

Clonal Hematopoiesis and Biological Aging: An Emerging Biomarker for Longevity Medicine

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Abstract

Chronological age does not fully capture the substantial interindividual variability in aging, prompting growing interest in biomarkers that reflect biological aging and susceptibility to age-related disease. Clonal hematopoiesis of indeterminate potential (CHIP), characterized by the age-related expansion of hematopoietic clones carrying somatic mutations in the absence of an overt hematologic malignancy, has emerged as a potential link between somatic evolution, chronic inflammation, and age-related disease. This narrative review examines the biological mechanisms linking clonal hematopoiesis to aging, evaluates the evidence supporting CHIP as an emerging biomarker of biological aging, and discusses its potential implications and current limitations in longevity medicine. CHIP becomes increasingly prevalent with age and reflects the interplay between somatic mutation accumulation, clonal selection, and an aging inflammatory microenvironment. Growing evidence links CHIP to epigenetic age acceleration, with associations influenced by the mutated gene, clone size, and clonal architecture. Beyond its established risk of progression to myeloid malignancy, CHIP is associated with cardiovascular disease, heart failure, and increased mortality. Experimental and clinical data suggest that clone-dependent inflammatory pathways, particularly IL-1 β signaling in *TET2*-mutated clonal hematopoiesis, may contribute to cardiovascular complications. However, the clinical significance of CHIP is highly heterogeneous, and its detection alone does not currently justify population-wide screening or CHIP-specific pharmacologic intervention. CHIP therefore represents a promising biomarker at the intersection of biological aging, inflammation, and age-related disease, but it should not yet be considered an established clinical biomarker of longevity. Future longitudinal studies and randomized interventional trials are needed to determine whether integrating clonal characteristics with epigenetic, inflammatory, cardiovascular, and functional biomarkers improves risk stratification and, importantly, whether CHIP-guided interventions can improve health span or survival.

Categories: Family/General Practice, Hematology, Geriatrics

Keywords: biological aging, chip, clonal hematopoiesis, epigenetic aging, inflammaging, longevity medicine

Introduction And Background

Aging is a major risk factor for chronic diseases, including cardiovascular disease, cancer, and hematologic malignancies. However, chronological age does not fully capture the substantial variability in aging between individuals, driving growing interest in biomarkers of biological aging. Biological aging refers to the progressive molecular, cellular, and functional changes associated with aging. No single biomarker is currently accepted as a gold standard for its assessment. Epigenetic clocks, inflammatory markers, functional measures, and frailty indices capture complementary but distinct aspects of this process.

Age-related clonal hematopoiesis is particularly relevant in this context. Clonal hematopoiesis broadly refers to the expansion of hematopoietic cell populations carrying acquired somatic mutations. Clonal hematopoiesis of indeterminate potential (CHIP) represents a more specific category, conventionally defined by the presence of a mutation associated with myeloid neoplasms at a variant allele frequency (VAF) $\geq 2\%$, in the absence of an overt hematologic malignancy or unexplained cytopenia. Smaller clones may also occur without meeting the conventional CHIP definition. CHIP becomes increasingly prevalent with age, with DNMT3A, TET2, and ASXL1 among the most frequently mutated genes [1,2].

Initially regarded primarily as a preleukemic condition, CHIP is now associated with a broader spectrum of age-related outcomes, including hematologic malignancies, cardiovascular disease, and mortality [1-3]. Chronic low-grade inflammation (inflammaging) and activation of pathways such as NLRP3-IL-1 β -IL-6 may contribute to these associations [3,4]. Furthermore, the association between CHIP and epigenetic age acceleration suggests that clonal hematopoiesis may reflect aspects of biological rather than chronological aging alone [5]. However, this association does not establish CHIP as a direct measure of biological aging or demonstrate a causal effect on longevity.

Longevity medicine aims to prevent age-related disease and preserve health and functional capacity throughout life. In this context, CHIP may represent a potential biomarker of aging, a marker of age-related disease risk, or a possible causal contributor to certain diseases. These roles must be distinguished, and

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CHIP testing has no established role in routine longevity practice.

This review examines the mechanisms linking clonal hematopoiesis to aging, the evidence supporting CHIP as an emerging biomarker of biological aging, and its potential implications and current limitations in longevity medicine.

Review

Literature search

This narrative review was based on a literature search conducted using PubMed/MEDLINE without restrictions on publication date. The search was last updated in September 2026. The search focused on publications addressing clonal hematopoiesis and its relationship with biological aging, epigenetic age acceleration, chronic inflammation, cardiovascular disease, hematologic malignancies, mortality, risk stratification, and potential therapeutic interventions.

The principal search concepts included “clonal hematopoiesis,” “clonal hematopoiesis of indeterminate potential,” “CHIP,” “biological aging,” “epigenetic aging,” “inflammaging,” “cardiovascular disease,” “mortality,” “risk stratification,” and “therapeutic interventions.”

Relevant original studies, observational cohorts, experimental investigations, and narrative reviews were considered, with particular attention to landmark publications and recent evidence directly related to the objectives of this review. Studies were selected according to their relevance to the biological mechanisms, clinical associations, and potential implications of clonal hematopoiesis in longevity medicine. The reference lists of relevant publications were also manually screened to identify additional studies of interest.

Given the narrative design of this review, no formal meta-analysis or systematic risk-of-bias assessment was performed.

Biological basis of age-related clonal hematopoiesis

Aging of the Hematopoietic Stem Cell Compartment

Hematopoietic stem cells (HSCs) progressively accumulate somatic mutations throughout life, at an estimated rate of approximately 17 mutations per year after birth [6]. Although most are neutral, some confer a competitive advantage that promotes clonal expansion.

Clonal selection becomes increasingly pronounced with age. In young and middle-aged adults, hematopoiesis remains largely polyclonal, relying on tens of thousands of HSCs and multipotent progenitors. After 70–75 years of age, this diversity declines markedly, and an increasing proportion of blood cell production may derive from a limited number of dominant clones [6]. Clonal hematopoiesis therefore represents the culmination of an evolutionary process that may begin decades before it becomes clinically detectable.

Driver Mutations and Clonal Selection

CHIP most commonly involves genes regulating epigenetic processes, particularly DNMT3A, TET2, and ASXL1, but may also affect signaling (JAK2), RNA splicing (SF3B1, SRSF2, and U2AF1), and DNA damage response genes (TP53 and PPM1D) [1,2]. According to the World Health Organization definition, CHIP is characterized by a somatic mutation in a gene associated with myeloid neoplasms at a variant allele frequency (VAF) $\geq 2\%$, in the absence of a diagnosed hematologic malignancy or unexplained cytopenia [7].

Clonal dynamics vary considerably by gene. DNMT3A-mutated clones may emerge relatively early and often expand slowly at older ages, whereas TET2-mutated clones continue to expand throughout life. In contrast, mutations in splicing genes such as SRSF2 tend to emerge later but may expand more rapidly [8]. Clone size and its evolutionary trajectory may therefore provide information beyond the simple presence or absence of CHIP.

Aging, Inflammation, and Selective Advantage

Clonal expansion is also shaped by the aging hematopoietic microenvironment, which is characterized by changes in the bone marrow niche, increased cellular stress, and chronic low-grade inflammation, or inflammaging. Within this environment, mutated HSCs may gain a survival or self-renewal advantage. In particular, HSCs harboring DNMT3A or TET2 mutations may be less susceptible to the detrimental effects of inflammatory and aging-related signals, favoring their selection [9].

This relationship may be bidirectional: aging and inflammation promote clonal expansion, while myeloid cells derived from these clones may increase the production of pro-inflammatory mediators. This

amplification loop may link CHIP, inflammaging, and age-related disease [3,4].

Overall, age-related clonal hematopoiesis reflects the interplay between somatic mutation accumulation, clonal selection, and an aging hematopoietic microenvironment. This may explain both its increasing prevalence with age and its potential to provide information beyond chronological age alone.

CHIP as a biomarker of biological aging

Beyond Chronological Age

Chronological age is a major determinant of CHIP but does not fully explain its occurrence or clinical significance. Among individuals of the same age, some retain largely polyclonal hematopoiesis, whereas others develop dominant clones accounting for a substantial proportion of blood cell production [6]. This variability suggests that clonal hematopoiesis may capture aspects of biological aging beyond chronological age alone.

This concept is particularly relevant to longevity medicine, which aims to identify biological processes associated with declining physiological reserve and age-related disease. CHIP may therefore provide a biological record of the cumulative effects of somatic mutations, selective pressures, and exposure to an aging hematopoietic microenvironment.

CHIP and Epigenetic Age Acceleration

Some of the strongest evidence linking CHIP to biological aging comes from epigenetic clocks, which estimate biological age from DNA methylation patterns. The difference between epigenetic and chronological age is commonly used as a measure of age acceleration.

Robertson et al. first reported an association between age-related clonal hematopoiesis and accelerated epigenetic aging [10]. In a study including 5,522 individuals from four cohorts, Nachun et al. reported that CHIP was associated with epigenetic age acceleration compared with non-carriers, ranging from 1.31 years for GrimAge (95% CI 0.82-1.80) to 3.08 years for extrinsic epigenetic age acceleration (EEAA; 95% CI 2.43-3.73), after adjustment for sex, self-reported ancestry, and cohort [5]. Individuals with multiple mutations showed the greatest acceleration and shorter DNA methylation-estimated telomere length.

The association also varies by genotype. TET2 mutations appear to be associated with greater epigenetic age acceleration than DNMT3A mutations for some clocks [5]. A study of elderly twins similarly found a particularly strong signal for TET2, suggesting that the relationship between CHIP and biological aging depends, at least in part, on the mutated gene [11].

Clone size as an indicator of biological severity

In a cohort of 381 patients, including 106 individuals with CHIP, Feldkamp et al. found that large CHIP clones (VAF $\geq 10\%$) were associated with a mean 4.5-year increase in 7-CpG epigenetic age acceleration compared with individuals without CHIP ($p = 0.01$). The overall difference across clone-size groups remained significant after adjustment for age and sex ($p = 0.022$), whereas no significant difference was observed between individuals without CHIP and those with smaller clones (VAF $< 10\%$; $p = 0.718$) [12].

These findings support a biological continuum in which a small detectable clone may not carry the same significance as one that has expanded to occupy a substantial proportion of hematopoiesis. VAF may therefore provide an indirect measure of clonal selection and help distinguish low-impact CHIP from clonal hematopoiesis associated with a less favorable aging profile. The main findings supporting the relationship between CHIP and biological aging are summarized in Table 1.

Feature	Main finding	Potential significance for biological aging	Reference
Increasing age	Hematopoietic diversity declines markedly after 70–75 years of age, with an increasing contribution of dominant clones to blood cell production	May reflect age-related changes in hematopoietic stem cell dynamics	[6]
Epigenetic age acceleration	CHIP was associated with epigenetic age acceleration ranging from approximately 1.31 years with GrimAge to 3.08 years with extrinsic epigenetic age acceleration (EEAA)	Supports an association between CHIP and biological aging beyond chronological age alone	[5]
Multiple mutations	Individuals with multiple mutations showed the greatest epigenetic age acceleration and shorter DNA methylation-estimated telomere length	Clonal complexity may identify a more pronounced aging-associated phenotype	[5]
Mutated gene	TET2 mutations showed greater epigenetic age acceleration than DNMT3A mutations for some epigenetic clocks; a strong association with TET2 was also observed in elderly twins	Suggests that the relationship between CHIP and biological aging is genotype-dependent	[5,11]
Clone size	Large CHIP clones (VAF ≥10%) were associated with approximately 4.5 years of 7-CpG epigenetic age acceleration compared with individuals without CHIP; this association was not observed for smaller clones	VAF may provide an indirect measure of clonal selection and biological severity	[12]
CHIP combined with epigenetic aging	Individuals with both CHIP and accelerated Hannum and GrimAge clocks had particularly high risks of all-cause mortality and coronary heart disease	Combining CHIP with other aging biomarkers may provide more information than CHIP alone	[5]

TABLE 1: Evidence Linking Clonal Hematopoiesis to Biological Aging

CHIP: clonal hematopoiesis of indeterminate potential; VAF: variant allele frequency; EEAA: extrinsic epigenetic age acceleration

A promising biomarker, but not yet a clinical biomarker of longevity

The association between CHIP and epigenetic aging does not establish CHIP as a direct measure of biological aging. Both increase with chronological age and may share determinants such as inflammation, environmental exposures, and changes in blood cell composition. Moreover, the biological and clinical significance of CHIP varies according to the mutated gene, number of mutations, VAF, and clonal dynamics.

Its greatest value may therefore lie in combination with other biomarkers rather than as a stand-alone measure. Nachun et al. found that individuals with both CHIP and accelerated Hannum and GrimAge clocks had a particularly high risk of all-cause mortality and coronary heart disease, whereas CHIP without epigenetic age acceleration did not identify the same level of risk [5].

Overall, CHIP has several features of an emerging biomarker of biological aging, including increasing prevalence with age, altered clonal architecture, associations with epigenetic age acceleration, and prediction of age-related outcomes. However, its added value over existing biomarkers and its ability to guide interventions that improve healthspan remain to be established before routine use in longevity medicine.

CHIP, age-related diseases, and longevity

Cardiovascular Risk

The association between CHIP and cardiovascular disease has substantially broadened its clinical significance beyond hematologic transformation. Jaiswal et al. reported an increased risk of coronary heart disease and ischemic stroke among individuals with CHIP [1]. A subsequent study confirmed these associations across four case-control cohorts. In two prospective cohorts, CHIP carriers had a higher risk of coronary heart disease than non-carriers (HR 1.9, 95% CI 1.4–2.7). In two retrospective case-control cohorts, CHIP was associated with substantially higher odds of early-onset myocardial infarction (OR 4.0, 95% CI 2.4–6.7). Larger clones (VAF ≥10%) were also associated with greater coronary heart disease risk, although this finding was distinct from the fourfold association with early-onset myocardial infarction [3].

This association is not explained solely by age or conventional cardiovascular risk factors and may partly

involve clone-dependent inflammation. Experimental models of TET2 deficiency have shown accelerated atherosclerosis and increased production of pro-inflammatory cytokines, particularly IL-1 β , by clonal macrophages [4]. These findings suggest that clonal hematopoiesis may actively contribute to atherogenesis rather than simply reflect aging.

Cardiovascular risk also varies by genotype. DNMT3A, TET2, and ASXL1 mutations have been associated with a moderately increased risk of coronary heart disease, whereas the association is particularly strong for JAK2 V617F [3]. CHIP should therefore not be viewed as a simple binary cardiovascular risk factor.

CHIP has also been associated with heart failure. In a pooled analysis of five prospective cohorts including 56,597 individuals without heart failure at baseline, Yu et al. reported 4,694 incident heart failure events during follow-up. Compared with non-carriers, individuals with CHIP had a 25% higher risk of incident heart failure after adjustment for demographic characteristics and conventional cardiovascular risk factors (HR 1.25, 95% CI 1.13-1.38). The association was particularly evident for TET2, ASXL1, and JAK2 mutations, while larger clones (VAF >10%) were associated with a slightly higher risk (HR 1.29, 95% CI 1.15-1.44) [13].

Recent evidence has further expanded the cardiovascular implications of clonal hematopoiesis beyond atherosclerotic disease and heart failure. Contemporary scientific statements and reviews emphasize associations with additional cardiovascular conditions, including atrial fibrillation and thrombotic complications, while highlighting substantial heterogeneity according to the mutated gene, clone size, and environmental factors. These publications also underscore the importance of distinguishing observational associations from experimentally supported causal mechanisms. Despite growing interest in targeted anti-inflammatory strategies, no clonal hematopoiesis-specific therapy has yet demonstrated clinical efficacy for cardiovascular prevention or treatment [14,15].

Risk of hematologic transformation

CHIP is also a precursor state for hematologic neoplasms. Although the absolute risk of transformation is relatively low, estimated at approximately 0.5-1% per year, it remains substantially higher than in individuals without detectable clonal hematopoiesis [16].

The risk is highly heterogeneous and depends on clone size, number of mutations, and the genes involved. Isolated DNMT3A mutations are generally associated with relatively low risk, whereas mutations involving SRSF2, SF3B1, ZRSR2, IDH1, IDH2, FLT3, RUNX1, JAK2, and TP53 are associated with a higher risk of progression to a myeloid neoplasm [17].

This distinction is particularly relevant to longevity medicine. A small clone detected in an older individual should not automatically be regarded as a preleukemic condition requiring treatment, whereas high-risk molecular features may identify individuals who warrant closer hematologic surveillance.

Mortality and healthspan

The relevance of CHIP to longevity medicine extends beyond leukemia prevention. Large population-based studies have associated CHIP with increased all-cause mortality, an association not fully explained by hematologic transformation alone [1,2]. Cardiovascular disease may contribute to this excess mortality, although the mechanisms and proportion directly attributable to clonal hematopoiesis remain uncertain [1-3].

CHIP may therefore reflect the convergence of several age-related processes, including somatic mutation accumulation, dysregulation of innate immunity, chronic inflammation, and increased susceptibility to disease. Its impact is nevertheless heterogeneous and influenced by the mutated gene, VAF, number of clones, and their expansion patterns.

CHIP may thus represent a marker of age-related vulnerability rather than simply a precursor to hematologic malignancy. However, its association with mortality and age-related disease does not demonstrate that CHIP screening improves healthspan, an important distinction before its incorporation into longevity medicine.

Implications for longevity medicine

Should Asymptomatic Individuals Be Screened for CHIP?

The ability to detect CHIP from a simple blood sample makes it particularly appealing in the context of preventive medicine. Next-generation sequencing can identify the mutations involved, determine their number and VAF, and provide an increasingly detailed picture of an individual's clonal architecture. However, current evidence does not support systematic screening for CHIP in the asymptomatic general population [18].

This caution is particularly important in longevity medicine. Clonal hematopoiesis becomes increasingly common with age, yet most individuals with CHIP will never develop a hematologic malignancy. Unselected screening could therefore identify large numbers of low-risk individuals without offering them a specific intervention with proven clinical benefit. It may also lead to unnecessary surveillance and anxiety associated with the discovery of a premalignant condition.

For now, CHIP is therefore most often detected incidentally, either through sequencing performed for another indication or in the research setting [16]. Before it can be used as a biomarker in longevity medicine, it will be necessary to demonstrate that CHIP provides meaningful prognostic information beyond chronological age, conventional risk factors, and other biomarkers of aging.

Toward individualized risk stratification

The discovery of CHIP should not be interpreted as a simple binary finding. Risk varies according to the mutated gene, clone size, number of mutations, age, and hematologic parameters. This heterogeneity led to the development of the Clonal Hematopoiesis Risk Score (CHRS), derived from data from more than 400,000 participants in the UK Biobank [17].

The CHRS incorporates several variables, including high-risk mutations, the number of mutations, a VAF $\geq 20\%$, age ≥ 65 years, selected red blood cell parameters, and the presence of cytopenia. It distinguishes the large majority of individuals at low risk from a much smaller group with a substantially higher risk of progression to a myeloid neoplasm [17]. This approach illustrates an important shift: the clinical value of clonal hematopoiesis may lie less in its mere detection than in a more detailed characterization of the clone and its trajectory.

From a longevity perspective, a similar strategy could eventually combine the molecular characteristics of CHIP with cardiovascular risk factors, inflammatory markers, and biomarkers of biological aging. Such an approach could help identify individuals in whom clonal hematopoiesis reflects meaningful biological vulnerability rather than an age-associated phenomenon with limited clinical consequences. The main clinical implications of CHIP relevant to longevity medicine are summarized in Table 2.

Clinical domain	Main evidence	Risk modifiers	Current implication
Cardiovascular disease	CHIP is associated with increased risks of coronary heart disease and ischemic stroke; clones with VAF ≥10% were associated with approximately fourfold higher odds of early-onset myocardial infarction	Clone size and genotype; particularly strong association with JAK2 V617F	Assessment and management of conventional modifiable cardiovascular risk factors
Heart failure	CHIP was associated with a 25% higher risk of incident heart failure	Stronger associations with TET2, ASXL1, JAK2, and larger clones	Reinforces the relevance of cardiovascular risk assessment
Hematologic transformation	Overall risk of progression to hematologic neoplasms is approximately 0.5–1% per year	Clone size, number of mutations, and mutated genes	Risk-adapted hematologic surveillance
Risk stratification	The CHRS distinguishes a large low-risk population from a smaller group with substantially higher risk of myeloid neoplasm	High-risk mutations, number of mutations, VAF ≥20%, age ≥65 years, selected red blood cell parameters, and cytopenia	Detailed clonal characterization may be more informative than CHIP detection alone
Population screening	Current evidence does not support systematic CHIP screening in the asymptomatic general population	Clinical significance varies substantially among individuals	Routine population-wide screening is not currently supported
CHIP-specific treatment	No therapy aimed specifically at eradicating a CHIP clone is currently recommended in individuals without cytopenia or other findings suggesting a hematologic disorder	Individual hematologic and cardiovascular risk profile	Surveillance and management of established modifiable risk factors
Targeting inflammation	TET2-mutated CHIP may enhance IL-1β-dependent inflammatory signaling; exploratory CANTOS data suggested a potential treatment signal with canakinumab	Genotype, particularly TET2	Investigational; current evidence does not support CHIP-directed anti-inflammatory therapy

TABLE 2: Clinical Implications of Clonal Hematopoiesis in Longevity Medicine

CHIP: clonal hematopoiesis of indeterminate potential; CHRS: Clonal Hematopoiesis Risk Score; VAF: variant allele frequency; IL-1β: interleukin-1 beta; CANTOS: Canakinumab Anti-inflammatory Thrombosis Outcomes Study

What should be done when CHIP is detected?

In the absence of cytopenia or other findings suggestive of a hematologic disorder, no therapy aimed specifically at eradicating a CHIP clone is currently recommended. Management primarily consists of hematologic surveillance tailored to the individual's risk profile, together with the assessment and management of modifiable cardiovascular risk factors [15].

Cardiovascular risk management is particularly relevant. In individuals with CHIP, it is reasonable to optimize measures with established benefits independently of CHIP, including blood pressure control, management of diabetes and dyslipidemia, smoking cessation, regular physical activity, and weight management. However, CHIP alone is not currently an established indication for initiating a specific pharmacologic treatment, including antiplatelet, lipid-lowering, or anti-inflammatory therapy. Treatment decisions should therefore continue to follow conventional cardiovascular indications.

Can CHIP-associated inflammation be targeted?

Evidence supporting a causal role for inflammation in some forms of CHIP has opened an intriguing therapeutic avenue. TET2-mutated clones can enhance IL-1β-dependent inflammatory signaling, raising the possibility that inhibition of this pathway could reduce some of the cardiovascular consequences of clonal hematopoiesis [4].

The relationship between clonal hematopoiesis and chronic inflammation appears to be bidirectional. While mutations affecting genes such as TET2 can promote inflammatory signaling, an inflammatory environment may also favor the expansion of certain hematopoietic clones. This reciprocal interaction suggests that CHIP

may both contribute to and be influenced by inflammaging. However, the underlying mechanisms and their clinical relevance may differ according to the mutated gene, inflammatory context, and clone characteristics [19].

An exploratory analysis of the CANTOS trial provided an initial clinical signal. Among patients with a previous myocardial infarction and residual inflammation, those carrying somatic TET2 mutations who received canakinumab, an IL-1 β -targeting antibody, experienced fewer major cardiovascular events than those receiving placebo [20]. However, this analysis involved a limited subgroup, and the interaction between TET2 mutation status and treatment effect was not statistically conclusive. These findings should therefore be considered hypothesis-generating rather than evidence supporting the current use of canakinumab in individuals with CHIP.

Nevertheless, these findings illustrate an important possibility for longevity medicine: moving beyond the use of CHIP as a purely predictive biomarker toward its potential use in identifying modifiable mechanisms of age-related disease. Prospective trials will be needed to determine whether anti-inflammatory interventions or other targeted strategies can reduce complications associated with specific CHIP genotypes.

CHIP therefore has several features that could make it relevant to precision approaches to aging. However, its clinical utility will ultimately depend on demonstrating that CHIP-guided interventions can improve healthspan, rather than simply refine risk prediction.

Limitations and future directions

Several challenges still limit the use of CHIP as a biomarker of biological aging. First, CHIP is highly heterogeneous: a single low-*VAF* DNMT3A mutation is unlikely to have the same biological significance as a large TET2- or JAK2-mutated clone or the presence of multiple mutations. Future approaches should therefore consider the mutated gene, *VAF*, number of mutations, and longitudinal clonal dynamics rather than simply the presence or absence of CHIP [8,17].

Second, the conventional *VAF* threshold of $\geq 2\%$ is an operational definition, historically influenced by sequencing performance rather than a clearly established biological boundary. High-depth sequencing can now detect much smaller clones whose clinical significance remains uncertain, while large-scale studies continue to identify new drivers of clonal hematopoiesis [21]. Standardization of analytical methods will therefore be essential before CHIP can be reliably used as an individual biomarker.

A further challenge is distinguishing whether CHIP is primarily a marker or a mediator of aging. Its associations with epigenetic age, inflammation, cardiovascular disease, and mortality do not demonstrate that reducing or eliminating a clone would slow biological aging. However, some mutations appear to exert causal effects on inflammatory pathways, suggesting that CHIP may contribute directly to age-related disease rather than merely reflect aging [4].

Most clinical evidence linking CHIP to biological aging and age-related outcomes comes from observational studies, which are susceptible to residual confounding and cannot establish causality. Chronological age, smoking, environmental exposures, comorbidities, and differences in blood cell composition may influence the observed associations. Selection effects in volunteer-based cohorts and biobanks may further limit the generalizability of findings. Reverse causality and competing risks, particularly in older populations with multiple comorbidities, may also complicate the interpretation of associations between CHIP and clinical outcomes. In addition, heterogeneity in study populations, sequencing depth, CHIP definitions, and epigenetic aging measures limits direct comparisons across studies. Although experimental findings support causal mechanisms for certain mutations and disease pathways, these results cannot necessarily be generalized to all CHIP genotypes or clinical outcomes.

Ongoing interventional studies are investigating strategies targeting IL-1 β -dependent inflammation in individuals with clonal hematopoiesis, particularly those carrying TET2 mutations [22]. These studies may clarify whether genotype-guided interventions can reduce inflammation and associated cardiovascular complications. However, no CHIP-directed treatment has yet been shown to improve survival or healthspan.

Ultimately, CHIP may be most informative when integrated into a multidimensional assessment combining clonal characteristics with epigenetic, inflammatory, cardiovascular, and functional biomarkers. Longitudinal studies and randomized trials are needed to determine whether such approaches improve risk stratification and, more importantly, guide interventions capable of improving healthspan.

Conclusions

Clonal hematopoiesis is a well-characterized molecular feature of hematopoietic aging whose relevance extends beyond the risk of myeloid neoplasms. Its associations with epigenetic age acceleration, chronic inflammation, cardiovascular disease, and mortality suggest that CHIP may both reflect biological aging and

contribute to age-related disease.

However, CHIP cannot yet be considered an established clinical biomarker of longevity. Its significance varies according to the mutated gene, clone size, and clonal dynamics, while the benefits of screening asymptomatic individuals and CHIP-guided interventions remain unproven. CHIP should therefore be viewed not as a clinical “aging test,” but as an emerging biomarker at the intersection of aging, inflammation, and disease. Longitudinal studies and interventional trials will determine whether it can evolve from a tool for risk stratification into a meaningful component of personalized longevity medicine.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Rida Fatima Ezzahra, Salma Fares

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