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CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL (CHIP): MOLECULAR LANDSCAPE, CLINICAL IMPLICATIONS, AND DIAGNOSTIC CHALLENGES

Hemato-Pathology

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ABSTRACT

The occurrence of somatic mutations in hematopoietic stem and progenitor cells in people without cytopenias or diagnostic evidence of hematologic malignancy is known as Clonal Haematopoiesis of Indeterminate Potential (CHIP), an age-related biological phenomenon. CHIP is prevalent in older persons and is linked to a higher risk of hematologic neoplasms, cardiovascular disease, and all-cause mortality, according to large-scale population sequencing studies. Significant overlap exists between the mutational spectrum of CHIP and myeloid malignancies; these mutations typically affect genes related to signal transduction and DNA damage response, as well as epigenetic regulators such as DNMT3A, TET2, and ASXL1. As next-generation sequencing (NGS) is widely used in hematopathology, oncology, and liquid biopsy platforms, CHIP is being discovered more frequently by accident, posing diagnostic, prognostic, and ethical issues for both pathologists and clinicians. With a focus on its applicability to pathology practice and multidisciplinary patient care, this study offers a thorough synthesis of the biological foundation, molecular landscape, epidemiology, diagnostic standards, and clinical implications of CHIP.

KEYWORDS

Clonal hematopoiesis, CHIP, DNMT3A, TET2, cardiovascular disease, myelodysplastic syndrome, liquid biopsy

INTRODUCTION AND BACKGROUND

Clonal Haematopoiesis as a Biological Concept

A little pool of hematopoietic stem cells (HSCs) with the capacity for multilineage differentiation and self-renewal sustains hematopoiesis throughout life. Haematopoiesis is polyclonal under healthy conditions, with contributions from many HSCs sustaining the synthesis of blood cells. However, mounting data suggests that the development and growth of genetically different stem cell clones cause haematopoiesis to frequently become more oligoclonal as people age [1,4].

When a somatic mutation gives an HSC a selection advantage that enables its offspring to contribute disproportionately to peripheral blood cell populations, clonal haematopoiesis occurs. Such clonal expansions were previously thought to be associated with hematologic malignancies. This perspective has been drastically changed by the development of high-depth sequencing technologies, which have shown that people with perfectly normal blood counts and no outward signs of illness can have clonal expansions carrying mutations identical to those found in leukemia and myelodysplastic syndromes [1,3].

Discovery of CHIP Through Population Sequencing

The modern understanding of CHIP emerged from landmark population-based sequencing studies published in 2014. Using whole exome sequencing of peripheral blood DNA from tens of thousands of individuals, Jaiswal et al. and Genovese et al. independently demonstrated that somatic mutations in genes recurrently mutated in myeloid neoplasms were surprisingly common in aging populations [1,3]. These studies showed a striking age-dependent increase in prevalence, from <1% in individuals younger than 40 years to >10% in those older than 70 years [1,3].

Crucially, these clonal mutations were associated with adverse clinical outcomes, including increased overall mortality and an elevated risk of subsequent hematologic malignancy, even in the absence of overt disease at the time of detection [1,3]. These observations challenged the traditional dichotomy between 'normal' haematopoiesis and malignant transformation, suggesting instead a continuum of clonal evolution.

Definition of Clonal Haematopoiesis of Indeterminate Potential

To address the clinical ambiguity surrounding these findings, Steensma et al. proposed the term Clonal Haematopoiesis of Indeterminate Potential (CHIP) in 2015 [2]. CHIP was defined by three core criteria: (i) presence of one or more somatic mutations associated with hematologic malignancy; (ii) variant allele frequency (VAF) of ≥2%; and (iii) absence of persistent cytopenias or diagnostic criteria for a hematologic neoplasm. This definition intentionally mirrors the concept of monoclonal gammopathy of undetermined significance (MGUS), framing CHIP as a premalignant or risk state rather than a disease entity [2].

CHIP Within the Spectrum of Pre-Malignant Hematologic Conditions

CHIP occupies a conceptual space alongside other clonal precursor states, including MGUS and monoclonal B cell lymphocytosis (MBL). However, CHIP differs in several important respects. Unlike MGUS and MBL, which involve lineage-restricted clonal expansions, CHIP originates at the level of multipotent HSCs and can contribute to both myeloid and lymphoid lineages [4,19]. Furthermore, CHIP-associated mutations frequently involve epigenetic regulators and DNA damage response genes, implicating fundamental mechanisms of stem cell biology and genomic stability [4,28]. This broad biological impact likely underlies the diverse systemic consequences of CHIP, including its association with cardiovascular disease and inflammatory conditions [5,29].

Why CHIP Matters to Pathologists

From the perspective of a pathologist, CHIP is no longer a theoretical construct but a daily diagnostic reality. The expanding use of large NGS panels in hematopathology, solid tumour diagnostics, and circulating cell-free DNA assays has resulted in frequent incidental detection of CHIP-associated mutations [6,16]. Without appropriate contextual interpretation, such findings may be misclassified as evidence of malignancy, leading to unnecessary investigations, patient anxiety, and inappropriate clinical management. Moreover, CHIP challenges traditional diagnostic frameworks by blurring the boundaries between normal aging, clonal evolution, and malignancy. Pathologists are uniquely positioned to navigate this complexity, integrating morphologic, molecular, and clinical data to provide accurate and clinically meaningful interpretations.

MOLECULAR LANDSCAPE OF CHIP

Overview of the Mutational Spectrum

Although there is no associated morphologic or clinical indication of disease, the mutational landscape of CHIP closely resembles that of myeloid neoplasms, specifically myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) [1-4]. CHIP-associated mutations are non-random and preferentially occur in a specific group of genes implicated in signal transduction, RNA splicing, transcriptional control, epigenetic regulation, and DNA damage response [1,3,4].

Across several cohorts, mutations in DNMT3A, TET2, and ASXL1 account for roughly 60–70% of all CHIP cases [1,4,13]. JAK2, TP53, PPM1D, SF3B1, SRSF2, U2AF1, and RUNX1 are less commonly mutated but clinically important genes [3,7,14,28].

DNMT3A Mutations

About 30–40% of CHIP instances are caused by mutations in DNMT3A (DNA methyltransferase 3A), the single most common gene [1,3,13]. De novo DNA methylation is carried out by DNMT3A, which is essential for hematopoietic stem cell development and lineage commitment. Functional research has shown that loss-of-function mutations in DNMT3A improve self-renewal of HSCs while hindering differentiation, giving them an advantage over wild-type stem cells [4,28]. In mouse models, DNMT3A-defective HSCs demonstrate increased clonal dominance over time, particularly under conditions of age or hematopoietic stress [28]. Clinically, DNMT3A mutant CHIP is typically linked to comparatively lower risk of progression to overt hematologic malignancy, especially when present as a single mutation at low VAF [3,14]. Nonetheless, DNMT3A mutations remain biologically significant as they frequently indicate early 'founder' events that may lead to accumulation of subsequent mutations [8,27].

TET2 Mutations

Ten Eleven Translocation 2 (TET2) mutations are the second most frequent genetic change in CHIP, occurring in 15–25% of patients [1,3,13]. TET2 is essential for DNA demethylation and gene expression control. TET2-deficient HSCs exhibit enhanced self-renewal and biased differentiation toward the myeloid lineage [4,10]. Significantly, systemic inflammation has been closely associated with TET2 mutations; TET2-deficient macrophages exhibit heightened inflammatory reactions, including elevated interleukin-1β and other pro-inflammatory cytokine production [5,10]. These molecular findings explain the strong correlation between TET2 mutant CHIP and cardiovascular disease seen in population research [5,29].

ASXL1 Mutations

About 10–15% of CHIP cases have ASXL1 (Additional Sex Combs Like 1) mutations, which are disproportionately linked to unfavourable outcomes [3,13,14]. ASXL1 interacts with polycomb repressive complexes to regulate gene transcription and remodel chromatin. In contrast to DNMT3A and TET2 mutations, ASXL1 mutations are more commonly linked to clonal instability, greater variant allele frequencies, and development of myeloid neoplasia [14]. ASXL1 mutant CHIP has been linked in long-term studies to an increased risk of transformation to MDS or AML [3,14]. Even in the absence of cytopenias, the existence of ASXL1 mutations should prompt thorough clinical correlation and long-term surveillance, especially when combined with additional mutations [14].

DNA Damage Response and Therapy-Selected Mutations

TP53 and PPM1D mutations represent a unique and clinically significant subset of CHIP, especially in patients subjected to cytotoxic chemotherapy or radiation therapy [7,11,12]. In the context of genotoxic stress, TP53 mutant CHIP clones have a significant selection advantage due to their resistance to DNA damage-induced apoptosis [7,12]. Truncating mutations in PPM1D result in gain-of-function consequences that reduce p53-mediated DNA damage responses [7]. Numerous studies have shown that therapy-related myeloid neoplasms (t-MNs), including therapy-related MDS and AML, are often preceded by TP53 and PPM1D mutant CHIP, with similar mutations found years before overt malignancy [7,12,21].

The identification of therapy-associated CHIP carries significant implications for oncology. Patients with preexisting CHIP who receive cytotoxic therapy are more likely to acquire t-MNs, especially with high-risk mutations such as TP53 [7,12]. These findings raise important concerns about risk assessment and long-term monitoring; however, routine CHIP screening before therapy is not currently advised outside of research settings [18,21].

Clonal Architecture and Evolution

Variant allele frequency serves as a surrogate measure of clonal size and is a major modifier of CHIP-related risk [3,14,27]. Increased clonal persistence, growth, and progression to overt hematologic malignancy are linked to higher VAFs [3,14]. Longitudinal sequencing studies have demonstrated that while certain CHIP clones stay stable for many years, others undergo stepwise expansion or acquire new mutations, resulting in clonal diversity [8,27]. The co-occurrence of multiple CHIP-associated mutations in a single individual strongly predicts adverse consequences, with multi-hit clones demonstrating higher VAFs and increased likelihood of progression to MDS or AML [14,30]. Abelson et al. demonstrated that healthy persons with numerous driver mutations could be retrospectively identified years prior to AML diagnosis, highlighting the protracted, sequential nature of leukemogenesis [8].

EPIDEMIOLOGY AND RISK FACTORS

Age-Dependent Prevalence of CHIP

Age is the most powerful and reliable risk factor for the development of CHIP. The incidence of CHIP has been shown to grow dramatically with age in large population-based sequencing studies; it is almost non-existent in people under 40 years and then sharply increases beyond that [1,3,4]. About 10% of people have detectable CHIP-associated mutations by the seventh decade of life, and the incidence rises to 15–20% in people over 80 [1,3]. This age-related increase results from the cumulative acquisition of somatic mutations over time as well as alterations in immune surveillance and hematopoietic stem cell function [4,19]. It is important to note that CHIP prevalence estimations rely on sequencing depth and analytical sensitivity.

Sex, Environmental, and Lifestyle Factors

Sex-based variations in CHIP prevalence have been reported, with some studies indicating a slight male predominance, albeit results are not totally consistent across cohorts [1,9]. CHIP risk is also influenced by lifestyle and environmental variables. Increased CHIP prevalence has been linked to cigarette smoking, especially mutations affecting ASXL1 and TP53, likely caused by smoking-induced genotoxic stress [3,9]. Exposure to environmental contaminants and chronic inflammatory conditions may also contribute to clonal selection, though clear causal linkages remain challenging to establish [29].

Inherited Genetic Predisposition

Recent whole-genome sequencing investigations have found inherited genetic variations that modify vulnerability to clonal haematopoiesis, despite the fact that CHIP is essentially an acquired somatic event [9]. Specific germline variations appear to influence hematopoietic stem cell fitness, DNA repair capacity, or inflammatory signaling, affecting the likelihood of clonal proliferation [9]. These results indicate that individual heterogeneity in CHIP risk reflects a complex interplay between inherited genetic background and acquired somatic events.

DETECTION OF CHIP IN CLINICAL PRACTICE

Next-Generation Sequencing Platforms

Next-generation sequencing techniques applied to peripheral blood or bone marrow DNA are the primary means of detecting CHIP. The most common assays in clinical labs are targeted myeloid gene panels, which typically contain genes such as DNMT3A, TET2, ASXL1, TP53, JAK2, and spliceosome components [2,6,14]. Sequencing depth and bioinformatic thresholds directly impact CHIP detection sensitivity. Traditionally, CHIP has been defined using a VAF criterion of ≥2%, striking a balance between technological reliability and biological relevance [2]. However, advances in sequencing technology now allow detection of clones at significantly lower allele frequencies, raising concerns about the clinical interpretation of sub-CHIP clones [19,27].

Variant Allele Frequency Thresholds and Their Limitations

Variant allele frequency is a useful proxy for clonal size but depends on sample composition, assay design, and sequencing depth [3,14]. Although a 2% VAF threshold is commonly used, it is an operational definition rather than a physiologically absolute cutoff [2]. Research has demonstrated that clones with VAFs less than 2% may endure and grow over time, especially under selective pressure such as inflammation or chemotherapy [27]. However, to prevent overdiagnosis and unnecessary clinical concern, it is currently recommended to reserve the CHIP designation for mutations meeting the ≥2% criterion [2,14].

Distinguishing CHIP from Technical Artefacts

Accurate identification of CHIP requires careful elimination of sequencing artefacts, which can result from PCR errors, alignment problems, or formalin-induced DNA damage in older specimens [6]. Strict quality control procedures, including bidirectional read support, adequate read depth, and validation of recurrent hotspot mutations, are necessary for high-confidence CHIP identification [6,16]. Pathologists and molecular diagnosticians must be vigilant in separating true

somatic variants from artefacts, particularly when interpreting low-VAF variants in clinically confusing circumstances.

CHIP and Liquid Biopsy: A Major Diagnostic Challenge

The emergence of circulating cell-free DNA (cfDNA) analysis has transformed cancer diagnostics and monitoring. However, CHIP is a significant confounding factor in liquid biopsy assays because somatic mutations from hematopoietic clones are discharged into plasma and can be confused with tumor-derived variants [6]. A significant percentage of variants seen in cfDNA, especially in genes such as DNMT3A, TET2, ASXL1, and TP53, originate from clonal hematopoiesis rather than solid tumors [6,16]. Older individuals and those without matched white blood cell sequencing are particularly vulnerable to this phenomenon. Strategies to reduce CHIP-related false positives include parallel sequencing of peripheral blood leukocytes, bioinformatic filtering based on known CHIP-associated genes, and interpreting VAFs in connection to tumor burden [6,16].

DIFFERENTIAL DIAGNOSIS

CHIP versus Clonal Cytopenia of Undetermined Significance (CCUS)
Clonal Cytopenia of Undetermined Significance (CCUS) is a comparable condition marked by somatic mutations similar to those observed in CHIP, but accompanied by persistent, unexplained cytopenias [2,14]. Compared to CHIP, CCUS carries a much-increased chance of developing MDS or AML [14]. The key clinical difference between CHIP and CCUS is the existence or absence of cytopenias. Thorough integration of clinical, morphologic, and molecular data is required, as early myeloid neoplasms may not meet all diagnostic criteria and morphologic assessment may be subtle [15].

CHIP versus Early Myelodysplastic Syndromes

Distinguishing CHIP from early or low-grade MDS is a major diagnostic challenge. Early MDS may not exhibit overt dysplasia or cytogenetic abnormalities, and both entities may share the same somatic mutations [14,15]. In these situations, establishing a clear diagnosis frequently requires longitudinal clinical follow-up, repeat marrow evaluation, and assessment of clonal development [14]. The WHO and ICC classifications stress that molecular results must be interpreted in conjunction with morphologic and clinical characteristics to diagnose myeloid neoplasms [15].

CHIP in Population Screening and Incidental Findings

Concerns about screening and reporting procedures are raised by the growing number of CHIP cases found through accidental testing and population sequencing studies. Given the dearth of effective treatments and the comparatively modest absolute risk of malignant transformation, there is currently no evidence to recommend population-wide screening for CHIP [18]. Nevertheless, inadvertent identification of CHIP is increasingly common, particularly in older persons receiving genetic testing for unrelated causes [6,16]. Pathologists are essential in helping clinicians understand CHIP findings; reports should avoid language suggesting malignancy and should explicitly state when identified mutations are consistent with clonal haematopoiesis [16,17].

CHIP AND HEMATOLOGIC MALIGNANCIES

Risk of Progression to Myeloid Neoplasms

People with CHIP are substantially more likely than people without CHIP to acquire myeloid neoplasms, especially AML and MDS [1,3]. Despite this heightened relative risk, the absolute annual risk of advancement remains low, estimated at around 0.5–1% per year [1,3,8]. Since most people with CHIP will never experience overt hematologic malignancy in their lifetime, this distinction is crucial for therapeutic counseling. Nonetheless, CHIP reflects a bona fide premalignant state, akin to other clonal precursor diseases such as MGUS and MBL [2].

Gene-Specific Risk Stratification

Not all CHIP-related mutations confer similar risk of malignant transformation. Mutations in epigenetic regulators such as DNMT3A and TET2, especially when occurring as isolated events at low VAFs, are typically linked to a lower risk of advancement [3,14]. In contrast, mutations in TP53, ASXL1, RUNX1, and spliceosome genes (such as SF3B1, SRSF2, and U2AF1) are associated with a significantly increased risk of developing MDS or AML [14,30]. These high-risk mutations frequently represent greater genomic instability and are more likely to be accompanied by further cooperative mutations over time [8,14].

Clonal Evolution and Leukemogenesis

CHIP-associated mutations frequently represent early 'founder' events in leukemogenesis [8,27]. Abelson et al. revealed that healthy patients who later developed AML commonly harboured identical somatic mutations years before clinical diagnosis, with progressive acquisition of additional mutations preceding overt disease [8]. This multi-stage clonal evolution model is consistent with traditional theories of cancer biology, according to which early driver mutations create a precancerous clone that persists and grows until further environmental or genetic insults cause transformation [27].

CHIP in Solid Tumour Patients

Patients with solid tumors, especially those undergoing genetic sequencing as part of precision oncology initiatives, are often found to have CHIP [6,11]. Because of both age-related risk and the selective pressures exerted by cancer therapy, CHIP is more common in cancer patients than in age-matched controls [7,11]. When matched normal tissue or peripheral blood controls are not sequenced, the presence of CHIP complicates interpretation of tumor genetic data, and variants resulting from clonal hematopoiesis could be mistakenly linked to the tumor, resulting in inappropriate treatment choices [6]. This is especially pertinent for mutations in genes like TP53, which are prevalent in both CHIP and a variety of solid tumors [6,16].

CHIP AND CARDIOVASCULAR DISEASE

Epidemiologic Evidence

One of the most paradigm-shifting discoveries in the study of clonal haematopoiesis has been the robust and reproducible relationship between CHIP and cardiovascular disease (CVD). Jaiswal et al. showed that, independent of conventional cardiovascular risk factors, people with CHIP had a roughly twofold higher risk of coronary heart disease and ischemic stroke compared to age-matched controls [5]. These results have been validated in separate cohorts, solidifying CHIP's status as a unique, non-traditional cardiovascular risk factor [9,26,29]. The level of cardiovascular risk associated with CHIP is comparable to or larger than that conferred by well-established risk factors such as hypercholesterolemia [5,29].

Gene-Specific Cardiovascular Risk

The cardiovascular risk associated with CHIP mutations varies by genotype. Atherosclerotic cardiovascular disease has been most frequently linked to mutations in TET2 and DNMT3A, but JAK2 mutations seem to carry a particularly high risk, even at relatively modest VAFs [5,9]. Pro-thrombotic and inflammatory signaling pathways may increase the risk of thrombosis and vascular events in individuals with JAK2 mutant CHIP, similar to findings in myeloproliferative neoplasms [9].

Mechanistic Links Between CHIP and Inflammation

CHIP-associated mutations, especially in TET2, have been shown in experimental models to convert myeloid cells toward a pro-inflammatory phenotype [5,10]. TET2-deficient macrophages exhibit greater activation of the NLRP3 inflammasome and enhanced production of pro-inflammatory cytokines such as interleukin-1β and interleukin-6, which are major mediators of atherogenesis [10]. These inflammatory alterations promote endothelial dysfunction, plaque development, and plaque instability, providing a direct mechanistic connection between clonal hematopoiesis and vascular disease.

The concept of 'inflammaging' — chronic, low-grade inflammation linked to aging — provides a broader framework for understanding the systemic impacts of CHIP [29]. CHIP-associated clones may amplify age-related inflammatory processes, resulting in a feed-forward loop where inflammation encourages clonal development, which in turn exacerbates inflammation [27,29]. This reciprocal interaction may explain why CHIP is linked not only to cardiovascular disease but also to chronic pulmonary disease and elevated all-cause mortality [13,26].

Therapeutic Implications

There are currently no approved treatments that explicitly target CHIP or eradicate CHIP-associated clones. However, the CANTOS study showed that canakinumab suppression of interleukin-1β reduced recurrent cardiovascular events in patients with a history of myocardial infarction, independent of cholesterol lowering [20]. Post-hoc analysis and mechanistic investigations suggest that patients with TET2 mutant CHIP may obtain disproportionate benefit from anti-inflammatory medications [10,20]. Given the paucity of CHIP-specific therapies, current expert opinion emphasizes aggressive management of

traditional cardiovascular risk factors, including blood pressure control, smoking cessation, and lipid optimization [18,26].

CLINICAL SURVEILLANCE AND MANAGEMENT

Current Recommendations

There are currently no evidence-based recommendations for routine CHIP surveillance or intervention [18]. For people with high-risk mutations or rising VAFs, most expert assessments advise cautious management, including routine blood count monitoring and clinical evaluation [14,17]. Given the low absolute risk of advancement and the lack of effective preventative measures, aggressive diagnostic workup or preventive therapy is not warranted in asymptomatic persons with stable CHIP [18].

Multidisciplinary Approach

Managing CHIP effectively requires close collaboration between pathologists, haematologists, oncologists, and primary care physicians [16,17]. Pathologists are essential in identifying CHIP, contextualizing molecular data, and directing appropriate clinical follow-up. Clear communication about the nature and implications of CHIP is crucial to prevent overdiagnosis, overtreatment, and patient anxiety.

IMPLICATIONS FOR PATHOLOGY REPORTING

Standardized Reporting Language

Standardized reporting procedures are required due to the growing incidental discovery of CHIP using NGS-based assays. Several expert evaluations and professional associations urge that variations compatible with CHIP be publicly identified as such and accompanied by interpretive remarks emphasizing their likely hematological origin and uncertain clinical implications [16,17]. Clear reporting language is crucial in the context of solid tumor sequencing and liquid biopsy assays, where CHIP-associated mutations could otherwise be confused with tumor-derived alterations [6,16].

Avoiding Overdiagnosis

In the age of extensive genomic testing, overdiagnosis poses a serious challenge. In the absence of supporting morphologic and clinical evidence, pathologists must avoid equating the presence of cancer-associated mutations with malignancy [15,18]. Pathologists play a vital role in maintaining diagnostic accuracy and avoiding harm from unnecessary investigations or procedures by combining molecular data with conventional diagnostic criteria.

Ethical and Psychosocial Considerations

Important ethical concerns about disclosure, patient anxiety, and informed consent are raised by the discovery of CHIP [18]. Discussions with patients and physicians are made more difficult by the lack of a clear management pathway or preventive therapy for CHIP. Ethical frameworks created for other incidental genetic findings may offer assistance, though CHIP presents particular difficulties because of its age-related nature and varying therapeutic implications [18]. Responsible CHIP management requires rigorous risk communication and collaborative decision-making.

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Future research should focus on identifying biomarkers predictive of clonal progression, evaluating targeted preventative therapies, and developing strong risk stratification models incorporating genetic, clinical, and environmental variables [14,17,27]. New technologies such as single-cell sequencing and longitudinal clonal tracking promise to improve understanding of CHIP biology and clonal evolution, potentially enabling earlier identification of high-risk clones [22,27]. Prospective studies specifically targeting CHIP-associated cardiovascular risk and anti-inflammatory interventions are urgently needed before such strategies can be integrated into standard clinical practice.

DISCUSSION

Clonal hematopoiesis of indeterminate potential (CHIP) is a unifying biological notion that blurs the lines between premalignant stages, overt hematologic disease, and normal aging. Data gathered over the last decade indicate that somatic mutations typically linked to myeloid cancers are often found in people without cytopenias or morphologic abnormalities, especially as they age [1-4]. The discovery of CHIP therefore calls into question the long-held belief that the existence of such mutations inevitably signifies neoplasia, emphasizing the necessity of nuanced interpretation in the age of extensive genomic testing.

The function of CHIP as a precursor state along a clonal evolution continuum is one of its most clinically significant features. According to longitudinal research, CHIP-associated mutations frequently serve as early 'founder' events that can last for years before acquisition of further cooperating mutations causes AML or MDS [3,8,14]. For the majority of people, the absolute risk of progression remains low despite a markedly elevated relative risk [1,3]. Mutational context, clonal load, and VAF significantly influence this risk heterogeneity; isolated DNMT3A or TET2 mutations are less risky than mutations in genes such as TP53, ASXL1, and spliceosome components [14,30].

In addition to hematologic cancer, CHIP has been strongly associated with systemic illness, particularly atherosclerotic cardiovascular disease. Regardless of conventional risk variables, a strong correlation between CHIP and cardiovascular events has been demonstrated by several independent cohorts [5,9,26]. Mechanistic investigations have given biological validity to this connection by showing that CHIP-associated mutations, specifically in TET2, drive pro-inflammatory reprogramming of myeloid cells and enhance atherogenesis [5,10]. These results place CHIP as a contributor to age-related inflammatory illness and elevated all-cause mortality, extending its clinical significance beyond haematology and oncology [1,26,29].

Significant diagnostic and interpretive difficulties have been brought about by the growing discovery of CHIP using next-generation sequencing, especially in solid tumor profiling and circulating cell-free DNA analysis. In the absence of matched normal sequencing, CHIP-derived mutations are known to cause false-positive results in liquid biopsy assays [6,16]. For genes such as TP53, frequently altered in both CHIP and solid tumors, this dilemma is particularly troublesome. Pathologists play a crucial role in integrating genetic discoveries with clinical and morphologic data to ensure proper interpretation and reporting.

Even while CHIP is becoming more widely acknowledged as a clinically significant illness, evidence-based therapeutic recommendations remain limited. Current professional opinion favours conservative care with strong control of traditional cardiovascular risk factors and periodic monitoring [17,18,26]. The incidental discovery of CHIP raises important ethical issues with informed consent, patient anxiety, and disclosure. Counseling is made more difficult by CHIP's probabilistic risk profile and absence of a clear therapeutic approach [18]. Uniform reporting language and clear communication of the uncertain clinical consequences of CHIP are crucial as genetic testing becomes more widespread [16,17].

CONCLUSIONS

Our understanding of aging, hematopoiesis, and disease risk has fundamentally changed as a result of Clonal Haematopoiesis of Indeterminate Potential. Once thought to be a benign incidental finding, CHIP is now understood to be a biologically relevant condition linked to an elevated risk of hematologic malignancies, cardiovascular disease, and all-cause mortality. CHIP presents both opportunities and obstacles for pathologists. Accurate identification, careful interpretation, and clear communication are crucial to fully utilize the diagnostic potential of modern genetic technologies while preventing overdiagnosis and patient harm. As evidence continues to develop, CHIP will remain a crucial point of confluence between pathology, genomics, and preventive medicine.

ADDITIONAL INFORMATION

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REFERENCES

[1] Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.
[2] Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9–16.
[3] Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477–87.
[4] Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472–8.
[5] Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. Clonal

hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111–21.
[6] Razavi P, Li BT, Brown DN, Jung B, Hubbell E, Shen R, et al. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. Nat Med. 2019;25(12):1928–37.
[7] Bolton KL, Ptashkin RN, Gao T, Braunstein L, Devlin SM, Kelly D, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 2020;52(11):1219–26.
[8] Abelson S, Collord G, Ng SW, Weissbrod O, Mendelson Cohen N, Niemeyer E, et al. Prediction of acute myeloid leukaemia risk in healthy individuals. Nature. 2018;559(7714):400–4.
[9] Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature. 2020;586(7831):763–8.
[10] Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842–7.
[11] Coombs CC, Zehir A, Devlin SM, Kishtagari A, Syed A, Jonsson P, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21(3):374–82.
[12] Gillis NK, Ball M, Zhang Q, Ma Z, Zhao Y, Yoder SJ, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof of concept, case-control study. Lancet Oncol. 2017;18(1):112–21.
[13] Buscarlet M, Provost S, Zada YF, Barhdadi A, Bourgoin V, Lépine G, et al. DNMT3A and TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. Blood. 2017;130(6):753–62.
[14] Malcovati L, Gallì A, Travaglino E, Ambaglio I, Rizzo E, Molteni E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371–8.
[15] Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703–19.
[16] Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating tumor DNA analysis in patients with cancer: ASCO and CAP joint review. Arch Pathol Lab Med. 2018;142(10):1242–53.
[17] Steensma DP. Clinical consequences of clonal hematopoiesis of indeterminate potential. Hematology Am Soc Hematol Educ Program. 2018;2018(1):264–9.
[18] Steensma DP. Clinical implications of clonal hematopoiesis. Mayo Clin Proc. 2018;93(8):1122–30.
[19] Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016;7(1):12484.
[20] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31.
[21] Takahashi K, Wang F, Morita K, Yan Y, Hu P, Zhao P, et al. Integrative genomic analysis of adult mixed phenotype acute leukemia. Nat Commun. 2018;9(1):2670.
[22] Nam AS, Kim KT, Chaligne R, Izzo F, Ang C, Taylor J, et al. Somatic mutations and cell identity linked by genotyping of transcriptomes. Nature. 2019;571(7765):355–60.
[23] Arends CM, Galan-Sousa J, Hoyer K, Chan W, Jäger M, Yoshida K, et al. Hematopoietic lineage distribution and evolutionary dynamics of clonal hematopoiesis. Leukemia. 2018;32(9):1908–19.
[24] Jan M, Ebert BL, Jaiswal S. Clonal hematopoiesis. Semin Hematol. 2017;54(1):43–50.
[25] Gibson CJ, Kennedy JA, Nikiforow S, Kuo FC, Alyea EP, Ho V, et al. Donor-engrafted CHIP is common among stem cell transplant recipients with unexplained cytopenias. Blood. 2017;130(1):91–4.
[26] Marnell CS, Bick A, Natarajan P. Clonal hematopoiesis of indeterminate potential (CHIP): linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. J Mol Cell Cardiol. 2021;161:98–105.
[27] Watson CJ, Papula AL, Poon GY, Wong WH, Young AL, Druley TE, et al. The evolutionary dynamics and fitness landscape of clonal hematopoiesis. Science. 2020;367(6485):1449–54.
[28] McKerrell T, Park N, Moreno T, Grove CS, Ponstingl H, Stephens J, et al. Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis. Cell Rep. 2015;10(8):1239–45.
[29] Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. Nat Rev Cardiol. 2020;17(3):137–44.
[30] Weeks LD, Niroula A, Neuberg D, Wong W, Lindsley RC, Luskin MR, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid. 2023;2(5):EVIDoa2200310.