

REVIEW

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Clonal hematopoiesis of indeterminate potential and heart disease: What every internist needs to know

ABSTRACT

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition defined by somatic mutations in hematopoietic stem cells that result in clonal expansion, without overt hematologic malignancy. It is now recognized as a potent risk factor for atherosclerotic cardiovascular disease, with emerging associations across a broader spectrum of cardiovascular phenotypes, including myocarditis, pericarditis, arrhythmias, valvular heart disease, and heart failure. The authors of this article review the epidemiology, pathophysiology, and management of this condition.

KEY POINTS

CHIP is common in older adults and increases cardiovascular risk independent of traditional risk factors.

In CHIP, several mutations promote proatherogenic inflammatory cytokine signaling (including interleukin 1 beta and interleukin 6), linking clonal hematopoiesis to atherosclerotic cardiovascular disease.

People with CHIP, particularly those carrying high-risk genotypes, should be regarded as having a cardiovascular risk-enhancing feature and should be considered for intensive management of lipids, blood pressure, blood glucose, and lifestyle factors.

Ongoing and future trials targeting inflammatory pathways and clonal expansion may enable CHIP-specific cardiovascular and hematologic therapies.

CLONAL HEMATOPOIESIS of indeterminate potential (CHIP) is an age-related condition in which hematopoietic stem cells acquire somatic mutations in genes commonly associated with leukemia, without evidence of hematologic malignancy. While CHIP was originally demonstrated to be a precursor of hematologic malignancies, large population studies show that people with CHIP also have a heightened risk of coronary artery disease, stroke, arrhythmias, myocarditis, pericarditis, valvular heart disease, and heart failure.¹⁻⁴

Recognizing CHIP as a cardiovascular risk factor provides an opportunity to refine risk assessment and implement preventive strategies. Here, we review what CHIP is, how it is detected, how it affects heart risk, and what can be done about it.

■ WHAT IS CHIP?

CHIP refers to expansion of a hematopoietic stem cell clone carrying a somatic mutation in a leukemia driver gene, in the absence of overt hematologic malignancy, cytopenia, or morphologic dysplasia.⁵ By convention, to meet the CHIP threshold, the mutation must be present in at least 2% of alleles tested, a metric called the *variant allele fraction*. CHIP becomes increasingly prevalent with age, reflecting accumulation of somatic mutations and selective clonal advantage over time.

The most commonly mutated genes include *DNMT3A*, *TET2*, and *ASXL1*, which influence epigenetic regulation, as well as *JAK2* and genes

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Glossary of terms pertinent to CHIP

Atherosclerotic cardiovascular disease—clinical conditions caused by atherosclerosis, including coronary artery disease, myocardial infarction, ischemic stroke, and peripheral arterial disease

CHIP—clonal hematopoiesis of indeterminate potential; the presence of somatic mutations in hematopoietic stem cells leading to clonal expansion without overt hematologic malignancy, cytopenia, or morphologic dysplasia

ctDNA—circulating tumor DNA; fragments of tumor-derived DNA found in peripheral blood, commonly analyzed in liquid biopsy assays

DNA damage response genes—genes involved in detecting and repairing DNA damage, including *TP53*, *PPM1D*, and *CHEK2*, frequently implicated in CHIP and cancer biology

Hematologic malignancy—cancers arising from blood-forming tissues, including myelodysplastic syndromes, myeloproliferative neoplasms, and acute leukemias

Liquid biopsy—a blood-based assay used to detect somatic mutations, often through sequencing of peripheral blood or ctDNA, without requiring tissue or bone marrow biopsy

Neutrophil extracellular traps—web-like structures of DNA and proteins released by activated neutrophils that promote inflammation and thrombosis

Next-generation sequencing—high-throughput DNA sequencing technologies used to detect somatic mutations in hematologic and solid tumor genomes

NLRP3 inflammasome—nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; a multiprotein intracellular signaling complex in innate immune cells that detects danger signals and triggers inflammatory responses, particularly through activation of interleukin 1 beta and interleukin 6 pathways

Variant allele fraction—the proportion of DNA sequencing reads that contain a specific somatic mutation, used as a measure of clone size; by convention, CHIP is defined by a fraction of at least 2%

involved in DNA damage repair, including *TP53* and *PPM1D*.⁶ These mutations may arise spontaneously or as a consequence of cytotoxic therapies, particularly after chemotherapy or radiation exposure.⁷

CHIP was first recognized for its preleukemic potential; the absolute annual risk of progression from CHIP to hematologic malignancy—most commonly myelodysplastic syndromes, myeloproliferative neoplasms,

chronic myelomonocytic leukemia, or acute myeloid leukemia—averages between 0.5% and 1% in the general population but is substantially higher in older people (particularly those older than 70) and those who have received cytotoxic chemotherapy or radiotherapy.⁸ Hematologists use these factors to determine the duration between visits and need for repeat bone marrow biopsy.

At the same time, carriers experience a markedly higher rate of cardiovascular events, which explains a large part of the excess mortality associated with CHIP (hazard ratio 1.4, 95% confidence interval 1.1–1.8).⁸ These observations have reframed CHIP from being a purely hematologic precursor condition to a multisystem disorder at the intersection of aging, inflammation, cancer biology, and cardiovascular disease.

■ WHEN DO CLINICIANS TEST FOR CHIP?

Most cases of CHIP are diagnosed incidentally by hematologists or oncologists, either during evaluation for unexplained cytopenia or abnormal differentials on the complete blood cell count. Driving the trend of incidental discovery is the widespread use of comprehensive genomic panels, most often in patients with solid tumors and less commonly in those with nonmyeloid hematologic malignancies. Other cases are detected through germline genetic testing in relatives of patients with cancer, although this is quite rare. CHIP is also often detected when hematologists and oncologists perform genomic sequencing to guide therapy for a patient with newly diagnosed cancer.

Of note, in contemporary hematology practice, next-generation sequencing is frequently performed on peripheral blood through liquid biopsy approaches and does not necessarily require a bone marrow biopsy. However, bone marrow biopsy is indicated in selected clinical scenarios, particularly when there is concern for an underlying hematologic malignancy or unexplained cytopenias, or when morphologic and cytogenetic evaluation are required. As technologies such as liquid biopsy and circulating tumor DNA assays are incorporated into routine care at diagnosis and for longitudinal surveillance, CHIP-associated variants are increasingly reported on these platforms.

Currently, no formal cardiology society guidelines recommend routinely screening for CHIP in adults without symptoms. Therefore, referral from hematologists or oncologists remains the most common route to cardiovascular medicine for patients with CHIP at present.

At Cleveland Clinic, patients with CHIP are evaluated in a special CHIP hematology clinic, where an

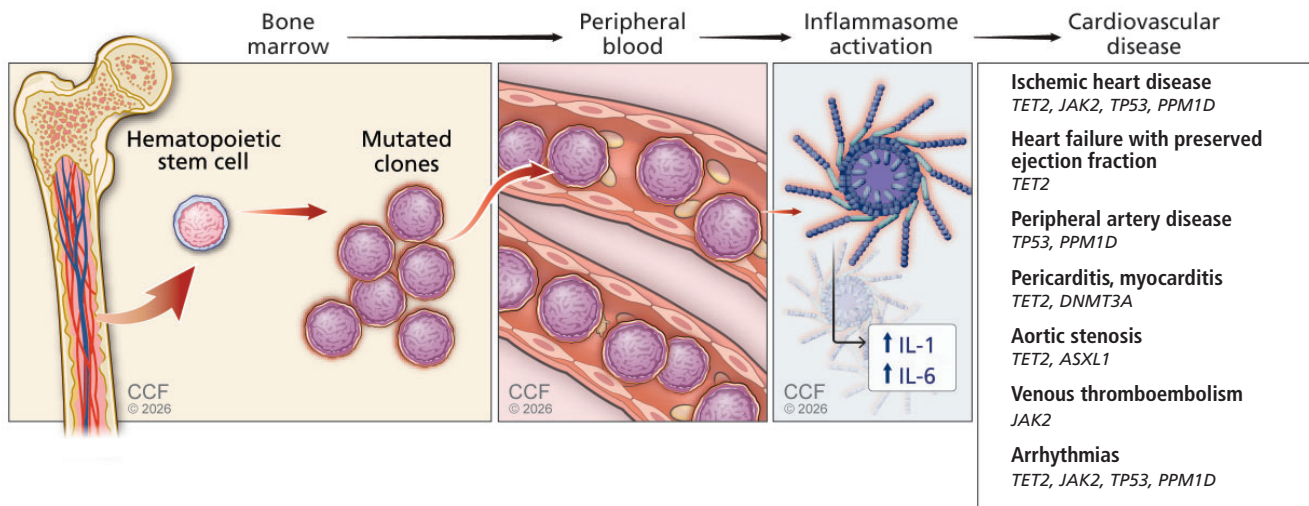


Figure 1. How clonal hematopoiesis of indeterminate potential leads to heart disease. A somatic mutation in a hematopoietic stem cell may lead to clonal expansion and the emergence of mutant myeloid cell populations with altered inflammatory signaling, promoting activation of the inflammasome, a cellular protein complex that senses danger signals and triggers innate immune inflammation, with increased downstream interleukin (IL) 1 beta and IL-6 signaling. These proinflammatory pathways contribute to the development of cardiovascular disease. Clonal hematopoiesis is associated with various cardiovascular phenotypes, including atherosclerotic cardiovascular disease, arrhythmias, aortic stenosis, pericarditis and myocarditis, heart failure, and venous thromboembolism, with differing risk patterns by driver mutation (eg, in *TET2, DNMT3A, ASXL1, JAK2, TP53, and PPM1D*).

internal consensus care path is used to stratify their risk (low, intermediate, or high) and surveil for evolution to myeloid neoplasms such as myelodysplastic syndromes, myeloproliferative neoplasms, chronic myelomonocytic leukemia, acute myeloid leukemia, and, in special contexts, less common lymphoid conditions. We monitor their complete blood cell count approximately every 3 to 12 months based on their risk, perform next-generation sequencing every year, and refer them to our CHIP cardiology clinic.

■ WHY IS CHIP ASSOCIATED WITH CARDIOVASCULAR DISEASE?

CHIP-associated mutations alter immune cell function, promote systemic inflammation, and enhance thrombotic potential. Examples of these mutations include the following:

TET2 mutations activate the NLRP3 inflammasome in macrophages, a multiprotein intracellular signaling complex that functions as an innate immune sensor and amplifier of inflammatory responses; activation of the NLRP3 inflammasome leads to increased interleukin 1 beta and interleukin 6 signaling.⁹ This inflammatory signaling is now understood to be a central driver of atherosclerotic plaque development and

progression, linking *TET2* clonal hematopoiesis and ischemic arterial events (Figure 1).

JAK2 mutations promote arterial and venous thrombosis through neutrophil extracellular trap formation and inflammasome-mediated inflammation.¹⁰ In addition, DNA replication stress and activation of the AIM2 inflammasome are observed in *JAK2* CHIP, explaining the propensity for increased atherosclerosis.¹¹ Similarly, *JAK2* V617F CHIP may drive arterial thrombosis through heightened platelet activation and cross talk between mutant and wild-type platelets.¹²

DNA damage response mutations in *TP53, PPM1D, and CHEK2* similarly enhance macrophage proliferation within plaque and contribute to the development and progression of peripheral arterial disease.¹³

Research is underway to elucidate the pathobiological underpinnings of CHIP in relation to nonischemic cardiovascular conditions such as atrial fibrillation and heart failure with preserved ejection fraction.

■ EPIDEMIOLOGY AND CLINICAL RELEVANCE

CHIP is rare before age 40, affecting less than 1% of people in this age group, but the prevalence rises to about 17% by the seventh decade, and about 30% by

age 80.¹⁴ People with CHIP face a higher risk of several types of heart disease (Figure 1):

Atherosclerotic cardiovascular disease. In the general population, CHIP carriers face a roughly 2-fold higher risk of incident coronary artery disease and myocardial infarction, independent of traditional atherosclerotic risk factors.¹ However, this risk is heterogeneous, being higher in those with *TET2*, *JAK2*, and DNA damage response mutations (eg, in *TP53* and *PPM1D*), while *DNMT3A* mutations show more variable associations across cohorts.¹⁵ Large clone size (defined as variant allele fraction $\geq 10\%$), clonal expansion, and the presence of multiple CHIP mutations further magnify risk.¹

In high-risk subgroups, such as patients with type 2 diabetes, UK Biobank data indicate that CHIP remains independently associated with incident cardiovascular disease (hazard ratio 1.21 for “any CHIP,” 1.25 for variant allele fraction $\geq 10\%$) even after adjustment for metabolic risk indicators.¹⁶

In the Women’s Health Initiative Long Life Study,¹⁷ *TET2* CHIP was associated with higher absolute rates of coronary heart disease events. The incidence of coronary heart disease was 15.4 per 1,000 person-years in women with *TET2* CHIP compared with 9.2 per 1,000 person-years in those without CHIP, corresponding to a 10-year absolute risk of 13.6% vs 9.0%.

Heart failure. CHIP is also linked to increased incidence and worse prognoses in heart failure, particularly heart failure with preserved ejection fraction in carriers of the *TET2* mutation,³ and to higher rates of mortality and adverse outcomes in patients with established cardiovascular disease or undergoing structural interventions such as transcatheter aortic valve replacement.¹⁸

Myocarditis and pericarditis. A large UK Biobank-based study found that CHIP (especially large clones) was associated with an approximately 1.75-fold increased risk of incident myocarditis or pericarditis after multivariable adjustment (particularly for *DNMT3A* and *TET2* mutations).²

Arrhythmias. Emerging data suggest an association between CHIP and new-onset cardiac arrhythmias independent of coronary artery disease or heart failure, with strong effects observed across examined driver genes except *DNMT3A*.^{4,19}

■ NEXT-GENERATION DNA SEQUENCING TO DETECT CHIP

CHIP is typically detected using next-generation sequencing panels designed to identify somatic muta-

tions in genes commonly associated with myeloid malignancies.²⁰ Most assays sequence about 40 to 60 leukemia-associated driver genes, with sensitivity sufficient to detect variant allele fractions as low as 1% to 2%.

By convention, a variant allele fraction of at least 2% defines CHIP, though this threshold is arbitrary and clones with lower variant allele fractions may still carry hematologic or cardiovascular risk.²¹ Targeted next-generation sequencing approaches are used, either hybrid-capture or amplicon-based, with bioinformatics pipelines to filter out germline variants and sequencing artifacts.²² Research techniques, such as error-corrected sequencing, can detect smaller clones ($< 1\%$ variant allele fraction), though these are not yet standard in clinical practice.²³

■ CARDIOVASCULAR RISK ASSESSMENT AND MANAGEMENT IN PATIENTS WITH CHIP

Given the growing recognition of CHIP as a potent cardiovascular risk enhancer, cardiovascular clinicians should integrate it into comprehensive risk assessment that also includes lipid levels, blood pressure, glycemic control, and family history of cardiovascular disease.²⁴ Assessment of additional risk markers such as high-sensitivity C-reactive protein may help quantify the inflammatory milieu associated with CHIP, although these tests are adjunctive and additional studies are needed to understand their incremental value in the context of CHIP.

Patients with CHIP, particularly those with high-risk mutations (*TET2*, *JAK2*, DNA damage repair genes) or large ($> 10\%$) clones, should receive intensive risk factor modification.²⁴ Proposed management targets include the following:

Low-density lipoprotein cholesterol levels below 70 mg/dL in patients with *TET2*, *JAK2*, or DNA damage repair CHIP, and below 55 mg/dL in those with large high-risk clones, multiple high-risk mutations, or concomitant atherosclerotic cardiovascular disease.

Blood pressure lower than 130/80 mm Hg, or lower than 120/80 mm Hg in patients with large high-risk clones, multiple high-risk mutations, or concomitant atherosclerotic cardiovascular disease.

Individualized glycemic targets based on age, comorbidity burden, functional status, and hypoglycemia risk. While hemoglobin A1c less than 6.5% may be appropriate in select, physiologically robust individuals with low hypoglycemia risk, less stringent targets (eg, $< 7.5\%$ – 8.5%) are recommended for older adults with complex comorbidities or limited life expectancy.

Lifestyle interventions, including regular physical activity, adherence to a Mediterranean diet, weight loss, and smoking cessation, are essential components of preventive care.

Low-dose aspirin can be considered for select patients, particularly those with *JAK2* mutations or a history of venous thromboembolism, after carefully weighing the risk of bleeding.²⁴

Vitamin C and colchicine. For patients with *TET2* CHIP, discussions about potential off-label strategies, including vitamin C, colchicine, or both, may be appropriate, given emerging evidence suggesting that vitamin C enhances DNA demethylation in *TET2*-mutant cells and that colchicine may slow clonal expansion and attenuate atherosclerosis.

Taira et al²⁵ reported that vitamin C boosts DNA demethylation in *TET2* germline mutation carriers.

In an exploratory substudy of the LoDoCo2 (Low-Dose Colchicine 2) trial,²⁶ colchicine use was associated with slower expansion of *TET2* CHIP clones, although effect sizes were small. Further, Zuriaga et al²⁷ reported that colchicine prevented accelerated atherosclerosis in *TET2*-mutant clonal hematopoiesis both in a mouse model and in humans.

■ A CHIP CARDIOLOGY CLINIC

The emergence of CHIP as a cardiovascular risk enhancer has prompted the development of specialized CHIP clinics at major academic medical centers.²⁸ These clinics reflect increasing collaboration among cardiologists and hematologists. For example, the CHIP Cardiology Clinic at Cleveland Clinic was established to integrate clinical, imaging, and genomic data to facilitate individualized cardiovascular assessment and risk factor optimization.

The typical referral population includes patients with CHIP detected during oncology care, who are subsequently referred for evaluation of elevated cardiovascular risk.²⁹ The clinic visit generally includes thorough cardiovascular risk assessment, review of genomic findings (mutation types and variant allele fraction), baseline laboratory tests including lipid profile, opportunistic review of previous imaging studies to assess for subclinical atherosclerosis or arterial calcification, and counseling regarding aggressive management of traditional risk factors.

A CHIP cardiology clinic also serves as a platform for research and clinical trial enrollment, enabling longitudinal study of disease biology and outcomes while facilitating access to investigational therapies.²⁹ Close multidisciplinary collaboration across programs

is essential to inform an integrated approach to the evaluation and treatment of these patients.

■ ONGOING TRIAL OPPORTUNITIES

Ongoing clinical trials are exploring targeted anti-inflammatory therapies in patients with CHIP and coronary artery disease, including colchicine (German Clinical Trials Register; DRKS00037089) and NLRP3 inhibitors and bispecific interleukin 1 beta and interleukin 18 inhibitors (ClinicalTrials.gov; NCT06097663). These studies aim to interrupt inflammasome-mediated pathways activated by *TET2*, while future research may focus on mutation-specific approaches, such as *JAK2*-driven clonal expansion inhibition or genome-editing strategies for pathogenic mutations.

Emerging “interception” strategies are now testing targeted agents such as inhibitors of mutant isocitrate dehydrogenase 1 and 2 (*IDH1/2*; eg, ivosidenib, olutasidenib, enasidenib) in premalignant states (like *IDH1/2*-mutant clonal hematopoiesis) to reduce clonal burden and improve cytopenias, with the goal of delaying or potentially preventing progression to overt hematologic malignancy.³⁰ Whether such targeted approaches have the potential to mitigate CHIP-associated cardiovascular risk in individuals with sequence variants linked to heightened cardiovascular risk remains to be determined.

Studies are also needed to explore the utility of CHIP-informed risk stratification in guiding preventive therapies. For example, whether intensive lipid-lowering or antiplatelet therapy provides additional benefit in high-risk CHIP remains unknown. Registries capturing long-term cardiovascular outcomes in CHIP patients will be critical for defining evidence-based practice and informing guideline development.

Ultimately, these studies may allow clinicians to move from treating CHIP as a risk enhancer to implementing mutation-specific precision interventions, bridging genomics with individualized cardiovascular care. Such interventions could include tailoring anti-inflammatory, antithrombotic, and preventive cardiovascular therapies according to the underlying CHIP genotype and its associated biological pathways, thereby enabling genotype-guided risk stratification and targeted prevention strategies.

■ MEETING THE CHALLENGE

Clonal hematopoiesis is increasingly recognized as a driver of different types of heart disease, including ischemic heart disease, heart failure, arrhythmias, valvular heart disease, and nonischemic cardiac inflammation.

With the commercialization of genomic sequencing and rapidly falling costs, detection of CHIP is increasing and may become widespread in clinical practice. This will lead to the identification of many individuals at heightened cardiovascular risk who are in need of tailored prevention and management. The next decade will require systems, strategies, evidence, and therapies capable of meeting this challenge. ■

DISCLOSURES

Dr. Oren reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest. Dr. Singh reported consulting for Geron and Syndax, research as a primary investigator for Novartis Pharmaceuticals, and research as a coprimary investigator for Rigel. Dr. Carraway reported consulting for BMS, Daiichi Sankyo, Inc., Genentech, Jazz Pharmaceuticals, Kura, and

Takeda, acting as an advisor or review panel participant for Celgene Corporation, Genentech, Jazz Pharmaceuticals, Novartis Oncology, and Stemline Therapeutics, Inc., and teaching and speaking for Jazz Pharmaceuticals, Novartis Oncology, and Stemline Therapeutics, Inc. Dr. Laffin reported research as a primary investigator for Arrowhead, CRISPR Therapeutics, Kardigan, and Madrigal, research as Executive Committee Member of SURMOUNT MMO trial and Executive Committee Chair of ATTAIN-HTN trial for Eli Lilly, Executive Committee Member for a phase 2 trial for Mineralys Therapeutics, and Executive Committee Member for hypertension and lipids trials for Novartis, research as secondary publications author for Esperioin, consulting for AstraZeneca Pharmaceuticals, Idorsia Pharmaceuticals, Ltd., Medtronic, Novo Nordisk, Inc., ReCor Medical, and Veradermics, teaching and speaking for Cardiometabolic Health Congress and ReCor Medical, and acting as an advisor or review panel participant for Gordy Health, LucidAct Health, and Ripple Medical. Dr. Nissen reported that the Cleveland Clinic Center for Clinical Research (C5Research) has received funding to perform clinical trials from Abbvie Pharmaceuticals, AstraZeneca Pharmaceuticals, Arrowhead, CRISPR Therapeutics, Eli Lilly, Esperion, Kardigan, Madrigal, MyoKardia, Inc., New Amsterdam, Novartis Pharmaceuticals, and Silence Therapeutics. Dr. Nissen is involved in conducting these clinical trials but receives no personal remuneration for his participation.

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