In contrast, somatic mosaicism arises from a mutation that occurs post-zygotically, from early embryonic events through to adulthood. Somatic variants are restricted to the descendants of the original mutant cell. When a somatic variant arises very early in embryonic development, distinct affected cell populations may coexist across primary germ layers endoderm, mesoderm, and ectoderm. These variants can present with intermediate VAFs (e.g., 20–40%). CH is a form of somatic mosaicism that can reach similar VAF thresholds to early embryonic events, but is confined to a subset of HSCs and their progeny[25, 26]. To accurately distinguish between a germline variant, early somatic mosaicism, and CH, paired sequencing of DNA from non-hematopoietic tissue (e.g., fingernail clippings, hair or fibroblasts) is recommended[27]. Orthogonal validation of the variant and its VAF using an independent assay (such as droplet digital PCR or Sanger sequencing) may be instructive[28]. Clarifying this ambiguity is particularly important with common germline variants that are also somatically mutated in CH (Table 2). Distinguishing between CH and germline variants or early somatic events present in paired, non-hematologic DNA testing can help avoid unnecessary family testing or delayed diagnosis and preventive care for an inherited cancer predisposition syndrome. However, the heterogeneous nature of early somatic mosaic events means that a degree of uncertainty due to potential false negative testing from sampling bias remains.

Approach to Vignette #3: Resolving the *TP53* Ambiguity

- Gold standard: paired sequencing of non-hematopoietic DNA from distinct germ layers (e.g., skin fibroblasts/hair follicles for ectoderm) compared with peripheral blood. Sequence fibroblast DNA from a skin punch biopsy.

- Avoid Buccal Swabs: Contaminated with leukocytes and produce false-positive "germline" results when CH burden is high.
- Interpretation of Results:
  - Positive in Non-Heme Tissue: Indicates germline predisposition or early embryonic somatic mosaicism, requiring genetic counseling and Li-Fraumeni surveillance.
  - Negative in Non-Heme Tissue: consistent with CH diagnosis, though risk of false-negative due to sampling bias remains.

Workup of a New Patient in Clinic / Testing and Diagnosis

Case Vignette #4: Unexplained Cytopenia in an Elderly Patient
A 74-year-old female presents with a 6-month history of progressive fatigue and dyspnea on exertion. Her CBC reveals normocytic anemia (Hb 95 g/L), mild thrombocytopenia (platelets 110 × 10^9/L), and normal WBC count. Extensive workup for iron deficiency, vitamin deficiencies, renal insufficiency, and autostructural conditions is negative. NGS panel testing identifies a somatic *SF3B1* mutation with a VAF of 12%. The genomic report classified this variant as a Tier II variant due to its known prognostic relevance in myeloid neoplasms. How to integrate this molecular finding with her persistent cytopenias to differentiate between clonal cytopenia of undetermined significance (CCUS), early myelodysplastic syndrome (MDS), or another underlying etiology for her cytopenia?

Clinical Interpretation of CH Variants

Open-access or subscription-based annotated databases (see Table 3) are routinely helpful in CH clinic workflow to support variant clinical interpretation, particularly in distinguishing true somatic pathogenic variants from sequencing artifacts or low-confidence variant calls. These challenges are often compounded by technical limitations such as high GC content in some genetic loci and repetitive sequences, which impair the reliable detection of key CH-associated genes like *ASXL1* and *TET2* [15, 29]. To aid clinical decision-making despite these limitations, the AMP/ASCO/CAP 2021 framework[30] classifies somatic variants by clinical significance rather than pathogenicity, using a four-tier system; in CH, recurrent mutations and genuine pathogenic, CH-driver variants in genes such as *DNMT3A*, *TET2*, and *TP53* may fall under Tier II due to their prognostic relevance, even when not traditionally actionable.

Further, when multiple CH variants are detected, understanding clonal dynamics and subclonal architecture is essential, as traditional variant calling treats mutations as independent events. Single cell sequencing studies[31] and advanced computational methods[32] such as PyClone[33], SciClone[34], and PhylogicNDT[35] have shown that many CH cases harbor complex subclonal hierarchies, with distinct temporal and evolutionary relationships between mutations that affects risk stratification and longitudinal monitoring. However, these methods and computational tools are currently research-only. Such complexity is especially relevant when CH mutations co-occur with cytopenias or cytoses, which may lead to diagnostic ambiguity and misclassification of CH as a myeloid neoplasm (MN). It is therefore critical to integrate genetic, clinical, and morphological data—rather than relying solely on sequencing to differentiate CH from early-stage MNs[36]. Similarly, standardization and internal controls are crucial for consistent longitudinal monitoring and for enhancing the consistency of results across laboratories.

Bone Marrow Biopsy Recommendations

Bone marrow examinations in CH are indispensable in patients with CCUS, t-CCUS or cytosis and are usually performed when high-risk mutations are detected even without CBC abnormalities. This may lead to early diagnosis of MN. However, interpreting post-treatment dysplasia in t-CCUS requires meticulous discrimination, as iatrogenic effects or reactive processes can phenocopy true MDS features.

Serial bone marrow assessments may be required to differentiate reversible treatment-related changes from bona-fide clonal dysplastic evolution. This approach refines diagnostic classification across the spectrum of CH or MN, however, it can be challenging to interpret in patients who remain on cancer therapy for a non-hematological tumour. . Moreover, longitudinal bone marrow analyses permit the assessment of evolving VAF and the detection of clonal evolution, both of which could guide prognostic stratification and therapeutic interventions.

CH interpretation in patients with Solid Tumors

An interesting clinical aspect of CH is its implications for patients with solid tumors (ST) who represent major fraction of CH clinic referrals. Liquid biopsy/circulating cell-free DNA (cfDNA) has become an integral component in prognostic assessment and determination of therapeutic strategies for ST[37]. Such sequencing panels for ST liquid biopsies or tumor-only sequencing often identify CH variants that upon careful investigation could have been derived from peripheral blood leukocytes reflecting CH rather than a tumor variant. This confounds the analysis of cfDNA and tumor-only sequencing. The presence of tumor-infiltrating CH (TI-CH) in ST also presents a challenge in differentiating tumor-associated variants from acquired CH. A nuanced solution is a tumor-informed ctDNA assay that filters CH variants in resected tumors for cfDNA analysis[38] while algorithmic and machine-learning approaches show promise for distinguishing between tumor- and CH-variants with a single, off-the shelf test[39].

Approach to Vignette #4: The identification of an *SF3B1* mutation (Tier II, prognostic relevance) in the context of persistent unexplained cytopenias establishes a working diagnosis of CCUS. However, distinguishing CCUS from early MDS cannot be achieved by sequencing alone. The "indolent" nature of the VAF (12%) does not rule out dysplasia. Perform aspirate and biopsy with iron stain (Prussian blue), look for dysplasia and specifically for ring sideroblasts to confirm if this represents *SF3B1* -mutated MDS or true CCUS.

- Significant Dysplasia/Ring Sideroblasts Present: Diagnosis is MDS with *SF3B1* mutation. Initiate anemia management (e.g., Luspatercept or ESAs).
- No Dysplasia: Diagnosis is CCUS. Monitor CBC every 3-4 months for progression.

In unexplained cytopenia, CH detection is the *start* of the diagnostic algorithm, not the end

Surveillance

Case Vignette #5: Risk Stratification and Longitudinal Monitoring
A 63-year-old female was incidentally diagnosed with Clonal Hematopoiesis (M-CHIP, *TET2* mutation, VAF 6%) two years ago during a genomic workup for a personal history of ovarian cancer. Although her ovarian cancer remains in remission and her blood counts have consistently remained stable since the CH diagnosis, she occasionally worries about the implications of this finding, particularly the risk of progression to a hematologic malignancy or other complications. She asks her hematologist about her specific risks, expressing a desire to avoid excessive medical follow-ups while ensuring proper oversight. This scenario emphasizes the critical need for accurate risk stratification and individualized surveillance protocols to guide patient management effectively.

While CH has a 0.5-1% annual risk of progression to MN[1], CCUS transformation to MN is over 10-fold higher[40]. *DNMT3A* and *TET2* mutations have modest predictive value, whereas mutations in *TP53*, *IDH1*, *IDH2*, splicing factors (*SRSF2*, *SF3B1*), and transcription factors (*RUNX1*) strongly predict myeloid transformation[21, 41, 42], particularly at a VAF $\geq 10-20\%$[43].

CH Outcomes Prediction Models

Currently, there is a significant lack of outcome prediction models for patients with CH, representing a vital gap in the clinical armamentarium (Table 4). Clonal Hematopoiesis Risk Score (CHRS)[21] is a straightforward multivariable model that stratifies CH or CCUS progression risk to MN[21]. CHRS is based on 438,890 UK Biobank participants; key risk factors include age ≥ 65 years, high-risk mutations, ≥ 2 mutations, VAF ≥ 20%, macrocytosis (MCV ≥ 100 fL), elevated RDW (≥ 15%), and cytopenias. CHRS categorizes patients into low-(≤ 9.5), intermediate-(10–12), and high-(≥ 12.5) risk groups, with 10-year MN incidences of 0.7%, 7.8%, and 52.2% respectively. While achieving reasonable accuracy (C-index: 0.74), its limitations are due to the constraints of the underlying data source, not the model's design. The UK Biobank's population is relatively homogeneous and non-oncology-focused, the data is inherently static and certain CH mutations like *U2AF1* were excluded from the analysis.

To address specific disease subtypes, the MN-predict tool uses competing risks Cox proportional hazards models to predict the time-dependent risk for three distinct myeloid neoplasm subtypes: AML, MDS, and MPN[44]. MN-predict demonstrated strong predictive power (AUCs of 0.78 for AML, 0.86 for MDS, and 0.82 for MPN) and provides a granular, year-by-year risk assessment via an online calculator. Conversely, for patients specifically presenting with unexplained cytopenias, the Clonal Cytopenia Risk Score (CCRS) was recently developed to stratify CCUS patients based on mutation number, splicing variants, and platelet counts[45].

Finally, second-generation models are shifting towards dynamic assessments and non-MN associations. The MACS120 model outperforms traditional VAF measurements by incorporating mutation context and fitness to predict future clonal growth[46]. Uniquely, this model links clonal dynamics to broader clinical outcomes, including cardiovascular events and all-cause mortality, highlighting the importance of sequential monitoring. Such dynamic models would be important for incorporating sequential clonal monitoring and clinical data for more accurate predictive capabilities.

Higher VAF correlates with adverse outcomes; CH VAF ≥10% links to negative clinical outcomes like MN and CV events[47–54]. Multiple CH mutations also impact CV outcomes[55], necessitating enhanced monitoring for VAF ≥10% clones[50]. While VAF ≤1% suggests lower risk and 1-10% intermediate risk[56], VAF-outcome relationships require mutation-specific, dynamic interpretation: *TP53* and *JAK2* mutations confer significant risk even at low VAF, whereas *DNMT3A* and *TET2* risk escalates with VAF[57, 58]. Lower VAF is clinically significant in therapy-related CH (t-CH) or t-CCUS, where clones expand under therapeutic pressure and inflammation[59, 60]. Besides, temporal VAF changes predict outcomes; annual increases >2% indicate higher risks while stable levels suggest indolent disease[48]. Sequential monitoring is essential for CH dynamics, particularly for high-VAF/high-risk clones or low-VAF clones in t-CH/t-CCUS[50, 61]. VAF stability depends on mutation type, co-mutations, hematopoietic demand, and stressors like chemotherapy/inflammation. For instance, *DNMT3A* and[62], *TET2* mutations lead to HSPC expansion in inflammatory states[63]. A study employing concurrent single-cell RNA-sequencing with genotyping in *DNMT3A* and *TET2* mutant CH donors identified a modulating effect of CH mutation status on inflammation response within HSCs, wherein the impact of systemic inflammatory stress was attenuated among CH-mutant HSCs compared to wild-type HSCs from the same donors[64]. Clones with *TP53, PPM1D, CHEK2,* and *ASXL1* mutations expand faster than *DNMT3A* or *TET2*, often preceding MN[5, 65]. Chemotherapy/radiation drive DNA repair mutation clone expansion and may even induce further mutations or copy number alterations that can contribute to clonal outgrowth[66].

Surveillance Protocols

Clinical management of patients with CHIP or CCUS is predicated on a dual-pronged, risk-stratified framework targeting both- risk of MN and CV sequelae (Figure 1). Hematologic surveillance intensity is directly guided by the clinical context, CBC abnormalities, CHRS risk stratification and type of mutations. High-risk cohorts—defined by a high CHRS, or the presence of any CCUS or t-CCUS—warrant frequent monitoring with CBC every 3-6 months and consideration of periodic bone marrow evaluation.

Conversely, low- and intermediate-risk individuals undergo less intensive surveillance, or no surveillance at all depending on patient preferences in shared decision making. Concurrently, universal CV risk mitigation is important. This involves systematic assessment using the 10-year ASCVD score, supplemented by coronary artery calcium (CAC) scoring for enhanced stratification, and pharmacologic interventions with statins and aspirin as clinically indicated for primary or secondary prevention. This structured approach ensures continued, risk-adapted surveillance in an attempt to mitigate risk, provide an opportunity for early diagnosis and enrollment in clinical trials, while respecting patient autonomy and potential harms from pathologizing an asymptomatic condition.

Clonal Hematopoiesis Beyond Myeloid Point Mutations

The clinical management of L-CHIP, mCA, LoX, and LoY requires tailored strategies for hematologists[67]. In lymphoid CH, close surveillance is needed to track progression to chronic lymphocytic leukemia or lymphoma, particularly when recurrent genetic aberrations are present[68]. Management of asymptomatic lymphoid CH is evolving, but must be individualized based on clonal burden, immunophenotype, and clinical signs of progression. Surveillance typically includes periodic complete blood counts, lymphocyte subset analysis, and imaging to detect early lymphadenopathy or splenomegaly and allow timely intervention.

For mCAs, management focuses on monitoring for cytopenias or development of an MDS phenotype, although clear guidelines for asymptomatic individuals with incidental mCAs are lacking[69]. The higher risk associated with autosomal mCAs, particularly in older men, highlights the need for targeted, age-stratified surveillance that reflects their impact on disease progression and therapy response[70].

Mosaic loss of the Y chromosome (mLOY) in males has been linked to increased risks, demanding the development of standardized protocols for monitoring individuals for the early detection and intervention of associated non-communicable diseases[71]. Similarly, the clinical management of individuals with mosaic loss of the X chromosome (mLOX) in females necessitates tailored surveillance strategies, akin to those for mLOY, yet adapted for the unique risks associated with female-specific hematologic and autostructural conditions[70].

Approach to Vignette #5: This patient falls into the CHRS low Risk category. Her age (< 65), single mutation (*TET2*), low VAF (< 20%), and absence of cytopenias confer a low 10-year probability of progression to myeloid neoplasm (< 1%).

- Surveillance: Intensive monitoring is unnecessary. An annual CBC is sufficient to monitor for developing cytopenias. A bone marrow biopsy is not indicated.
- CV Risk: This is the primary clinical concern. Assess 10-year ASCVD risk and manage lipids/hypertension aggressively, as *TET2* mutations accelerate atherosclerosis and related conditions even in the absence of hematologic progression.

Interventions and Recommendations

Case Vignette #6: Holistic Management for a CH Patient with Comorbidities
A 68-year-old male recently diagnosed with CHIP (*TET2* mutation, VAF 10%) after participating in an aging-related genetic research study, presents with a complex medical history including poorly controlled type 2 diabetes (HbA1c 8.5%), obesity (BMI 34 kg/m^2), and coronary artery disease. He is an active smoker. He is highly motivated to understand how CHIP diagnosis relates to his other health conditions and asks for a comprehensive plan to reduce both hematologic and non-hematologic complications.

Lifestyle Risk Mitigation

Modifiable lifestyle factors significantly influence CH risk. Tobacco use increases CH prevalence, particularly for clones with *ASXL1* and *TP53* mutations[66, 72, 73], and is also linked to mosaic chromosomal alterations[74]. Sex-specific factors include higher alcohol consumption increasing CH risk in women[73]. Environmental exposures like particulate matter (PM2.5) are also implicated; World Trade Center first responders show a markedly higher CH prevalence (11.9% vs. 1.9%)[75] and leukemia risk[76], and data link CH and PM2.5 to lung cancer risk[77].

Metabolic syndrome, more common in individuals with CH (especially *TET2* mutations), creates a selective pressure favoring clonal expansion. Murine models show that insulin resistance and obesity promote the growth of *Tet2* - and *Dnmt3a*-mutant HSPCs[78, 79]. Poor diet quality is associated with increased CH prevalence and cardiovascular events[80], whereas nutritious diets, such as the Mediterranean diet, are linked to lower occurrence and are a feasible intervention[80, 81]. While exercise does not seem to influence CH clone size, it may protect patients with CH from cardiovascular events[82]. Therefore, clinical guidance supports physical activity, smoking cessation, a Mediterranean diet, and weight management as part of a comprehensive guide for healthy living that may also modulate inflammation and restrain clonal growth. Since interventions for pre-malignant states must delicately balance potential benefits and harms, there is significant opportunity for low-risk lifestyle modifications that may ameliorate overall health while suppressing the pathological effects of CH.

Reproductive and Hormonal Considerations

Sex hormones modulate age-related CH, which exhibits sexual dimorphism[83]. Although males experience a more rapid decline in HSC function, *DNMT3A*-mutant CH is more prevalent in females, while mutations like *ASXL1* are more frequent in males[84]. Estrogen is presumed to underlie this disparity through its modulation of cell cycle activity and apoptosis[85, 86], which exerts selective pressure that may favor the expansion of *DNMT3A*-mutant clones. Murine models demonstrate that estrogen-induced proliferative stress provides a competitive advantage to *Dnmt3a*-mutant HSCs, which preserve their stemness via an estrogen receptor alpha (ERα)-dependent mechanism[87]. Clinically, this is underscored by the correlation between premature menopause and increased CH[88]. Consequently, managing CH in women requires a holistic approach that incorporates reproductive history and hormonal factors into risk assessment.

Pharmacologic Risk Modifiers

Emerging pharmacologic strategies aim to control CH-mediated inflammation or the clone itself, often by re-purposing existing drugs. For instance, colchicine prevents accelerated atherosclerosis in murine models of *TET2* -mutant CH and shows a protective trend against myocardial infarction in human cohorts with *TET2* mutations, positioning it as a potential precision therapy[89]. Statin use is associated with reduced cardiovascular events and may slow *TET2* clonal expansion[5]. Furthermore, IL-1β antagonists like canakinumab, proven to reduce cardiovascular events in patients with high inflammatory risk, may benefit individuals with CH, particularly those with *TET2* mutations by reducing cardiovascular events and incident cancers[90, 91]. Metformin shows considerable promise in reducing the competitive advantage of *DNMT3A*-mutant HSPCs by inhibiting their reliance on mitochondrial metabolism[92, 93]. While these agents are not yet standard of care for CH, their use is being explored in clinical trials for high-risk individuals.

Approach to Vignette #6: Holistic management This patient's *TET2* clonal expansion could be driven by an inflammatory metabolic state.

- Metabolic Control as Hematologic Therapy: Multimodal management of diabetes, regular exercise, and weight loss could reduce factors (IL-1β/insulin resistance) driving *TET2* clone growth and are associated with improved health outcomes even in the absence of CH.

- Smoking Cessation: Smoking is a potent driver of *ASXL1* and *TP53* expansion and CVD risk.
- Inflammation-Targeted Therapy: Initiate statin therapy to lower LDL, statins additionally have anti-inflammatory properties.
- Diet: Prescribe a Mediterranean diet, which has been observationally linked to lower CH progression rates.

Risk factor reduction for CH in Solid Tumor patients

Case Vignette #7: CH Impact on Solid Tumor Therapy and Outcomes
A 65-year-old female with stage IV non-small cell lung cancer is about to start immunotherapy. Pre-treatment molecular profiling of her peripheral blood, performed as part of a research protocol, identifies a *JAK2* V617F mutation with a VAF of 18%. Her oncologist is concerned that this high-VAF CH clone might influence her response to immunotherapy or increase her risk of hematologic complications. This case exemplifies the complex interplay between CH and solid tumor treatment, highlighting the need to understand CH as a biological modifier.

The management of ST is complicated in the presence of CH. Cytotoxic therapies create a selective bottleneck that could promote the expansion of therapy-resistant CH clones, particularly those with mutations in DNA damage response genes like *TP53*, *CHEK2* and *PPM1D*, elevating the risk of t-MN[66, 94]. Targeted agents also drive clonal selection; for example, PARP inhibitors enrich for pre-existing *TP53* -mutant clones in patients with ovarian cancer, increasing t-MN risk[95, 96]. The effect of immunotherapy on CH clones remains an active area of investigation, with multiple reports linking CH, or TET2-mutant CH to better outcomes following structural checkpoint blockade[97–99]. Although no risk stratification exists for CH in ST patients, tools like the CHRS can help understand risk profile to guide decisions regarding myelotoxic therapies but with a caveat that this tool was developed on non-oncology population[21]. For patients with high-risk CH, alternative ST treatments may be warranted, balancing primary tumor control against the risk of hematologic progression. Given the lack of ST specific predictive model and prospective clinical trials utilizing CH either as biomarker or inclusion criteria for treatment pathway selections with t-MN as either primary or secondary outcome, this population of patients has the highest unmet need for such strategies.

Approach to Solid Tumor Vignette:
A *JAK2* V617F mutation at 18% VAF is a high-risk finding. It represents a increased thrombotic risk factor superimposed on the hypercoagulable state of active lung cancer.

- Exclude MPN: Check blood counts, EPO levels and a bone marrow biopsy to diagnose underlying MPN).
- Thrombosis Prevention: This patient has a high risk of VTE. Assess Khorana score; if elevated, consider primary thromboprophylaxis (DOAC or LMWH) during active cancer therapy.
- Therapy Selection: while there are correlative reports of diminished or enhanced benefits and toxicities with CH in the setting of various cancer therapies, we lack the prospective, randomized evidence that altering cancer treatment based on CH status can improve outcomes.

Interventions for de-novo CCUS or t-CCUS

Case Vignette #8: Managing Symptomatic Anemia in CCUS A 72-year-old female with a known diagnosis of CCUS, driven by a *SRSF2* mutation (VAF 15%), presents with worsening fatigue, dyspnea on exertion, and dizziness. Her baseline Hb has consistently hovered around 100 g/L, but over the past 3 months, it has

dropped to 85 g/L. She denies any new bleeding. Her hematologist is considering erythropoiesis-stimulating agents (ESAs) to alleviate her symptoms but is worried about the potential for clonal selection and expansion of her *SRSF2* clone under growth factor pressure. The clinical challenge is to effectively manage her symptomatic anemia while minimizing the theoretical risks associated with hematopoietic growth factor administration in the context of CCUS.

Growth Factors

Consultation requests for patients with CH frequently involve individuals diagnosed with de-novo CCUS or t-CCUS. A primary concern, albeit without any convincing data, revolves around the potential for growth factors to expand existing CH clones, thereby increasing the risk of progression to MN, a risk that compounds the pre-existing hazards from myelotoxic treatments (Table 5).

Erythropoietin Dynamics

Erythropoietin (EPO) demonstrates complex and context-dependent effects on CH. Mendelian randomization analyses, a method designed to infer causal relationships, indicate that higher genetically predicted plasma EPO levels are associated with reduced risks of overall clonal hematopoiesis, including both *DNMT3A*- and *TET2* -mutant clones[100], though these findings await peer- review and confirmation through additional studies[100]. This observation challenges a simplistic view of EPO as uniformly pro-clonal. If naturally higher EPO levels are protective, it suggests that EPO itself is not inherently detrimental in all contexts. In contrast, in frequent blood donors, where hematopoiesis is under chronic stress from blood loss, elevated endogenous EPO selectively promotes the expansion of *DNMT3A*-mutant clones (including frameshifts, premature stop codons, and structural variants, that affect amino acids other than arginine 882), while *TET2* -mutant clones remain stable[101]. Murine models further corroborate that EPO enhances proliferation of *DNMT3A*-mutant HSPCs. Clinical response to EPO in CCUS may depend on baseline EPO levels and mutation type. Although no direct data exists for CCUS, a meta-analysis of low-risk MDS patients indicates poor ESA response with high EPO levels and high-risk mutations[102]. Emerging evidence also suggests that alternative erythroid-support strategies, such as TGF-β inhibition with luspatercept, may be more effective and safer. A recent case report described clinical improvement in a patient with CCUS who was refractory to androgens and cyclosporine but responded to luspatercept combined with eltrombopag[103].

Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF is a common therapeutic agent for managing neutropenia, yet its influence on the CH dynamics of is not fully elucidated. In pediatric cases of severe congenital neutropenia, prolonged G-CSF treatment has been associated with the preferential selection of mutant clones[104]. Additionally, recent findings have linked CH with increased levels of G-CSF in peripheral blood[105]. Despite these insights, there is a paucity of comprehensive research or established clinical guidelines specifically addressing the use of G-CSF in patients with CH or t-CCUS. The use of G-CSF in patients with t-CCUS, in general, lacks a standard of care, meaning that such treatment, if initiated, is largely extrapolated from data on MDS, despite the inherent differences between CCUS and overt MDS. The persistent and unresolved debate regarding G-CSF's impact on clonal evolution in early myeloid neoplasms indicates that its effects are likely highly context-dependent, influenced by patient-specific factors, underlying mutations, disease stage, and concomitant therapies. This means that the potential for G-CSF to accelerate disease progression in t-CCUS cannot be definitively dismissed, even if direct evidence is lacking. Clinicians must acknowledge this uncertainty and understand that "no statistical difference" in progression to AML in some studies does not equate to "no biological effect." The decision to use G-CSF in t-CCUS must therefore be made with a full appreciation of this inherent uncertainty and the possibility of unforeseen long-term consequences, emphasizing the need for rigorous monitoring.

Thrombopoietin Receptor Agonists

Thrombopoietin Receptor Agonists (TPO-RAs) demonstrably impact CH clonal dynamics. In patients with ITP, approximately 18.5% show detectable CH with TPO-RA use. Mutations in *TET2*, *ASXL1*, and *U2AF1* are observed to expand preferentially compared to *DNMT3A* clones in this context. Higher endogenous TPO levels correlate with clonal expansion in these patients. Importantly, despite clonal expansion, patients typically do not progress to MN[106] In aplastic anemia, 19% patients show clonal evolution, often without hematologic progression indicating that TPO-RAs may act as permissive signals affecting clonal competition or selection[107]. As robust evidence regarding the use of TPO-RAs in t-CCUS is currently limited, a thorough evaluation of their risk-benefit profile is crucial to effectively sustain platelet counts and ensure the continuity of treatment for primary ST.

Approach to Vignette #8: The morbidity of symptomatic anemia often outweighs the theoretical risk of clonal expansion. Meta-analyses in low-risk MDS support safety, though specific CCUS trial evidence are lacking.

- Check endogenous EPO: If < 500 mU/mL, a trial of ESA is indicated.
- Monitoring: Initiate ESA trial or 8-12 weeks with monthly CBC monitoring.
- Alternatives: If ESA refractory, consider clinical trials for luspatercept.

Clinical Actionability of Clinical Strategies

Although CH is associated with multiple adverse outcomes, the strength of the evidence differs substantially. To contextualize clinical management, we outline interventions according to their current evidentiary status in Table 6.

This framework aligns expectations with current evidence and highlights where further trial data are essential.

CH implications across other diseases

Case Vignette #9: Multidisciplinary Management of CH in Cardiovascular Disease A 70-year-old male with recurrent coronary syndromes has a high-VAF *TET2* mutation (15%) found during risk stratification. His cardiologist and hematologist consult on its prognostic influence and potential interventions. This highlights CH's role as a biological modifier, requiring interdisciplinary collaboration.

Solid Tumors: Tumor-infiltrating CH

Our understanding of CH's impact on solid tumor (ST) progression is evolving. While there is concern for transformation into t-MN, recent reports highlight that CH also reshapes tumor biology through the infiltration of mutant cells into the tumor microenvironment. The presence of CH-mutant leukocytes within ST, has been described as CH-Tumor (CH-Tum) or tumor-infiltrating CH (TI-CH)[108, 109] . Remarkably, TI-CH has been reported in approximately 5% of all ST patients, and is associated with higher risk of death and tumor relapse[108, 109]. TET2 CH is associated with TI-CH, and TI-CH correlates with an inflamed tumor microenvironment[108]. Worse outcomes with TI-CH are presumed to be due to disease progression, though CH has also been linked to worse cardiovascular outcomes and non-relapse mortality following lymphoma therapy. In several smaller studies of gastrointestinal or prostate cancer, CH was not prognostic after age adjustment[110, 111]. Similarly, CH did not affect radiation therapy response or tumor progression in ST patients[112]. Conversely, in NSCLC, pre-operative CH predicted poor survival and correlated with more non-cancer deaths, implying broader vulnerability[113]. More research is

required to unravel potential cancer-, treatment-, or driver mutation-specific effects of CH on ST patient outcome.

Myeloid neoplasms: MPN, MDS, Acute Myeloid Leukemia and Allogeneic stem cell transplant

In acute myeloid leukemia (AML), CH mutations in remission marrow complicate minimal residual disease (MRD) evaluation. Though founder mutations (*DNMT3A, TET2, ASXL1*) persist post-remission without increasing relapse risk[114], persistent *DNMT3A* and *IDH2* clones in *NPM1* -mutated AML are linked to a "pre-leukemic" immunophenotype, requiring differentiation from MRD[115]. In low-risk MDS, inflammatory signals enhance mutant HSPC growth and suppress normal hematopoiesis[116]. In allogeneic stem cell transplantation (allo-SCT), both donor and recipient CH affect outcomes. Recipient CH, particularly *DNMT3A* mutations in patients over 45, is linked to higher acute graft-versus-host disease (aGVHD) rates[117, 118]. Donor-derived CH may cause leukemia, increasing interest in donor screening[119]. The Clonal Hematopoiesis Risk Score (CHRS) helps estimate myeloid malignancy risk in CCUS and CHIP, guiding trial enrollment. At MN diagnosis, high-risk clones often expand, though new driver mutations can also appear.

Lymphoma, Multiple Myeloma, CLL, and Autologous Transplants

CH significantly affects lymphoid malignancies' progression and outcomes. In chronic lymphocytic leukemia (CLL), CH resembles monoclonal B lymphocytosis (MBL) and acts as a potential precursor[120]. In multiple myeloma (MM), CH is linked to aggressive disease, weakened T-cell immunity, increased frailty, shorter event-free survival, and greater treatment toxicity[121]. Myeloid-associated CH mutations influence MM progression and survival[122].

In alloBMT for lymphoid malignancies, recipient CH predicts post-transplant and non-relapse mortality (NRM), with worse survival linked to CH burden, but not relapse. Donor CH is associated with higher GVHD incidence and donor-derived leukemia risk.

In autologous transplants, DTA mutations (*DNMT3A, TET2, ASXL1*) show little impact on relapse or survival[123, 124]. However, *TP53* and *PPM1D* mutations appear in poor mobilizers and predict clonal expansion, stem cell dysfunction, and therapy-related myeloid neoplasm (t-MN) risk[125]. In lymphoma patients post-ASCT, CH (especially *PPM1D* mutations) is associated with increased non-lymphoma-related death and worse overall survival, suggesting a need for intensified surveillance.

Classical hematology

In idiopathic aplastic anemia (AA), compromised T-cell surveillance due to restricted HLA diversity facilitates clonal evolution and CH-driven dysplasia[126]. Inflammatory signaling boosts mutant HSPC expansion while inhibiting normal hematopoiesis, suggesting structural evasion drives CH progression in autostructural or hypoplastic marrow conditions[50, 127]. In hemoglobinopathies, chronic inflammation and oxidative stress trigger somatic mutations and promote CH clone expansion[**Swierczek.2020b**, 62, 128], with single-cell analysis revealing distinctive HSPC behaviors[129]. In allo-SCT for hemoglobinopathies, recipient-derived HSPCs increase risks of graft failure and mixed chimerism[130].

CH in Non-hematological, non-malignant conditions

Pre-clinical studies link CH to adverse outcomes in cardiovascular diseases (CVD), including atherosclerosis, stroke, and heart failure[6, 63, 131, 132]. Higher VAF and specific *TET2* and *PPM1D* mutations confer higher risk[51]. *DNMT3A* and *TET2* mutations in aortic valve replacement patients led to higher 4-year all-cause mortality. Their prothrombotic potential also links to worse outcomes in CTEPH, correlating with elevated inflammatory markers[50].

CH also associates with autostructural diseases like ITP, AITD, AOSD, and VEXAS syndrome[133–136]. A

UK Biobank study found CH more than doubled ITP risk, especially with *JAK2* and *SRSF2* mutations[137]. CH, especially with *TET2* or *ASXL1* mutations and larger clone sizes, was linked to increased AITD risk[134]. In AOSD, CH mutations are linked to NLRP3 inflammasome and type I IFN signaling[135]. VEXAS syndrome results from somatic *UBA1* mutations in hematopoietic stem cells, causing CH and systemic inflammation[136].

Conversely, CH is negatively associated with Alzheimer's disease (AD); a meta-analysis found CH patients had significantly lower AD dementia incidence. CH mutations were found in microglia-enriched brain regions, and sequencing confirmed CH clones in brain-resident myeloid cells, potentially influencing neurodegeneration[138]. This suggests some CH mutations may be neuroprotective by modulating microglial function or neuroinflammation.

Approach to Vignette #9: This patient has "CHIP-associated" high-risk cardiovascular disease.

- Targets: Treat as "Very High Risk" ASCVD. Target LDL < 1.4 mmol/L.
- Inflammation: Consider hs-CRP testing; if elevated, consider anti-inflammatory agents per cardiology recommendations.

Multidisciplinary teams for Clonal Hematopoiesis

Case Vignette #10: Navigating a New CH Diagnosis and the Need for Comprehensive Care A 60-year-old male with an incidental *DNMT3A* mutation (VAF 3%) is referred to a CH clinic. Though asymptomatic, he is distressed by the uncertain risk and seeks clarity on his prognosis and care plan.

CH has evolved into a distinct clinical discipline requiring dedicated programs (Table 7) that bridge molecular diagnostics with preventive medicine[139].

Core Components and Infrastructure

Referrals to CH clinics often stem from incidental genomic findings, unexplained cytopenias, or genetic screening for malignancies[140]. Effective CH clinical care requires advanced molecular diagnostics and multidisciplinary expertise (hematology, cardiology, genetics). This includes facilities for low-VAF detection, bio-banking, and use of matched germline controls and non-hematological tissues for accurate interpretation for variants of unclear origin[1]. CH clinics should also integrate patient care with research through natural history studies, clinical trials, and participation in multi-center data registries like CHIVE[139]. Another key component is patient anxiety management. A study of young breast cancer survivors revealed that while many were interested in testing, nearly 30% of participants reporting moderate to severe anxiety and their preferences were heavily influenced by how risks were communicated and the availability of actionable management strategies which as we describe are still under evaluation[141]. Therefore, effective risk communication through genetic counselors, clinicians and robust psychosocial support is important element of CH clinic.

Economic and Operational Considerations

CH clinics require significant financial planning. Testing costs range from $\$200 - 1,000$ for targeted NGS panels to over $1500 for WES[142], with matched normal tissue analysis adding $\$500 - 1000$ per case. Taking into account the expenditure associated with human resources, including nursing support, genetic counselors, and research coordinators, academic CH clinics may incur annual operating expenses exceeding $500,000. These clinics are dependent on a combination of funding sources due to lack of reimbursement models.[143]. Various prediction models are now available to predict the presence of CH (Table 8). In the

future, the implementation of targeted screening using such models may contribute to the development of targeted screening criteria for CH, thereby enhancing the efficiency of resource utilization. However, the value of CH testing, whether broader or targeted and its intervention remains unclear at present and will continue to evolve from payor's and health economy perspective.

Resolution of Multidisciplinary Care Vignette #10: This patient has low-risk M-CH. The primary clinical challenge is his "diagnosis anxiety" rather than the immediate biological risk of the clone.

- Hematology: Provide clear, evidence-based reassurance. Explain that *DNMT3A* mutations are common age-related findings with a very low risk of leukemic transformation (< 0.5 − 1% per year). Establish a non-invasive surveillance plan (e.g., annual CBC) to provide safety netting without medicalizing his condition.
- Cardiology: Refer for cardiovascular risk stratification. While the VAF is low, CH is a risk enhancer. Optimizing lipids and blood pressure provides an actionable way for the patient to "manage" his risk, potentially alleviating anxiety.
- Psychosocial/Genetic Counseling: Since he is distressed, a genetic counselor can play a pivotal role in deconstructing the "pre-leukemia" label, reinforcing that this is a risk factor (like high cholesterol) rather than a cancer diagnosis.

Towards Personalized Preventive Medicine

Case Vignette #11: Considering Novel Therapies for High-Risk CHIP
A 68-year-old male was diagnosed with high-risk CH two years ago, characterized by a *TP53* mutation (VAF 12%) and rapidly expanding clone size (VAF increased by 3% annually). He has no overt cytopenias but is highly anxious about his elevated risk of myeloid neoplasm progression. Despite lifestyle modifications, his anxiety persists, and he frequently asks about any new treatments that could directly target his CH clone to prevent progression. This case highlights the unmet need for targeted interventions in high-risk CHIP and the potential role of novel therapies being explored in clinical trials to shift from reactive management to proactive prevention.

Molecular progression predictors have advanced anti-inflammatory and mutation-specific interventions (Table 9), while preventive strategies focus on environmental exposures. Recent studies have illuminated *TET2* loss mechanisms[144]. The absence of *TET2* with cholesterol accumulation in macrophages intensifies inflammatory responses through NLRP3 inflammasome pathway. This mechanism involves Dusp10 promoter hypermethylation, leading to JNK1 phosphorylation and inflammasome activation.

Research shows holomycin, a BRCC3 deubiquitinase inhibitor, can reverse atherosclerosis progression and pathological neutrophil extracellular trap formation, offering a therapeutic strategy for *TET2* -associated clonal hematopoiesis. STING pathway inhibitors are emerging as a treatment for CH[145], particularly for *TET2* and *DNMT3A* mutations[146]. C-176 suppresses abnormal self-renewal and inflammatory signaling[147], addressing disease progression[148]. H-151, C-176, and SN-011 show potential in reducing mutant stem cells' competitive advantage[149], indicating a shift toward targeted treatments. Clinical trials are evaluating targeted therapies for CCUS and early-stage myeloid malignancies. Enasidenib studies[150, 151] assess *IDH2* inhibition through hematologic responses and VAF changes. The EVITA trial[152] investigates high-dose Vitamin C efficacy in *TET2* mutations. New approaches with olutasidenib[153] and luspatercept[154] reflect interest in low-intensity interventions. These studies aim to understand CH's clinical impact through biomarker data, mutation tracking, and clonal kinetics. Observational components (Table 10) collect longitudinal data on mutation types and disease evolution, supporting the shift from reactive treatment to proactive management through clinical thresholds and molecular markers in asymptomatic carriers.

Approach to High-Risk CHIP Vignette #11: This patient represents the "highest risk" stratum of CH due to the specific mutation (*TP53*), its size (> 10%), and rapid clonal expansion kinetics. He is at significant risk for progression to MDS/AML.

- Clinical Trials: Since no FDA-approved preventive therapies exist, the most proactive step is enrollment in a natural history study or an intervention trial (e.g., evaluating anti-inflammatory agents or metabolic modifiers).
- Avoid Cytotoxicity: Strict avoidance of cytotoxic chemotherapy or radiation for other medical conditions is paramount, as *TP53* clones expand explosively under such therapeutic pressure.
- Intensified Monitoring: Increase CBC and molecular monitoring frequency (e.g., every 3-4 months) to detect early signs of transformation (emerging cytopenias or blasts), at which point standard MDS therapies (e.g., hypomethylating agents) would become indicated.

Conclusions and Future Directions

CH links aging biology, cancer evolution, and systemic disease, reshaping our understanding of age-related illnesses. Its impact extends beyond hematology to cardiovascular disease and solid tumors. We are only beginning to unravel the connections between mutation patterns, clone sizes, and disease outcomes. Although most CH patients do not progress to malignancy , some develop incurable cancers or suffer from debilitating non-malignant disease, emphasizing the need for better risk prediction tools. As sequencing becomes cheaper and more integrated clinically, the challenge is not detecting mutations but using this information to make clinical decisions that improve outcomes. Future CH management must balance identifying high-risk patients who need intervention while minimizing unnecessary anxiety for others.

Search Methodology

The literature search was conducted using multiple electronic databases including Ovid MEDLINE, Embase, PubMed, and Web of Science from their inception to December 2025. The primary search strategy was developed in Ovid MEDLINE using a combination of Medical Subject Headings (MeSH) and free-text terms, then adapted for other databases. The search terms included: ("clonal hematopoiesis" OR "CHIP" OR "clonal haematopoiesis of indeterminate potential" OR "age-related clonal hematopoiesis") AND ("management" OR "therapy" OR "treatment" OR "clinical decision-making" OR "patient care").

Additional keywords related to specific clinical aspects were included: "cardiovascular risk," "malignancy risk," "monitoring," and "intervention." The search was restricted to English-language publications and human studies. To ensure comprehensive coverage, we also conducted manual searches of reference lists from relevant reviews and included studies. The search results were filtered to include clinical trials, observational studies, systematic reviews, and practice guidelines. Conference abstracts from the past five years from major hematology conferences (ASH, EHA) were also screened for relevant ongoing studies.

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Table 1. Strategies to mitigate false positive CH variant calls

Strategy	Target Scope	Primary Purpose	Mechanism	Clinical Advantage	Considerations	Key References
Advanced Bioinformatics Filtering	Sequencing Artifacts	Distinguish true CH from errors	Multi-step filtering; identification of DNA structure-specific artifacts; flagging multiallelic variants	Neutralizes artifacts and ambiguous calls; improves specificity	Filters must be continuously refined	155–157
Machine Learning & AI	cfDNA Analysis	Classify variant origin (CH vs. Tumor)	Frameworks (e.g., MetaCH) predicting origin without matched normal samples	Critical for liquid biopsy diagnosis; reduces need for matched tissue	Emerging technology; model validation required	158
Multi-biospecim Analysis	PB, Plasma, Saliva	Validation of mutation calls	Cross-comparison of DNA from distinct compartments (e.g., paired WBC and cfDNA)	Confirms true events; excludes CH interference in MRD monitoring	cfDNA may show higher false positives at low VAF	159–161
Flexible VAF Thresholds	Low-level Hotspots	Detect biologically significant clones	Flagging known CH "hotspots" regardless of rigid cutoffs (e.g., <2% VAF)	Captures critical driver mutations that would be missed by standard thresholds	Significance varies by gene; requires curated lists	43, 155, 162
QC & Manual Review	Novel/Rare Variants	Final verification of variant calls	Visual inspection (IGV); use of high-quality reference materials	Essential for unusual/recurrent mutations not in public databases	Labor-intensive; requires trained expert interpretation	163

Abbreviations: AI, Artificial Intelligence; cfDNA, Cell-free DNA; CH, Clonal Hematopoiesis; IGV, Integrative Genomics Viewer; ML, Machine Learning; MRD, Minimal Residual Disease; PB, Peripheral Blood; VAF, Variant Allele Frequency; WBC, White Blood Cell.

Table 2. CH variants requiring evaluation for potential germline inheritance

Gene	Inheritance	Syndrome/Condition	Penetrance
RUNX1	AD	Familial platelet disorder with AML	High (35–50% lifetime risk)[1]
GATA2	AD	GATA2 deficiency (Emberger, MonoMAC, etc.)	Very High (75–80% by age 40)[2]
DDX41	AD	Familial MDS/AML	Incomplete, late-onset (□50% by age 90)[3]
ETV6	AD	Thrombocytopenia with predisposition to malignancy	Moderate (□30% for malignancy)[4]
CEBPA	AD	Familial AML	Location-dependent: >90% (N-term) or □50% (C-term)[5]
TERT/TERC	AD/AR	Telomere biology disorders	Variable and incomplete; age-dependent[6]
ANKRD26	AD	Thrombocytopenia	Low–moderate (□8–10%)[7]
FANCA-G	AR	Fanconi anemia	High (near 100% for syndrome if biallelic)[8]
SAMD9/SAMD9L	AD	MIRAGE syndrome, ataxia-pancytopenia	Variable; modulated by somatic reversion[9]
SRP72	AD	Familial MDS/Bone marrow failure	Unknown; likely incomplete[10]
PAX5	AD	B-ALL predisposition	Incomplete (estimated □30%)[11]

[1] RUNX1: Lifetime risk for MDS/AML is high. A median incidence of 35% was reported in the initial pedigrees[164], with more recent estimates suggesting a lifetime risk of 35–50%. Progression requires secondary somatic mutations.

[2] GATA2: Penetrance for any clinical feature is >80% by middle age. The risk for myeloid neoplasms is highly age-dependent, reaching 75–80% by age 40. The syndrome has highly variable expressivity[165].

[3] DDX41: A late-onset syndrome (median >60 years) first identified by[166]. Subsequent studies estimate the risk of myeloid neoplasm reaches 50% by age 90, with a strong male predominance.

[4] ETV6: A syndrome of highly penetrant thrombocytopenia (>90%) and a moderate (30%) lifetime risk for malignancy, most commonly B-ALL[167].

[5] CEBPA: Familial AML first described by[168]. Penetrance is critically location-dependent: germline N-terminal variants confer a >90% risk, while C-terminal variants confer a 50% risk.

[6] TERT/TERC: Penetrance is variable, incomplete, and age-dependent. Risk is a function of accelerated telomere shortening, and genetic anticipation is a key feature[169].

[7] ANKRD26: Associated with a low-moderate lifetime risk for myeloid neoplasms of 8–10%. The causative mutations are typically in the 5' UTR, leading to gene overexpression[170].

[8] FANCA-G: Near 100% penetrance for FA syndrome in biallelic carriers, with 90% risk of bone marrow failure by age 40[171]. Heterozygous carriers of *FANCA/G* do not have a clearly established increased cancer risk.

[9] SAMD9/SAMD9L: Caused by gain-of-function variants. The clinical phenotype and variable penetrance are modulated by somatic rescue events, such as monosomy 7 or acquired inactivating mutations[172].

[10] SRP72: An extremely rare syndrome, first identified by[173]. It appears highly penetrant in the few reported families, but this is subject to ascertainment bias, so true penetrance is unknown.

[11] PAX5: An incomplete penetrance syndrome for B-ALL first described by[174]. Lifetime risk is estimated at 30%, requires a somatic second hit, and may be influenced by environmental triggers.

Table 3. Concise Comparison of Variant Databases for Clinical Use in CH clinic

Database	Variant Type(s)	Primary Purpose	Key Features	Advantages	Limitations	Best Use Cases
ClinVar[175]	Germline / Somatic	Clinical variant interpretation	ACMG/AMP classifications; germline/somatic tracks; public archive	NCBI-integrated; community-curated; standardized terms	Variable data quality; conflicting interpretations; requires submitter evidence assessment	Clinical assertion checks; hereditary cancer testing; standardized reclassification
gnomAD[176]	Germline	Population allele frequency reference	>141K individuals; constraint metrics (pLI/LOEUF); multi-ethnic data	Filters common polymorphisms; benchmark for variant rarity	Significant CH somatic variant contamination; healthy-population bias	Rare variant filtering; background frequency control
COSMIC[177]	Somatic	Cancer somatic variant catalog	Curated somatic mutations; drug associations; Cancer Gene Census	Gold standard for cancer somatic variants; deep hematology coverage; pathway data	Commercial license required; cancer-only scope; complex format	Confirming somatic drivers in hematologic cancer; biomarker discovery; therapeutic links
IARC TP53[42]	Somatic / Germline	Locus-specific *TP53* database	Curated *TP53* variants; functional/structural data; literature links	Unmatched *TP53* depth; expert-reviewed; functional evidence	*TP53* -only focus; manual updates can lag	In-depth *TP53* variant analysis; functional impact studies for high-risk CHIP
dbSNP[178]	Germline / Somatic	Universal short variant registry	Stable rsIDs; catalogs SNVs/indels; polymorphism backbone	Universal rsIDs for standardization; broad pipeline integration	Not clinically curated; contains mixed, unclassified variants	Variant normalization; cross-database mapping; stable ID searching
DECIPHER[1]	Germline / Mosaic	Rare variant interpretation in developmental disorders	Phenotype-genotype mapping (HPO); CNV & SNV data	Rare disease/pediatric focus; patient matchmaking	Limited for adult somatic CH; pediatric/neurodev bias	Rare germline variant investigation; gene-phenotype discovery
VarCards2[180]	Germline / Somatic	AI-assisted variant interpretation	Automated ACMG/AMP scoring; >150 data sources; ML predictions	One-stop annotation; accelerates triage; non-coding variant support	New tool, needs validation; ML bias risk; source-dependent quality	High-throughput annotation; variant prioritization; AI-assisted research classification
HGMD (Pro)[181]	Germline	Curated inherited disease variants	Literature-derived germline mutations; phenotype mapping; historical data	Gold standard for pathogenic germline variants; expert manual curation	Subscription for current data; germline-only focus; no allele frequencies	Investigating unknown origin variants; reference for known pathogenic mutations
HSMD[182]	Somatic	Hematologic/onco mutation database	Real-world clinical case data; curated hematologic malignancy annotations	Oncology-focused; hematology-specific; includes proprietary case frequencies	Subscription required; proprietary data; complex interface	Hematologic diagnostics; mutation-based stratification; AML/MDS studies

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AI, Artificial Intelligence; AML, Acute Myeloid Leukemia; AMP, Association for Molecular Pathology; CH, Clonal Hematopoiesis; CNV, Copy Number Variant; HPO, Human Phenotype Ontology; LOEUF, Loss-of-function Observed/Expected Upper bound Fraction; MDS, Myelodysplastic Syndrome; ML, Machine Learning; NCBI, National Center for Biotechnology Information; pLI, probability of being Loss-of-function Intolerant; rsID, Reference SNP ID; SNV, Single Nucleotide Variant.

Table 4. Prediction models in CH

Study/Model	Patient Population	Prediction Variables	Outcomes	Risk Stratification	Statistical Model	Performance	Limitations
Clonal Hematopoies Risk Score (CHRS)[21]	Individuals with CHIP and CCUS	High-risk mutations (*SRSF2, SF3B1, ZRSR2, IDH1, IDH2, FLT3, RUNX1, JAK2, TP53*); Clone VAF ≥20%; RDW ≥15%; MCV ≥100 fl); Presence of cytopenia (CCUS vs. CHIP); Age ≥65 years. *DNMT3A* mutation alone-favorable	10-year risk of progression to MN; also reflected in overall survival	Low (≤9.5) Intermediate (10-12) High (≥12.5)	Weighted sum of factors. Developed and validated in a large cohort (U.K. Biobank, n=438,890). Static model	10-year MN risk Low risk: □90% of CH patients, <1%. Intermediate risk: □10% of CH patients, 8%. High risk: □1% of CH patients, 52%.	Relies on single time-point genomic and clinical data, may not fully capture dynamic clonal evolution.
MN-predict[44]	Individuals with CH (UK Biobank)	Age, Sex, blood indices (Hb, MCV, RDW, Plt, WBC), Variant features (Gene, VAF, number of mutations)	Time-dependent risk of specific MN subtypes: AML, MDS, MPN	Continuous probability (0-15 years); no fixed risk tiers	Competing risks Cox proportional hazards models	AUC in validation: AML: 0.78 MDS: 0.86 MPN: 0.82	Calculation is complex (requires web tool); relies on UK Biobank data which has "healthy volunteer" bias; limited external validation in clinical cohorts.
Clonal Cytopenia Risk Score (CCRS)[45]	Patients with CCUS	Splicing mutation(s) (2 points) Platelets < 100 ×10^9/L (2.5 points) ≥2 mutations (3 points)	Progression to MN	Low: <2.5 Intermediate: 2.5 to <5 High: ≥5	Weighted sum of factors derived from a stepwise Cox proportional hazards model, validated in an independent cohort.	2-year cumulative incidence of MN Low 6.4% Intermediate 14.1% High 37.2%. Validation model c-index 0.64 (p=.005).	Lack of central review for bone marrow-potential variability in diagnosis. Lack of uniformity in sequencing platforms. Academic center cohorts- more advanced or high-risk patient population. Relatively short follow-up duration (median 27.3 months)
MACS120[46]	Individuals with CH in longitudinal aging cohorts (n=713 with 2,341 observation	Combines mutation context, inferred timing of mutation acquisition, and variant fitness	Prediction of future clonal growth, directly linked to all-cause mortality, leukemia risk, and cardiovascular disease	Not explicitly stratified into tiers; predicts future clonal growth	Unified analytical framework for standardized clonal dynamics inference across cohorts. Dynamic model	Outperforms traditional VAF measurements in predicting clinical outcomes. Statistically significant association with survival (p=0.04)	Detailed methodology (how mutation context, timing, and variant fitness are precisely combined, or exact algorithms) is not extensively detailed in available literature

Note. CHIP = Clonal Hematopoiesis of Indeterminate Potential; CCUS = Clonal Cytopenia of Undetermined Significance; CHRS = Clonal Hematopoiesis Risk Score; OS = Overall Survival; VAF = Variant Allele Frequency; MN = Myeloid Neoplasms; RDW = Red Cell Distribution Width; MCV = Mean Corpuscular Volume

Table 5. Contextual Effects of EPO, G-CSF, and TPO-RAs on Clonal Hematopoiesis

Erythropoietin (EPO)	
General population	Higher genetically predicted EPO levels linked to reduced CH risk, especially *DNMT3A* and *TET2* clones[100].
Frequent donors	EPO elevation under hematopoietic stress expands *DNMT3A*-mutant clones[101].
Murine models	EPO promotes Dnmt3a-mutant HSPC proliferation; *TET2* clones unaffected[101].
ESA use	High EPO levels and high-risk mutations predict ESA resistance in low-risk MDS[102].
Alternative therapies	Luspatercept and eltrombopag improved erythropoiesis in ESA-refractory CCUS[103].
Granulocyte Colony-Stimulating Factor (G-CSF)	
Severe congenital neutropenia with chronic G-CSF use	Clonal selection noted[104].
Therapy-related CCUS	Prior cytotoxic exposure worsens outcomes, but G-CSF-specific risk unproven[183].
Clinical use	G-CSF use could improve chemotherapy adherence in CH patients.
Thrombopoietin Receptor Agonists (TPO-RAs)	
ITP	□ 18.5% of patients show clonal expansion (*TET2*, *ASXL1*, *U2AF1*); *DNMT3A* clones less responsive[106].
Aplastic anemia	□ 19% clonal evolution with TPO-RA; hematologic response typically without transformation[107].
Mechanism	TPO-RAs may modulate clonal competition via permissive signals.
Clinical use	After risk-benefit assessment to maintain platelet counts and therapy continuity.

Table 6.Actionability of CH-direct interventions

Intervention	Readiness Level	Evidence Summary
Cardiovascular risk factor optimization (statins, BP control)	Ready now	Consistent epidemiologic data showing increased CVD risk in CH; guidelines support aggressive CVD prevention in high-risk populations.
Aspirin for primary prevention in CH	Near-future / conditional	Preliminary mechanistic rationale; no CH-specific RCTs. Consider only if otherwise indicated.
Early bone marrow biopsy for high-VAF or high-risk mutations	Ready now	Strong evidence that high-risk CHIP/CCUS predicts MN progression; marrow evaluation recommended by consensus.
Anti-inflammatory therapies targeting IL-1β/IL-6 pathways	Experimental	Mechanistic data strong; no outcome-driven RCTs in CH populations.
Hormone-related modifiers (e.g., reproductive hormone context)	Exploratory	Observational studies only; mechanisms not yet validated.
Lifestyle interventions (exercise, smoking cessation)	Ready now	Supported by general CVD-prevention data; reasonable given elevated baseline risk.

Table 7. Key Components of a Dedicated Clinical Program for Clonal Hematopoiesis

Domain	Key Components
Multidisciplinary Team	Hematologist, molecular and hempathopathologist, clinical geneticist, genetic counselor, cardiologist, geriatrician, bioinformatician, translational researchers.
Referral/Screening Criteria	Unexplained persistent cytopenias or cytosis, incidental CH on unrelated testing, family history of hematologic malignancy, or unexplained cardiovascular events.
Diagnostic Infrastructure	Targeted myeloid NGS panels with low-VAF sensitivity, matched normal controls, centralized biobank.
Risk Stratification	Assessment based on mutation type, VAF, co-mutations, blood counts, and risk scoring models (e.g., CHRS); categorize as ARCH, low/int/high-risk CH, and CCUS.
Surveillance Protocols	Periodic CBCs, molecular monitoring, inflammatory markers, and bone marrow biopsy when indicated.
Clinical Management	Cardiovascular risk reduction (e.g., statins, lifestyle modification), monitoring for transformation, and longitudinal care planning.
Patient & Family Counseling	Germline vs. somatic variant interpretation, structured pre- and post-test counseling, use of health literacy tools, and psychosocial support.
System Integration	Shared care coordination with oncology, cardiology, geriatric medicine, and hereditary cancer programs; integration into existing EHR systems.
Research & Data Infrastructure	Longitudinal patient registry (e.g., CHIVE), clinical trial enrollment, biomarker studies, clonal kinetics tracking, and continuous quality improvement.

Table 8. Prediction CH presence

Study	Patient Population	Prediction Variables	Outcomes	Risk Stratification	Statistical Model	Performance	Limitations
Dunn et al. (2024)[184] *medRxiv*	Adults with CBC, WES data (UK biobank)	Age, sex; 18 CBC parameters such as RDW, Platelet count; PDW, Plateletcrit, MCH	High-risk CH mutations (*JAK2, CALR, SF3B1, SRSF2, U2AF1*)	CHIC model stratifies risk of CH based on CBC features	Random Forest classifier	AUC: 0.85	Requires validation in external cohorts
Arango-Argoty et al. (2025)[158] *Nature*	Individuals undergoing cfDNA testing in the absence of matched WB sample	cfDNA features (VAF, genomic context)	Classification of variants as CH vs. tumor-derived	MetaCH model classifies variants in cfDNA from plasma-only samples as CH or tumor origin	Machine learning	Improved accuracy over prior methods	Limited by need for high-quality cfDNA input
Ryu et al. (2024)[185] *arXiv*	Cardio-oncology patients	Cardiac MRI images	CHIP status prediction	Image-based DL model distinguishes CHIP	Convolutional Neural Network	AUC: 0.85; Accuracy: 82%	Requires MRI infrastructure; not yet validated

Table 9. Ongoing Interventional Studies in CH/CCUS

Study	Population	Intervention / Summary	Primary Objective	Secondary Objective	Phase	N
Interventional studies						
NCT02958462[186]: Pre-Myeloid Clinic Study	Clonal cytopenias, cytosis, bone marrow failure, germline predisposition	NGS, functional genomics QOL, clinical evaluations	Diagnose, prognosticate and potentially offer treatments for patients with precursor features of myeloid neoplasms	MDS/AML transformation	—	2000
NCT03418038[187]: High dose Vitamin C in CCUS (Arm D)	CCUS (*TET2* mutations +/-concurrent mutations in *SRSF2, U2AF1, SF3B1, and ZRSR2, DNMT3A, EZH2, IDH1, IDH2*	High dose IV ascorbic acid	ORR (Arms A/B)	Hematological response (Arm D)	Phase 2	80
NCT03682029[152]: EVITA Study (completed recruitment)	CCUS	Vit C vs placebo	Change in VAF at 12 mo	Global 5hmC/5mC ratio	—	109
NCT05102370: Enasidenib in CCUS	CCUS with *IDH2* mutation	Enasidenib	Rate of hematologic improvement evaluated as the best response at any point in up to 18 months of treatment with enasidenib	—	Phase 1	4
NCT06240754[151]: Decentralized Enasidenib Trial	CCUS with *IDH2* mutation	Enasidenib	Hematologic response (IWG)	Adverse events (CTCAE v5.0)	Phase 2	15
NCT06566742[153]: Olutasidenib	CCUS with *IDH1*	Olutasidenib	Adverse event incidence	—	Phase 2	15
NCT06630221[188]: Eltrombopag for low-risk MDS/CMML	MDS, CMML with *TET2* mutation	Eltrombopag	Hematologic response rate	AML-free survival, PFS	Phase 2	25
NCT05641831[189]: Canakinumab for CCUS	Unexplained, clinically meaningful cytopenias > 4 months), HgB <110 g/L, ANC 0.5 −1.8 $\times 10^9/L$	Canakinumab IL-1β inhibitor vs. placebo (double-blind)	Time to MN development	Hematologic response rate overall survival cardiovascular events	Phase 2	110
NCT06788691[154]: Luspatercept in CCUS	CCUS with cytopenias (Hb < 13 g/dL in males, < 12 g/dL in females, ANC < 1.8 $\times 10_9$/L for leukopenia, and platelets < 150 $\times$ 10_9/L for thrombocytopenia.	Luspatercept	Cytopenia response (HI-E/P/N as per IWG 2018 MDS response criteria)	Duration of response (months)	Phase 2	50

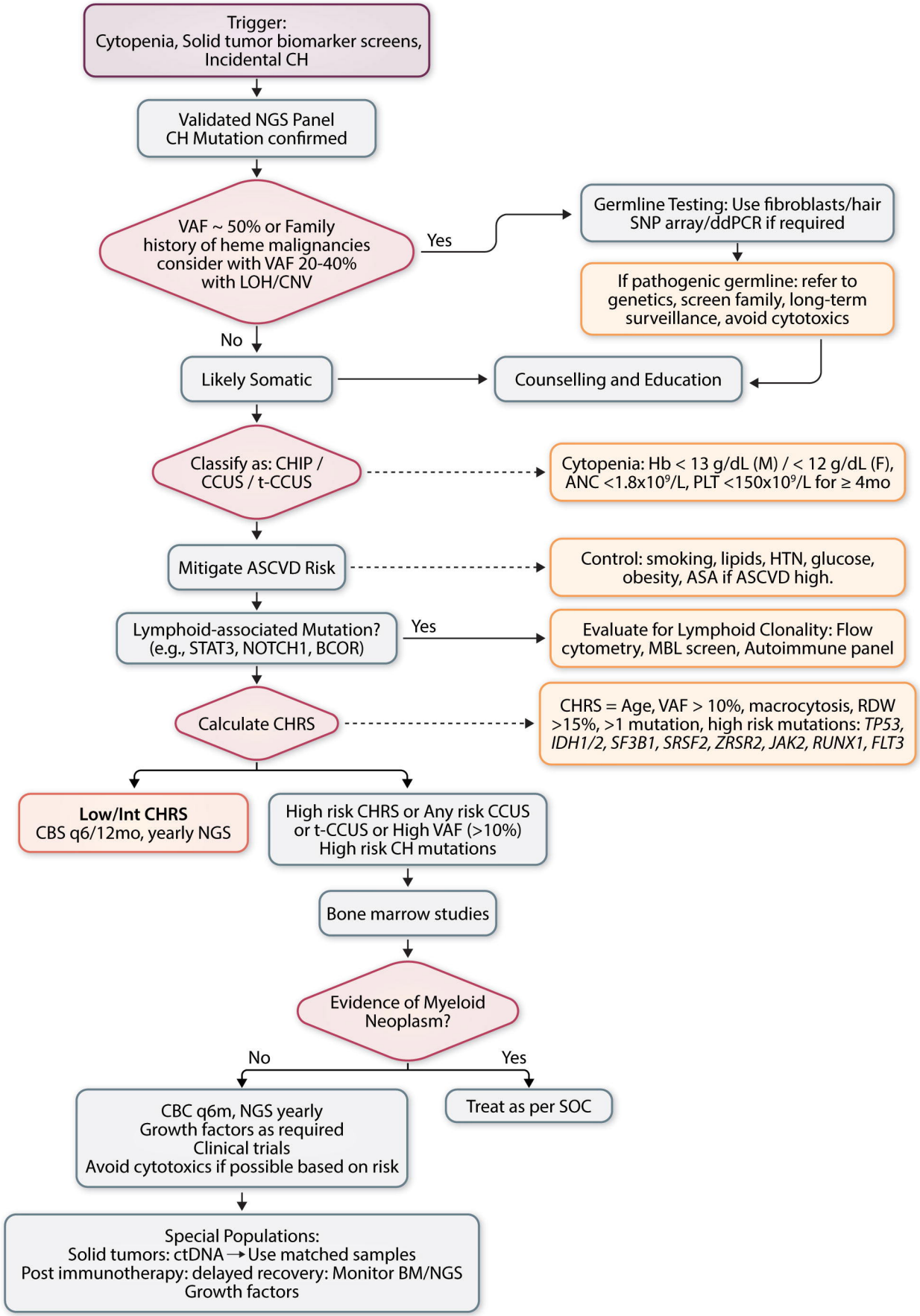
Table 10. Ongoing Observational studies in CH

Study	Population	Intervention / Summary	Primary Objective	Secondary Objective	N
Observational studies					
NCT04102423[190]: CHIP/CCUS Natural History	CHIP, CCUS (Adults)	—	verify the association of myeloid somatic mutations with CVD and MN	new clinical associations	306
NCT04541654[191]: LiFT UP	Li-Fraumeni, *TP53* CH/mosaicism	Genetic data/specimen collection	Cancer risk estimation	cancer prevention, early detection, and treatment	1500
NCT04689750[192]: Donor CHIP and Allo-HSCT	CHIP in donors/recipients	NGS: donors at the time of stem cell donation; recipients: at 1-mo, 6-mo, 12-mo post-HSCT, at relapse	Overall survival, Progression-free survival	GVHD, donor-derived leukemia, cardio-pulmonary complications	850
NCT05246813[193]: Metabolic Profiling	≥65 yr with hip fracture or hip OA	Blood/marrow collection for single-cell transcriptomics and mutation-specific single-cell genotyping	Gene Set Enrichment Analysis (GSEA) Normalized Enrichment Score (NES)	—	24
NCT05705531[194]: CHIP in HL Survivors	Hodgkin Lymphoma (HL) survivors	NGS for t-CH and Cardiac screening	t-CH frequency with CVD after HL treatment	VAF dynamics, CHIP expansion	230
NCT05969821[195]: Clonal Hematopoiesis of Immunological Significance (CHIS) study	autoimmune/autoin disease with or without CH	Observation only	VEXAS, other phenotypes	—	1000
NCT06156319[196]: CH in acute myocardial infarction (AMI)	AMI patients with renal failure undergoing PCI	NGS for CH	all-cause death, cardiac death, and nonfatal myocardial infarction.	—	500
NCT06244069[197]: CH in Giant Cell Arteritis (GCA)	GCA	PB sequencing + transcriptomics	Correlation of GCA with M-CHIP-driven by DNMT3A mutations	TET2/ASXL1/JAK2/L-C correlation	326
NCT06295965[198]: Clonal Hematopoiesis and Therapy-Emergent Myeloid Neoplasms in Patients With CancersCHANCES Study	Solid tumor patients	NGS	*TP53* VAF vs CH expansion, clonal evolution, t-MN risk	—	2000
NCT06701214[199]: The Clonal Hematopoiesis & Inflammation in Vasculature (CHIVE) Registry and Biorepository	ICUS, Idiopathic cytosis, CCUS, CH or at high risk of CH	Blood, saliva, marrow collection	Registry establishment	Biorepository development	800
NCT06870760[200]: Firefighters Study	Firefighters aged 40-49 yrs with ≥ 5 years on job	NGS for CH	CH detection rate	MGUS detection	300
NCT05711173[201]: CLODETTE Study	Age ≤ 50 yrs with thrombosis	PB NGS	CH detection	NETosis (MPO-DNA complex, Histone 3-DNA complex, citrullinated histone 3, DNAse) markers vs control	150

Figure Legends

Figure 1. Algorithm for management of CH and CCUS The algorithm guides clinicians through initial assessment, risk stratification based on mutation type and burden, and recommended surveillance strategies.

Abbreviations and Definitions: ASCVD: Atherosclerotic cardiovascular disease; CH: Clonal hematopoiesis; CHIP: Clonal hematopoiesis of indeterminate potential; CHRS: Clonal Hematopoiesis Risk Score; CCUS: Clonal cytopenia of unknown significance; t-CCUS: Therapy-related clonal cy-topenia of unknown significance; NGS: Next-generation sequencing; VAF: Variant Allele Fraction.


Trigger:
Cytopenia, Solid tumor biomarker screens,
Incidental CH
Validated NGS Panel
CH Mutation confirmed
VAF ~ 50% or Family history of heme malignancies consider with VAF 20-40% with LOH/CNV
Yes
Germline Testing: Use fibroblasts/hair SNP array/ddPCR if required
If pathogenic germline: refer to genetics, screen family, long-term surveillance, avoid cytotoxics
No
Likely Somatic
Counselling and Education
Classify as: CHIP / CCUS / t-CCUS
Cytopenia: Hb < 13 g/dL (M) / < 12 g/dL (F), ANC <1.8x10⁹/L, PLT <150x10⁹/L for ≥ 4mo
Mitigate ASCVD Risk
Control: smoking, lipids, HTN, glucose, obesity, ASA if ASCVD high.
Lymphoid-associated Mutation? (e.g., STAT3, NOTCH1, BCOR)
Yes
Evaluate for Lymphoid Clonality: Flow cytometry, MBL screen, Autoimmune panel
Calculate CHRS
CHRS = Age, VAF > 10%, macrocytosis, RDW >15%, >1 mutation, high risk mutations: TP53, IDH1/2, SF3B1, SRSF2, ZRSR2, JAK2, RUNX1, FLT3
Low/Int CHRS
CBS q6/12mo, yearly NGS
High risk CHRS or Any risk CCUS or t-CCUS or High VAF (>10%) High risk CH mutations
Bone marrow studies
Evidence of Myeloid Neoplasm?
No
Yes
CBC q6m, NGS yearly
Growth factors as required
Clinical trials
Avoid cytotoxics if possible based on risk
Treat as per SOC
Special Populations:
Solid tumors: ctDNA → Use matched samples
Post immunotherapy: delayed recovery: Monitor BM/NGS
Growth factors