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What's hidden in plain sight? Impact of clonal hematopoiesis on the risk and progression of non-hematologic cancers

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Abstract

Clonal hematopoiesis (CH) is a frequently observed phenomenon in aging individuals without apparent illness and exhibits an increased prevalence in cancer patients. Mechanistic studies indicate that mutant immune cells alter the tumor microenvironment, leading to increased inflammation, blood vessel formation, and immune cell exhaustion. Paradoxically, these changes also preserve stem-like T-cell pools that can be utilized by immunotherapy. CH may be incidentally detected in patients whose solid tumors are profiled by next-generation sequencing. Clinically, CH confers higher risks of therapy-related myeloid neoplasms, cardiovascular and inflammatory toxicities, and context-specific changes in treatment efficacy. Moreover, tumor-infiltrating CH independently shortens survival. Two validated risk scores can inform the risk for myeloid malignancy, yet surveillance, cardiometabolic management, and regimen selection still primarily rely on expert consensus. Because CH may be discovered incidentally, rigorous confirmation of variant origin when CH is suspected is essential to avoid misdirected therapy. We propose a pragmatic approach: confirm CH with paired blood sequencing when feasible; integrate high-risk features into risk stratification, counseling, and monitoring for cytopenias and cardiovascular events; and prefer less genotoxic regimens when the oncologic benefit is comparable. Early trials blocking interleukin-1β suggest that targeting inflammation driven by CH may improve outcomes in patients with solid tumors. Prospective studies informed by mutation analysis and tracking clonal changes and inflammatory markers are needed to determine if routine CH assessment can be integrated into precision oncology to improve outcomes for patients with solid tumors and CH.

Introduction

In the early 1960s, Mary Lyon's discovery of random X-chromosome inactivation provided a clever genetic "barcode," enabling investigators to trace the clonality of cell populations with unprecedented precision.[1–3] Using this principle, Philip Fialkow and colleagues provided the first convincing evidence demonstrating the clonal origin of chronic myeloid leukemia.[4] Similar lineage-tracing studies revealed that even healthy adults, particularly aging women, harbor skewed, clonally restricted hematopoiesis.[5,6] These experiments demonstrated that the clonal expansion of hematopoietic stem cells (HSCs) can occur with age but did not identify the genetic drivers of this clonality.

We now understand that most cancers arise from somatic mutations that quietly accumulate in tissue-specific stem cells as they divide throughout life.[7,8] Most of these mutations appear long before a tumor develops and do not portend malignant transformation.[9–11] In HSCs, the steady accrual of single-base changes, small insertions/deletions, and larger structural variants creates a genetically diverse pool of progenitors. The gap between skewed X-inactivation and the driver of clonal hematopoiesis (CH) emerged with the discovery of somatic *TET2* mutations in aging women.[12] Additional work tracing somatic mutations in the pre-leukemic and remission samples of patients with acute myeloid leukemia (AML) further supported this concept.[13–15] The application of next-generation sequencing to large-scale surveys of blood DNA from thousands of individuals has firmly established the presence of age-related somatic mutations associated with CH.[16–18]

Broadly, CH refers to any detectable expansion of a single HSC-derived clone, whether driven by malignant transformation, neutral drift due to age-related stem cell constriction, or selective

advantage conferred by somatic mutations. Among the various forms of CH, two clinically relevant entities include CH of indeterminate potential (CHIP) which refers to the presence of somatic mutations in leukemia-associated driver genes at a variant allele fraction (VAF) of ≥2% in individuals without cytopenias or a diagnosed hematologic disorder, and clonal cytopenia of undetermined significance (CCUS) which describes similar mutational events occurring in the context of persistent, unexplained cytopenias without meeting diagnostic criteria for myelodysplastic syndromes (MDS).

CH carries significant clinical implications, increasing lifetime risk for hematologic malignancies,[16,17,19] and contributing to excess morbidity and mortality from cardiovascular disease,[20,21] chronic liver disease,[22] kidney disease,[23,24] and pulmonary disease,[25] as reviewed elsewhere.[21] CH is likewise enriched in patients with solid tumors, where it may influence clinical outcomes.[21,26–28] Although findings vary across studies, a growing body of evidence suggests that the clinical impact of CH depends on the clonal burden, the specific gene and type of mutation, and the extent to which mutant clones infiltrate the tumor microenvironment (TME).[29,30]

In this review, we synthesize the emerging literature on CH in patients with solid tumors, covering its incidence and the biological underpinnings that these mutant hematopoietic cells may exert within the TME. We review the literature on the clinical implications of CH in various types of cancer. We discuss the settings in which CH is found incidentally and provide recommendations on how to best counsel and monitor individual patients when this occurs based on the current understanding of its clinical implications. Finally, we highlight opportunities for clinical trials to test whether targeted immune-modulating strategies can mitigate the detrimental consequences of CH in patients with solid tumors.

Prevalence of clonal hematopoiesis: from the general population to patients with solid tumors

The prevalence of CH increases steadily with age, but its observed frequency is closely tied to the sensitivity of the detection method, population ancestry, and inherited genetic variation.[31] Using the conventional VAF threshold of ≥2% for CHIP, large-scale sequencing studies consistently report CH in ~5% of middle-aged individuals, with this figure rising to 10–20% or more in those over 70 years old. For instance, whole-exome sequencing of 416,118 UK Biobank (UKB) participants detected CHIP in 4.9%, a figure nearly identical to the 4.3% crude prevalence found in 97,691 whole-genome sequences from the TOPMed cohort.[32,33] The measured prevalence of CH can be substantially higher with more sensitive assays; ultra-deep, error-corrected sequencing has detected clonal mutations in up to 95% of individuals, underscoring that the observed frequency scales with technical sensitivity.[34]

Beyond age and assay sensitivity, CH frequency is modulated by population ancestry and germline genetics. A comparative analysis found CH to be significantly less common in a Mexico City-based cohort compared to UKB participants (3.1% vs. 4.9%), with a prevalence that increased among individuals with greater European ancestry.[32] Genome-wide analyses have identified ancestry-specific and common germline variants at loci such as *TCL1B*, *TERT*, *CHEK2*, and a *TET2* enhancer, which influence the risk of developing CH by impacting pathways related to telomere maintenance, stem cell self-renewal, and DNA repair.[32,33]

CH is commonly found in the general population but occurs even more frequently among patients with solid tumors, a consistent observation from multiple large-scale sequencing studies.[26,28,35] This higher prevalence is important for understanding how cancer and its

treatments influence the clonal evolution of hematopoietic stem cells. In a study of over 8,800 patients with solid tumors, CH was reported in 25%, with high-risk driver mutations identified in 4.5%.[35] An expanded cohort of 24,146 individuals confirmed a CH prevalence of 30%, with over half of the mutations classified as putative drivers (CH-PD).[26] Similarly, a recent study of a Chinese cancer cohort reported CH in 28.6% of patients.[36]

These studies in cancer patients reveal distinct patterns of CH. The most mutated genes include *DNMT3A*, *TET2*, *PPM1D*, *ASXL1*, *ATM*, and *TP53*. Furthermore, exposure to specific cancer therapies, such as platinum agents and radiotherapy, appears to exert selective pressure, leading to the enrichment of clones with mutations in DNA damage response (DDR) genes like *TP53*, *PPM1D*, and *CHEK2*.[26] Age and smoking also influence the clonal landscape, with aging preferentially selecting for spliceosome mutations and smoking being associated with *ASXL1* mutations.[26]

Notably, the presence of CH, especially CH-PD, is clinically significant in cancer patients, independently associated with shorter overall survival (OS) even after adjusting for age, sex, and smoking status.[35] Most deaths among individuals with CH were due to the progression of their solid tumors rather than the development of subsequent hematologic malignancies. Additionally, specific high-risk CH profiles can increase the likelihood of developing therapy-related myeloid neoplasms (tMN), which could influence decisions about adjuvant chemotherapy.[26,35]

The association between CH and poorer patient outcomes suggests the existence of underlying biological mechanisms. Immune cells originating from CH can exert both systemic effects by dysregulating the immune system and local effects within the TME. These CH-derived immune cells can infiltrate solid tumors, a process termed tumor-infiltrating CH (TI-CH) or CH-Tum. The impact of this infiltration stems from how CH mutations modify the function of immune

cells, thereby influencing the trajectory of cancer development, which is the focus of the next section.

Tumor-infiltrating clonal hematopoiesis

TI-CH refers to the presence of canonical CH mutations within bulk tumor DNA at a VAF of ≥2%, indicating the infiltration of mutant leukocytes into the TME. Large-scale sequencing efforts have demonstrated that TI-CH is common but heterogeneously distributed across cancers and is associated with adverse clinical outcomes.[29,30]

A recent integrated analysis of 421 patients with early-stage non-small cell lung cancer (NSCLC) from the TRACERx study and 49,351 patients across the MSK-IMPACT pan-cancer cohort provided key insights into the prevalence and prognostic relevance of TI-CH.[30] Among patients with NSCLC, 42% of those with CH exhibited TI-CH, translating into an adjusted HR of 1.80 (95% CI, 1.23–2.63) for disease recurrence or death compared to patients without CH and an HR of 1.62 (95% CI, 1.02–2.56) compared to those with CH confined to peripheral blood. Across the broader MSK-IMPACT cohort, TI-CH was observed in 26% of CH-positive patients and associated with a 17% increased risk of death. *TET2* mutations emerged as the strongest predictor of TI-CH, and mechanistic studies demonstrated that *TET2*-mutant monocytes exhibit enhanced migration toward tumor cells, fueling a myeloid-rich, proangiogenic microenvironment that accelerates tumor progression. These findings position TI-CH as a clinically meaningful and biologically active contributor to cancer evolution.

Complementary evidence is provided by the Clinical Proteomic Tumor Analysis Consortium (CPTAC) study, which analyzed 1,550 treatment-naïve tumors across multiple cancer types.[29] CH was present in 18.3% of patients, with approximately one-third of CH-positive cases

showing detectable tumor infiltration (CH-Tum). In concordance with the TRACERx and MSK-IMPACT findings, CH-Tum was associated with significantly shorter OS. Molecular analyses revealed that tumors with CH-Tum exhibited distinct immune and inflammatory profiles, characterized by dense macrophage and neutrophil infiltration, heightened NF-κB and interferon signaling, and activation of angiogenic and mitogenic pathways. Notably, these effects were most pronounced in glioblastoma, where CH-Tum correlated with an aggressive, mesenchymal tumor phenotype—a shift associated with inflammatory macrophage activity within the TME. Across datasets, TI-CH emerges as a pan-cancer phenomenon that may shape tumor biology independently of age-related immune shifts.

Together, these studies establish that TI-CH is not merely a technical artifact of tumor sequencing but a biologically and clinically significant event. TI-CH portends worse outcomes across multiple cancer types, remodels the immune microenvironment toward a proinflammatory, pro-tumorigenic state, and may offer novel opportunities for biomarker development and therapeutic intervention.

The potential impact of clonal hematopoiesis on immunity and cancer progression

The somatic mutations that drive CH are increasingly understood not merely as passive markers of clonal expansion but as active modulators of host immunity, often creating conditions that favor tumor development. Mounting mechanistic evidence suggests that pathogenic variants in key epigenetic regulators, such as *TET2*, *DNMT3A*, and *ASXL*1, as well as the tumor suppressor *TP53*, can reprogram the TME toward a pro-tumorigenic, immunosuppressive state by suppressing anti-tumor immunity and promoting vascularization (**Figure 1**).

For instance, in *Tet2*-deficient mice, heightened IL-6 secretion drives a pronounced expansion of granulocytic myeloid-derived suppressor cells (G-MDSCs). These cells impair the cytotoxic function of CD8 T-cells, leading to accelerated tumor growth. Neutralizing IL-6 or depleting G-MDSCs restores immune surveillance and slows cancer progression.[37] Clinically, this suggests that IL-6–targeting therapies, currently approved for rheumatologic diseases, could be investigated to limit tumor progression in patients with TET2 mutations. However, the immunological impact of *TET2* loss appears context dependent. In melanoma models, *Tet2* deletion in myeloid cells unexpectedly enhances antitumor immunity by shifting tumor-associated macrophages toward a pro-inflammatory (M1-like) phenotype, increasing effector T-cell infiltration, and suppressing tumor growth.[38] Beyond immune suppression, *Tet2*-mutant myeloid cells promote angiogenesis through a secreted S100a8/S100a9-Emmprin-VEGFA signaling cascade. Pharmacologic blockade of Emmprin disrupts neovascularization and abrogates the growth advantage conferred by mutant infiltration.[39] These findings highlight the complexity of CH, where the same mutation can either promote or inhibit tumor progression depending on specific circumstances.

Beyond *TET2*, several CH-associated gene mutations converge on common pathways involving inflammation, vascular remodeling, and immune dysfunction. For instance, mice with reduced *Dnmt3a* activity develop more severe colitis-associated colon cancer, characterized by increased tumor size, greater tissue damage, and excessive blood vessel growth.[40] Notably, these effects are largely reversed by anti-angiogenic therapy, suggesting that mutant hematopoietic cells contribute to both tumor initiation and progression via inflammatory amplification and vascular remodeling. Loss of wild-type TP53 in myeloid cells further reinforces this paradigm: elevated

IL-6 and NOS2 signaling polarizes macrophages toward a tumor-promoting M2-like state, promotes angiogenesis, and facilitates malignant outgrowth.[41]

The immune-modulatory effects of CH clones extend beyond myeloid cells to lymphoid compartments, influencing both innate and adaptive immunity. Mutations in *ASXL1* trace a complementary yet distinct path: *Asxl1*-mutant T cells exhibit hallmarks of premature aging, including a naïve-to-memory imbalance and high PD-1 expression, resulting in dysfunctional tumor immune surveillance leading to enhanced growth of breast, colon, lung, and melanoma tumors.[42]

While these findings highlight the immunosuppressive consequences of ASXL1 mutations in T cells, emerging evidence suggests that the impact of CH on lymphoid compartments is more nuanced. Notably, loss of CH-associated genes can enhance the effectiveness of immunotherapy by promoting specific T-cell populations that sustain long-term anti-tumor responses.[43] Under chronic antigen stimulation, loss of *Dnmt3a*, *Tet2*, or *Asxl1* help maintain a stem-like subset of progenitor-exhausted (Tpex) T cells, enabling sustained responsiveness to immune checkpoint therapies without progression to malignancy.[43] This unexpected persistence of stem-like T cells indicates that specific loss-of-function CH-associated mutations might be leveraged to prolong the effectiveness of adoptive T-cell therapies. Collectively, these findings underscore the dual role of CH mutations: while they can impair anti-tumor immunity through their impact on myeloid cells, they simultaneously present an opportunity to enhance T-cell-based immunotherapies. Together, these studies emphasize the complex, context-dependent influence of CH mutations on tumor progression and highlight the importance of defining mutation-specific interactions within distinct TMEs. Understanding these mechanisms and identifying

predictive biomarkers for immunotherapy response are essential steps toward translating insights from CH biology into personalized, clinically effective cancer treatments.

Clinical outcomes associated with clonal hematopoiesis in solid tumor patients

Studies inclusive of multiple tumor types

A seminal study by Bolton *et al.* analyzed over 24,000 cancer patients, demonstrating that specific cancer therapies actively promote the expansion of hematopoietic clones with specific mutations in DDR genes.[26] Treatments such as radiation, platinum-based chemotherapy (e.g., carboplatin), and topoisomerase II inhibitors were found to selectively favor clones harboring mutations in genes like *TP53*, *PPM1D*, and *CHEK2*. This therapy-associated CH significantly elevates the risk of developing often fatal tMN, including AML and MDS. Analysis of outcome data from 9,437 patients revealed that those with CH mutations at VAFs greater than 2% had a 6.9-fold increased hazard ratio (HR) for developing tMN ($p < 10^{-6}$). This risk further escalated with the number and size of CH clones. Notably, patients with *TP53* or spliceosome gene mutations, such as *SRSF2*, *SF3B1*, and *U2AF1*, exhibited the highest risk of transformation. A synthetic risk model for women with early-stage breast cancer indicated that adjuvant chemotherapy could increase the absolute 10-year risk of AML/MDS by approximately 9% for individuals in the top 1% of baseline risk, potentially negating the chemotherapy's survival benefit in this subgroup. With 5-year OS rates for tMNs hovering around 10%, the clinical importance of risk stratification is paramount. Serial sampling crucially showed that these DDR-mutant clones expanded significantly after cancer therapy but not in its absence, providing direct evidence of gene-by-environment interactions driving malignant progression.

Expanding on the prevalence and impact of pre-existing CH, a multi-cohort analysis by Krishnan *et al*. utilized cell-free DNA (cfDNA) sequencing to investigate CH in patients with solid tumors.[44] CH mutations, in *DNMT3A*, *TET2*, or *ASXL1*, were identified in 10% to 30% of patients, with a prevalence that increased significantly with age (P=0.003). Interestingly, the study found potential interactions between CH and treatment modality. In the PA.7 trial involving patients with metastatic pancreatic adenocarcinoma, individuals with CH treated with immune checkpoint inhibitors (ICIs) showed a trend toward improved progression-free survival (PFS) (HR=0.55; 95% CI: 0.28–1.07; P=0.079). Conversely, in the real-world PREDiCT-l cohort, patients with CH undergoing chemotherapy demonstrated a non-significant trend toward shorter PFS (HR=1.82; 95% CI: 0.98–3.38; P=0.059). OS was also unaffected by CH status in both the CO.26 (colorectal cancer (CRC)) and PA.7 trials; OS data for PREDiCT-l were unavailable. These observations suggest that CH might affect treatment efficacy differently depending on the tumor type and therapeutic approach, potentially enhancing the response to immunotherapy in certain scenarios. Given this variability, integrating CH screening into cell-free DNA (cfDNA) analyses is important, and prospective studies are needed to assess whether such screening can effectively inform clinical decisions.

A study by Tao et al. investigated whether CH affects radiation therapy (RT) efficacy in 412 patients with solid tumors.[45] CH was present in 39% of patients but was not associated with an increased risk of tumor progression after irradiation. The 12-month progression rates (16.5% for patients with CH vs. 14.5% for those without) and PFS were similar between the groups, though the lack of difference in PFS may be related to the specific study population, where 82.7% of patients were undergoing RT for palliation of metastatic disease as opposed to definitive treatment. However, consistent with its role as an adverse prognostic marker, CH was associated

with significantly shorter survival (median OS: 11.9 vs. 13.5 months; P=0.036). While subgroup analyses suggested a negative impact on prostate and thyroid cancers, this was not significant after adjusting for age. Notably, the study observed that CH may counteract the high radiosensitivity typically seen in tumors with biallelic *ATM* mutations. While CH generally does not seem to alter local tumor control after radiation therapy in this heterogeneous cohort, it remains a marker of shorter OS and may influence therapeutic responses depending on genetic context. Larger studies that can explore differences in radiation location and delivery mechanism, which may result in varying levels of bone marrow exposure, should help further clarify the impact of CH on RT.

Taken together, these early studies highlight CH as a potentially valuable prognostic factor in oncology that could help refine patient risk assessments, guide therapy selection, and ultimately improve clinical outcomes. Additional studies have examined CH's specific role within different cancer subtypes as it may be used to refine risk assessment, tailor treatments, and improve patient outcomes. We next focus on several tumor types for which the literature supports unique implications of CH on the risk of cancer development, response to therapy, toxicity, and OS.

Thyroid Cancer

In thyroid cancer, the interplay between CH and radioactive iodine (RAI) therapy is a key concern. A study of 279 patients with advanced thyroid cancer found a high prevalence of CH (37%) and CH with potential leukemogenic drivers (CH-PD) (5.2%).[46] Both were linked to age and cumulative RAI dose, with each 10 mCi of RAI increasing the odds of CH by 2% and CH-PD by 4%. Clinically, CH-PD was associated with significantly shorter OS in RAI-exposed patients (HR=3.75, P=0.02), with most deaths due to underlying thyroid cancer.

These concerns are heightened in anaplastic thyroid cancer (ATC), where a recent study elucidated how TET2-mutant CH contributes to poor outcomes.[47] In mouse models treated with BRAF/MEK inhibitors, the presence of TET2-mutant CH significantly reduced median OS from 147 to 68 days. Analysis of the expanded MSK-IMPACT cohort (47,530 patients) further demonstrated that CH-PD mutations were associated with a 2.68-fold increase in the hazard of death among 89 ATC patients ($p < 0.001$). Mechanistically, tumor infiltration by TET2-mutant macrophages promoted drug resistance, which could be reversed by pharmacologically blocking this pathway. Thus, TET2-mutant CH may serve as both a prognostic biomarker and a potential therapeutic target. Notably, TET2-mutant clones were particularly enriched in tumor samples with lower purity, indicating that relying solely on blood-based assessments could underestimate the prevalence of tumor-infiltrating CH.

Colorectal Cancer

CH also influences CRC risk and progression. A UK Biobank study of over 5,000 cases of CRC found that CH was associated with a 20% higher risk of CRC (odds ratio (OR) = 1.20, P=0.006), particularly in females and those over 60.[48] *ATM* mutations conferred a nearly threefold increased risk (OR = 2.98, $p < 0.001$). Notably, pathogenic germline mutations in several DDR genes have been established as risk factors for developing CH, suggesting an interplay between germline status and the risk of both CH and future cancer risk.[49–51]

Clinical data from the FIRE-3 trial comparing FOLFIRI with cetuximab or bevacizumab for frontline treatment in metastatic CRC demonstrated longer survival among patients who had CH compared to those without (HR=0.64 with P=0.007) even despite higher rates for some toxicities among patients with CH (such as grade 3 or 4 diarrhea in 17.4% vs. 6.6%, P=0.014 and

thromboembolic events in 7.0% vs. 1.3%, P=0.28).[52] This emphasizes a context-dependent impact of CH on patient outcomes.

Prostate Cancer

In prostate cancer, the role of CH is complex. A large-scale study analyzing whole-exome sequencing data from over 75,000 men found no association between CH and increased risk of developing prostate cancer.[53] Among men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide ± abiraterone/prednisone,[54] CH did not affect PFS or OS. Among men treated with poly (ADP-ribose) polymerase (PARP) inhibitors, the treatment itself may promote CH expansion, as seen in a small study where 45% of CH clones grew or newly appeared after therapy,[55] raising concerns about long-term hematologic safety.

Breast Cancer

In breast cancer, CH is linked to age and treatment toxicity, but its direct impact on survival is less clear (reviewed in [56]). In a study of older women (age ≥65), CH is common, present in 44% at baseline, and clones in DDR genes (*TP53*, *PPM1D*) expanded during chemotherapy.[57] This clonal expansion associated with a twofold higher rate of severe neutropenia and dose reductions (P=.02).

Conversely, in young women (age ≤ 40) with early-stage disease, CH is rare (2.7%) and did not have an association with relapse or survival over a 9-year follow-up.[58] In a larger analysis of patients with both early-stage and metastatic triple-negative breast cancer (mTNBC), pretreatment CH is common (15%) at similar incidence for early-stage and metastatic patients. By examining clonal kinetics, the emergence of new clones is rare, though chemotherapy can triple the odds of small clones emerging[59]. There was no impact of CH on survival in mTNBC; however, the median OS is short for both patients with and without CH at 9.3 months. While

these findings appear reassuring, it is important to note that the follow up from this study is short, and lack of impact of CH on younger patients where the prevalence is lower would not apply to broader populations.

Ovarian Cancer

In relapsed ovarian cancer, CH is common and dynamic. A study found DDR-gene CH (*TP53, PPM1D, CHEK2, ATM*) in 35% of patients.[60] During treatment with carboplatin and niraparib (a PARP inhibitor) with or without ganetespib, an HSP90 inhibitor, *TP53,* and *PPM1D* mutant clones expand rapidly, and two cases of tMN were traced directly to pre-existing CH. This clonal expansion is linked to the cumulative drug dose. Another ovarian cancer study identifies CH-associated mutations in 22% of patients, with an increase in prevalence with age and number of prior platinum-containing regimens.[61]

Lung Cancer

The relationship between lung cancer and CH is complex due to common risk factors for both conditions, such as smoking and age, in addition to therapy exposures and underlying genetics. Baseline CH increases the future risk of lung cancer by ~35%, independent of smoking, as determined by two large case-control studies.[62] Similarly, mosaic chromosomal alterations (mCAs) are a risk factor for the development of lung cancer.[63] A study of nearly 2,000 individuals identified family history of lung cancer as the main predictor for CH development in younger subjects[64]. In addition to the aforementioned associations with inferior outcomes for early non-small cell lung cancer patients (NSCLC),[30] another study links CH with shorter survival in patients with NSCLC undergoing adjuvant therapy (multivariable analysis, HR=1.58, P=0.019).[65]

Taken together, the seemingly discordant clinical outcomes linked to CH likely reflect significant methodological and contextual heterogeneity across studies, rather than true biological contradictions. The definition of CH itself is variable—from deep, error-corrected sequencing that captures small subclones to broader surveys with higher VAF thresholds—meaning the very clones being analyzed differ in their clinical potential. Furthermore, cohort composition is critical; large population-based studies assessing cancer risk are fundamentally different from smaller therapeutic trials in heavily pre-treated patients, where the specific cancer type and therapies administered create distinct selective pressures. A crucial distinction emerging from recent work is the location of the clone; CH confined to the blood carries a different, and often less ominous, prognosis than CH that has infiltrated the tumor microenvironment, where it can directly shape tumor progression. Finally, the underlying driver biology is paramount. Mutations in epigenetic regulators like DNMT3A and TET2 often remodel the tumor through local inflammation, whereas mutations in DNA damage response genes like PPM1D and TP53 primarily confer risk through therapy-driven selection and an increased propensity for myeloid transformation. Harmonizing CH definitions and pairing tumor-blood sequencing will therefore be essential to untangle these layers and clarify the mutation- and context-specific impact of CH on patient outcomes.

Clonal Hematopoiesis as an Incidental Finding and Implications on Patient Care

CH can be encountered as an incidental finding in a variety of clinical contexts, which is important for practicing clinicians to recognize, given the potential for misguided therapeutic decision-making (**Figure 2**). The first context is germline testing, as several commonly mutated CH genes overlap with cancer predisposition syndrome genes, such as *TP53*, *CHEK2*, and *ATM*.[66–70] Among patients undergoing germline testing from peripheral blood draws, CH should

be suspected for patients with mutations detected at a lower VAF than is typical for germline mutations. As expected, the risk of detecting CH variants on germline testing is higher among older patients.[71] Testing DNA from multiple tissues can establish mutation origin (hematopoietic or germline source such as skin fibroblasts) in unclear cases.[72–75]

Abundant evidence has demonstrated that CH may lead to challenges when interpreting cell-free DNA (cfDNA) testing among solid tumor patients in a variety of tumor types.[76–78] Filtering strategies have been successfully employed to ascertain mutation origin as tumor-based vs. CH.[79] Paired sequencing of white blood cells, when available, assists in accurate identification of mutation origin.[80–82] Alternatively, artificial intelligence techniques have also been used to classify cfDNA origin from plasma-only samples.[83] Correct attribution of mutation origin is critical, as reports have identified misattribution as a potential source for incorrect application of targeted therapies (such as using PARP inhibitors in patients with CH-derived (as opposed to tumor-derived) mutations in DDR genes or in the selection of therapy for CRC patients with CH-derived *KRAS*/*NRAS*/*BRAF* mutations).[84–86] Circulating tumor DNA (ctDNA) testing has been associated with similar concerns regarding CH identification; novel algorithms and filtering strategies have been developed to assist with the accurate interpretation of data.[87]

CH may also complicate the interpretation of variants from tumor biopsies performed in the absence of paired blood sequencing. In one study, "inferred CH" (based on reporting of common CH mutations in tumor biopsies, excluding *TP53* due to its high incidence in solid malignancies) was found in 12% of men with prostate cancer undergoing tumor sequencing by a clinical-grade assay.[88] Another study compared results of clinical-grade sequencing reports with matched blood sequencing, establishing that 8% of mutations reported from tumor sequencing were CH-derived as opposed to tumor-derived (defined by higher VAF in blood than tumor).[27] CH mutations were

typically present at low VAF within the tumor sequencing reports, with the majority of reported *DNMT3A* mutations being CH-derived (7/11) in contrast to the minority of *TP53* mutations (2/50) being CH-derived. An analysis of sequencing reports from over 110,000 patients with solid malignancies also noted that CH variants are present at low VAF and inversely correlate with tumor purity.[89] Similar to cfDNA, paired blood sequencing can assist in the accurate ascertainment of mutation origin.[28] As the correct interpretation of mutation origin is critical for the selection of appropriate oncologic therapy, flagging suspicious variants and performing confirmatory testing when necessary with paired blood sequencing is imperative for achieving optimal clinical outcomes.[90]

Impact of CH on Adverse Effects of Oncologic Therapy

Risk for future myeloid neoplasm

Multiple cancer-specific studies indicate an elevated risk for tMN among patients with CH compared to those without CH.[35,91,92] Elevated risk is not isolated to conventional cytotoxic chemotherapy and has been observed with novel agent classes, including PARP inhibitors,[93,94] and peptide receptor radionuclide therapy.[95] Given these risks, some advocate for CH screening before starting PARP inhibitor maintenance therapy.[96] Importantly, not all cancer therapies lead to clonal expansion and subsequent risk for tMN, as evidenced by the stability of clones on serial sampling of patients undergoing ICI.[97]

Two scoring systems have been developed to help risk-stratify individuals with CH for the risk of developing a myeloid neoplasm. First is the CH risk score (CHRS), which was developed using data from 438,890 participants with exome sequencing in the U.K. Biobank, with a derivation and validation cohort.[19] The scoring system divided patients into low-, intermediate-,

and high-risk CHIP/CCUS categories, where the 10-year rates of myeloid neoplasm varied between 0.669% ± 0.0827%, 7.83% ± 0.807%, and 52.2% ± 4.96%, respectively. Factors contributing to a higher score included absence of single *DNMT3A* mutation, presence of high-risk mutations (*JAK2*, *TP53*, splicing factor genes including *SRSF2*, *SF3B1*, *ZRSR2*, and AML-like genes including *IDH1*, *IDH2*, *FLT3* and *RUNX1*), greater than one mutation, VAF > 0.2, RDW > 15, MCV > 100, presence of cytopenia, and age ≥65.

Next is CCRS, which was developed specifically to understand the risk of myeloid neoplasm in CCUS patients, incorporating data from 357 patients, 67 of whom had solid tumors.[98] Three adverse prognostic variables were identified through multivariate analysis: the presence of splicing mutations, a platelet count under 100, and two or more mutations. This allowed for the stratification of patients into low-, intermediate-, and high-risk groups, with 2-year incidences of myeloid neoplasm of 6.4%, 14.1%, and 37.2%, respectively. The scoring system was independently validated in a cohort of 104 patients.

Beyond myeloid neoplasm: Risk on other adverse events

The effects of CH on overall health are increasingly being established among otherwise healthy individuals, though patients with solid tumors have additional considerations. With the known adverse effect of CH on cardiovascular health, it is important to understand if oncologic therapies associated with cardiac risk may lead to additive risk in patients with CH. In a prospective study examining the incidence of new cardiomyopathy among 236 patients undergoing treatment for solid tumors, patients with CH had a higher incidence of new cardiomyopathy compared to those without (35.6% vs. 4.8%), with CH serving as an independent predictor of cardiomyopathy on competing risk Cox regression models (HR=2.01, P=0.042).[99] Among 88 patients receiving ICI therapy, there was a higher incidence of ICI-

associated myocarditis among patients with CH compared to those without (73% vs. 41%, P=0.003).[100] Patients with CH also had a higher risk of death (60% vs. 31%, P=0.011). Outcomes may be influenced by the specific patient population, which had a high baseline incidence of coronary artery disease (84% for patients with CH vs. 45% in patients without CH) and single-center study design focused primarily on patients followed by cardiology.

Additional studies have supported CH as a risk factor for adverse cardiovascular outcomes, including an association with a risk of doxorubicin-associated cardiomyopathy.[101] In a study of prostate cancer patients treated with androgen-receptor pathway inhibitors as part of a cooperative group clinical trial of enzalutamide ± abiraterone/prednisone, a higher incidence of cardiovascular adverse events was observed for patients with high-VAF (>10%) CH and *TET2*-mutated CH.[54] Increased toxicity is not a universal finding among patients with CH undergoing oncologic therapies, as no increase in adverse events was noted in another study, inclusive of three trial cohorts of patients treated with ICI, chemotherapy, and targeted agents.[44]

Recommendations for Counseling Patients with Solid Tumors and Clonal Hematopoiesis

With respect to what is likely the most important topic for practicing clinicians, namely, how to appropriately counsel patients when CH is identified, there is perhaps the greatest paucity of data; however, expert opinion can provide guidance.[102,103] In this final section, we will discuss our approach to counseling patients with solid tumors when CH is detected and identify areas of ongoing uncertainty for which further research is needed.

As in all areas of medicine, context is critical. For example, an incidental finding of CH may have entirely different health implications for a cytopenic patient with localized breast cancer

treated with curative intent chemotherapy compared to a patient with a refractory metastatic solid tumor. In addition, the impact of CH on health outcomes is highly variable. Factors contributing to worse outcomes, especially as they relate to risk for future myeloid malignancy, have been established, albeit in largely cancer-free populations.

While not appropriate to discuss with all patients, for those seeking to understand the odds of their CH evolving to myeloid neoplasm, both the CHRS and CCRS scoring systems can provide useful information. However, it is important to note that the minority of individuals in these studies had solid tumors, and that ongoing cytotoxic therapy may increase the chance for clonal evolution. This may impact the relative risk and benefit of some oncologic therapies. For example, given the risk of PARP inhibitors, some advocate for CH screening before starting maintenance therapy,[96] though if a PARP inhibitor is the most appropriate oncologic therapy for a patient, presence of a high-risk mutation may cause significant anxiety, so we suggest an individualized approach based on patient preference and risk tolerance.[104] Broadly speaking, in the setting of a high-risk CH mutation in a patient requiring ongoing therapy for an underlying solid tumor, especially therapy known to promote clonal expansion, our philosophy is that it is more important to focus on the existing cancer as opposed to one that might develop or on potential complications. However, counseling and closer monitoring for such complications are prudent, in addition to optimizing underlying risk factors. However, in a scenario where a patient has multiple therapeutic options, it is preferable to select the less genotoxic therapy, assuming similar efficacy.

As there is immense heterogeneity among patients with CH and solid tumors, we suggest individualizing counseling and monitoring based on both the risk of CH and the risk of the solid tumor. For patients with high-risk mutations, as defined by the risk scoring systems (CHRS and

CCRS), especially patients expected to live many more years, more frequent (every 3-6 months) blood count monitoring is suggested in addition to counseling regarding known health implications such as elevated cardiovascular risk and employing risk mitigation strategies. In patients with lower-risk mutations and/or patients whose prognosis from the underlying solid tumor is unlikely to be impacted by the CH, a "less is more" approach may be more prudent. For example, for patients with estimated survival under 1 year, the likelihood to experience adverse clinical consequence from the CH is low, such that additional monitoring above what is required for their oncologic care is unlikely necessary, assuming blood counts are not unexpectedly low.

The role for bone marrow biopsy for additional workup depends on the clinical context. In patients with CH in absence of cytopenias, bone marrow biopsies are generally not necessary. In the context of CCUS, especially when cytopenias are clinically significant and are unexplained by blood-based testing, a bone marrow biopsy is crucial for excluding overt myeloid malignancy. While there is a precedent to offer growth-factor support for patients with CCUS,[105] prospective data for this practice are lacking. This may be considered on a case-by-case basis, and we feel it is appropriate after a risk/benefit discussion if it may help support the patient to safely receive necessary oncologic therapies.

Future directions: leveraging biological insights to guide therapeutic interventions and clinical trials

Mounting evidence implicates CH in driving a pro-inflammatory milieu that promotes both cardiovascular disease and cancer progression.[106,107] Accordingly, therapeutic strategies have focused on targeting inflammatory cytokine pathways, particularly interleukin-1β (IL-1β), to mitigate CH-mediated disease. In atherosclerotic models, *Tet2*-deficient macrophages secrete

excessive amounts of IL-1β and IL-6, thereby accelerating the formation of plaques. Pharmacologic or genetic inhibition of IL-1β signaling largely reverses vascular inflammation and restores endothelial function.[20,108,109]

Translational evidence from the CANTOS trial strongly supports the potential of IL-1β blockade in modifying CH-driven disease.[110] In an exploratory analysis, patients harboring TET2-mutant clones derived the greatest reduction in major adverse cardiovascular events with canakinumab and experienced the lowest incidence of new non-hematologic malignancies, particularly lung cancer. These findings suggest that targeting IL-1β can mitigate both vascular and oncologic consequences of CH-associated inflammation. However, subsequent attempts to translate these observations into the oncology setting faced challenges. In the CANOPY-A phase III trial, canakinumab added to adjuvant therapy after resection and chemotherapy for early-stage NSCLC failed to improve disease-free survival despite robust inhibition of the IL-1β pathway and reductions in C-reactive protein (CRP) levels.[111] Possible explanations include lower baseline inflammatory status compared to CANTOS, differences in timing relative to tumor development, and the distinct biology of established versus preclinical disease. Together, these studies highlight that while IL-1β inhibition shows promise for cancer prevention in high-risk CH carriers, it may be ineffective once a CH-primed TME is fully established, suggesting that cytokine blockade alone is insufficient at later stages of disease progression. Careful attention to timing, patient selection, and biomarker-driven approaches will be essential to realize the full clinical potential of targeting IL-1β in this context.

Together, these insights justify the design of prospective, mutation-informed clinical trials that intervene earlier in the disease trajectory. Potential strategies include preventing cardiovascular events and second cancers in high-risk CH carriers or integrating anti-inflammatory therapies

into peri-operative and minimal residual disease settings for patients with tumor-infiltrating CH clones. Future trials should incorporate serial genomic monitoring to track clonal dynamics, integrate inflammatory biomarkers, and explore rational therapeutic combinations—for example, IL-1β blockade combined with immune checkpoint inhibition—to target both myeloid-driven inflammation and T cell exhaustion simultaneously. Determining whether early, targeted cytokine blockade can translate the biology of CH into tangible clinical benefit represents a critical next frontier for the field.

Conclusions

CH is common in oncology and is not always harmless: most studies, including those in patients with solid tumors, link it to poorer outcomes, although its impact varies with the mutation and clinical context. There is wide variability in the studies that have been discussed in this review, including the definition of CH, the methodology by which mutations were detected, and the uniformity (or lack thereof) of patients being studied, especially with respect to the ways in which the underlying cancers were being treated, and so it is important to understand the clinical context in which mutations are detected in practice, to determine the applicability to any given patient. Future studies should focus on larger populations with uniform definitions of CH, with exploration into the impact of individual mutations, as some variants may be more or less harmful than others. Although we do not advocate for routine CH testing, practicing oncologists should be aware of its potential as an incidental finding during routine testing of solid tumor patients. We recommend specifically testing for CH in the setting of an unexplained cytopenia, as this may inform the risk of developing either de novo myeloid neoplasm or tMN upon exposure to therapies that promote clonal expansion. Further studies examining CH may refine its clinical implications and guide mechanistic-based interventional approaches, which should be

focused on those patients at highest risk for CH-driven complications, which could then lead to improved patient outcomes.

References

1. Lyon MF. Gene Action in the X-chromosome of the Mouse (Mus musculus L.). Nature. 1961;190(4773):372-373.

2. Lyon MF. Sex chromatin and gene action in the mammalian X-chromosome. Am J Hum Genet. 1962;14(2):135-148.

3. Beutler E, Yeh M, Fairbanks VF. The normal human female as a mosaic of x-chromosome activity: studies using the gene for g-6-pd-deficiency as a marker. Proc Natl Acad Sci. 1962;48(1):9-16.

4. Fialkow PJ, Gartler SM, Yoshida A. Clonal origin of chronic myelocytic leukemia in man. Proc Natl Acad Sci. 1967;58(4):1468-1471.

5. Fey MF, Liechti-Gallati S, Rohr A von, et al. Clonality and X-inactivation patterns in hematopoietic cell populations detected by the highly informative M27 beta DNA probe. Blood. 1994;83(4):931-938.

6. Champion KM, Gilbert JGR, Asimakopoulos FA, Hinshelwood S, Green AR. Clonal haemopoiesis in normal elderly women: implications for the myeloproliferative disorders and myelodysplastic syndromes. Br J Haematol. 1997;97(4):920-926.

7. Alexandrov LB, Jones PH, Wedge DC, et al. Clock-like mutational processes in human somatic cells. Nat Genet. 2015;47(12):1402-1407.

8. Tomasetti C, Vogelstein B. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015;347(6217):78-81.

9. Welch JS, Ley TJ, Link DC, et al. The Origin and Evolution of Mutations in Acute Myeloid Leukemia. Cell. 2012;150(2):264-278.

10. Tomasetti C, Vogelstein B, Parmigiani G. Half or more of the somatic mutations in cancers of self-renewing tissues originate prior to tumor initiation. Proc Natl Acad Sci. 2013;110(6):1999-2004.

11. Martincorena I, Campbell PJ. Somatic mutation in cancer and normal cells. Science. 2015;349(6255):1483-1489.

12. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet. 2012;44(11):1179-1181.

13. Shlush LI, Zandi S, Mitchell A, et al. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature. 2014;506(7488):328-333.

14. Jan M, Snyder TM, Corces-Zimmerman MR, et al. Clonal Evolution of Preleukemic Hematopoietic Stem Cells Precedes Human Acute Myeloid Leukemia. Sci Transl Med. 2012;4(149):149ra118.

15. Miyamoto T, Weissman IL, Akashi K. AML1/ETO-expressing nonleukemic stem cells in acute myelogenous leukemia with 8;21 chromosomal translocation. Proc Natl Acad Sci. 2000;97(13):7521-7526.

16. Genovese G, Kähler AK, Handsaker RE, et al. Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence. N Engl J Med. 2014;371(26):2477-2487.

17. Jaiswal S, Fontanillas P, Flannick J, et al. Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes. N Engl J Med. 2014;371(26):2488-2498.

18. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472-1478.

19. Weeks LD, Niroula A, Neuberg D, et al. Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis. NEJM Evid. 2023;2(5):evidoa2200310.

20. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med. 2017;377(2):111-121.

21. Jaiswal S. Clonal hematopoiesis and nonhematologic disorders. Blood. 2020;136(14):1606-1614.

22. Wong WJ, Emdin C, Bick AG, et al. Clonal haematopoiesis and risk of chronic liver disease. Nature. 2023;616(7958):747-754.

23. Vlasschaert C, Robinson-Cohen C, Chen J, et al. Clonal hematopoiesis of indeterminate potential is associated with acute kidney injury. Nat Med. 2024;30(3):810-817.

24. Dawoud AAZ, Gilbert RD, Tapper WJ, Cross NCP. Clonal myelopoiesis promotes adverse outcomes in chronic kidney disease. Leukemia. 2022;36(2):507-515.

25. Miller PG, Qiao D, Rojas-Quintero J, et al. Association of clonal hematopoiesis with chronic obstructive pulmonary disease. Blood. 2022;139(3):357-368.

26. Bolton KL, Ptashkin RN, Gao T, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 2020;52(11):1219-1226.

27. Coombs CC, Gillis NK, Tan X, et al. Identification of clonal hematopoiesis mutations in solid tumor patients undergoing unpaired next-generation sequencing assays. Clin Cancer Res. 2018;24(23):5918-5924.

28. Ptashkin RN, Mandelker DL, Coombs CC, et al. Prevalence of Clonal Hematopoiesis Mutations in Tumor-Only Clinical Genomic Profiling of Solid Tumors. JAMA Oncol. 2018;4(11):1589.

29. Buttigieg MM, Vlasschaert C, Bick AG, Vanner RJ, Rauh MJ. Inflammatory reprogramming of the solid tumor microenvironment by infiltrating clonal hematopoiesis is associated with adverse outcomes. Cell Rep Med. 2025;6(3):101989.

30. Pich O, Bernard E, Zagorulya M, et al. Tumor-Infiltrating Clonal Hematopoiesis. N Engl J Med. 2025;392(16):1594-1608.

31. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science. 2019;366(6465):aan4673.

32. Wen S, Kuri-Morales P, Hu F, et al. Comparative analysis of the Mexico City Prospective Study and the UK Biobank identifies ancestry-specific effects on clonal hematopoiesis. Nat Genet. 2025;57(3):572-582.

33. Bick AG, Weinstock JS, Nandakumar SK, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature. 2020;586(7831):763-768.

34. 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.

35. Coombs CC, Zehir A, Devlin SM, et al. Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes. Cell Stem Cell. 2017;21(3):374-382.e4.

36. Li Z, Huang W, Yin JC, et al. Comprehensive next-generation profiling of clonal hematopoiesis in cancer patients using paired tumor-blood sequencing for guiding personalized therapies. Clin Transl Med. 2020;10(7):e222.

37. Li S, Feng J, Wu F, et al. TET2 promotes anti-tumor immunity by governing G-MDSCs and CD8+ T-cell numbers. EMBO Rep. 2020;21(10):e49425.

38. Pan W, Zhu S, Qu K, et al. The DNA Methylcytosine Dioxygenase Tet2 Sustains Immunosuppressive Function of Tumor-Infiltrating Myeloid Cells to Promote Melanoma Progression. Immunity. 2017;47(2):284-297.e5.

39. Nguyen YTM, Fujisawa M, Nguyen TB, et al. Tet2 deficiency in immune cells exacerbates tumor progression by increasing angiogenesis in a lung cancer model. Cancer Sci. 2021;112(12):4931-4943.

40. Feng Y, Yuan Q, Newsome RC, et al. Hematopoietic-specific heterozygous loss of Dnmt3a exacerbates colitis-associated colon cancer. J Exp Med. 2023;220(11):e20230011.

41. He X-Y, Xiang C, Zhang C-X, et al. p53 in the Myeloid Lineage Modulates an Inflammatory Microenvironment Limiting Initiation and Invasion of Intestinal Tumors. Cell Rep. 2015;13(5):888-897.

42. Liu X, Sato N, Shimosato Y, et al. CHIP-associated mutant ASXL1 in blood cells promotes solid tumor progression. Cancer Sci. 2022;113(4):1182-1194.

43. Kang TG, Lan X, Mi T, et al. Epigenetic regulators of clonal hematopoiesis control CD8 T cell stemness during immunotherapy. Science. 2024;386(6718):eadl4492.

44. Krishnan T, Vasconcelos JPS, Titmuss E, et al. Clonal Hematopoiesis of Indeterminate Potential and its Association with Treatment Outcomes and Adverse Events in Patients with Solid Tumors. Cancer Res Commun. 2025;5(1):66-73.

45. Tao JJ, Setton J, Vela PS, et al. Impact of Clonal Hematopoiesis on Solid Tumor Progression Following Radiation Therapy. JCO Precis Oncol. 2025;9(9):e2400548.

46. Boucai L, Falcone J, Ukena J, et al. Radioactive Iodine–Related Clonal Hematopoiesis in Thyroid Cancer Is Common and Associated With Decreased Survival. J Clin Endocrinol Metab. 2018;103(11):4216-4223.

47. Tiedje V, Vela PS, Yang JL, et al. Targetable treatment resistance in thyroid cancer with clonal hematopoiesis. bioRxiv. 2024 Oct 11. doi: 10.1101/2024.10.10.617685. [preprint, not peer-reviewed].

48. Liu Y, Xi Z, Zhou J, et al. Clonal Hematopoiesis of Indeterminate Potential as a Predictor of Colorectal Cancer Risk: Insights from the UK Biobank Cohort. Cancer Epidemiol Biomarkers Prev. 2025;34(3):405-411.

49. Slavin TP, Tsang KWK, Longmate J, et al. Effect of germline ATM mutations on clonal hematopoiesis. J Clin Oncol. 2019;37(15_suppl):1509.

50. Marshall CH, Arafa AT, Jaeger E, et al. Germline DNA Repair Gene Mutations and Clonal Hematopoiesis (CH) in 24,849 Patients with BRCA-Associated Cancers. Cancers. 2025;17(9):1432.

51. Franch-Expósito S, Mehine M, Ptashkin RN, et al. Associations Between Cancer Predisposition Mutations and Clonal Hematopoiesis in Patients With Solid Tumors. JCO Precis Oncol. 2023;7(7):e2300070.

52. Arends CM, Dimitriou S, Stahler A, et al. Clonal hematopoiesis is associated with improved survival in patients with metastatic colorectal cancer from the FIRE-3 trial. Blood. 2022;139(10):1593-1597.

53. Wang A, Xu Y, Yu Y, et al. Clonal hematopoiesis and risk of prostate cancer in large samples of European ancestry men. Hum Mol Genet. 2022;32(3):489-495.

54. Jensen JL, Bobek O, Chan ICC, et al. Clonal Hematopoiesis and Clinical Outcomes in Metastatic Castration-Resistant Prostate Cancer Patients Given Androgen Receptor Pathway Inhibitors (Alliance A031201). Clin Cancer Res. 2024;30(21):4910-4919.

55. Marshall CH, Gondek LP, Daniels V, et al. Association of PARP inhibitor treatment on the prevalence and progression of clonal hematopoiesis in patients with advanced prostate cancer. Prostate. 2024;84(10):954-958.

56. Mayerhofer C, Freedman RA, Parsons HA, Partridge AH, Miller PG. Clonal Hematopoiesis in Women With Breast Cancer. J Clin Oncol. 2025;43(7):861-867.

57. Mayerhofer C, Sedrak MS, Hopkins JO, et al. Clonal hematopoiesis in older patients with breast cancer receiving chemotherapy. J Natl Cancer Inst. 2023;115(8):981-988.

58. Gibson CJ, Fell G, Sella T, et al. Clonal Hematopoiesis in Young Women Treated for Breast Cancer. Clin Cancer Res. 2023;29(13):2551-2558.

59. Morganti S, Gibson CJ, Jin Q, et al. Prevalence, Dynamics, and Prognostic Role of Clonal Hematopoiesis of Indeterminate Potential in Patients With Breast Cancer. J Clin Oncol. 2024;42(31):3666-3679.

60. Arends CM, Kopp K, Hablesreiter R, et al. Dynamics of clonal hematopoiesis under DNA-damaging treatment in patients with ovarian cancer. Leukemia. 2024;38(6):1378-1389.

61. Weber-Lassalle K, Ernst C, Reuss A, et al. Clonal Hematopoiesis–Associated Gene Mutations in a Clinical Cohort of 448 Patients With Ovarian Cancer. J Natl Cancer Inst. 2021;114(4):565-570.

62. Tian R, Wiley B, Liu J, et al. Clonal Hematopoiesis and Risk of Incident Lung Cancer. J Clin Oncol. 2023;41(7):1423-1433.

63. Cheng C, Hong W, Li Y, et al. Mosaic Chromosomal Alterations Are Associated With Increased Lung Cancer Risk: Insight From the INTEGRAL-ILCCO Cohort Analysis. J Thorac Oncol. 2023;18(8):1003-1016.

64. Hong W, Li A, Liu Y, et al. Clonal Hematopoiesis Mutations in Lung Cancer Patients are Associated with Lung Cancer Risk Factors. Cancer Res. 2021;82(2):199-209.

65. Yun JK, Kim S, An H, et al. Pre-operative clonal hematopoiesis is related to adverse outcome in lung cancer after adjuvant therapy. Genome Med. 2023;15(1):111.

66. Slavin TP, Coffee B, Bernhisel R, et al. Prevalence and characteristics of likely-somatic variants in cancer susceptibility genes among individuals who had hereditary pan-cancer panel testing. Cancer Genet. 2019;235-236:31-38.

67. Mester JL, Jackson SA, Postula K, et al. Apparently Heterozygous TP53 Pathogenic Variants May Be Blood Limited in Patients Undergoing Hereditary Cancer Panel Testing. J Mol Diagn. 2020;22(3):396-404.

68. Bougeard G, Renaux-Petel M, Flaman J-M, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015;33(21):2345-2352.

69. Hall MJ, Bernhisel R, Hughes E, et al. Germline Pathogenic Variants in the Ataxia Telangiectasia Mutated (ATM) Gene are Associated with High and Moderate Risks for Multiple Cancers. Cancer Prev Res. 2021;14(4):433-440.

70. Stubbins RJ, Korotev S, Godley LA. Germline CHEK2 and ATM Variants in Myeloid and Other Hematopoietic Malignancies. Curr Hematol Malig Rep. 2022;17(4):94-104.

71. Slavin TP, Sun C-L, Chavarri-Guerra Y, et al. Older breast cancer survivors may harbor hereditary cancer predisposition pathogenic variants and are at risk for clonal hematopoiesis. J Geriatr Oncol. 2020;11(2):316-319.

72. Castillo D, Yuan T-A, Nehoray B, et al. Clonal Hematopoiesis and Mosaicism Revealed by a Multi-Tissue Analysis of Constitutional TP53 Status. Cancer Epidemiology, Biomark Prev. 2022;31(8):1621-1629.

73. Schwartz AN, Cahill SR, Stokes SM, et al. Evaluation of TP53 Variants Detected on Peripheral Blood or Saliva Testing: Discerning Germline From Somatic TP53 Variants. JCO Precis Oncol. 2021;5(5):1677-1686.

74. Ward A, Farengo-Clark D, McKenna DB, et al. Clinical management of TP53 mosaic variants found on germline genetic testing. Cancer Genet. 2024;284-285:43-47.

75. Berry DK, Gillis N, Padron E, et al. Interpretation of ambiguous TP53 test results: Mosaicism, clonal hematopoiesis, and variants of uncertain significance. J Genet Couns. 2024;33(4):916-926.

76. Hu Y, Ulrich BC, Supplee J, et al. False-Positive Plasma Genotyping Due to Clonal Hematopoiesis. Clin Cancer Res. 2018;24(18):4437-4443.

77. Mayrhofer M, Laere BD, Whitington T, et al. Cell-free DNA profiling of metastatic prostate cancer reveals microsatellite instability, structural rearrangements and clonal hematopoiesis. Genome Med. 2018;10(1):85.

78. Xu E, Su K, Zhou Y, et al. Comprehensive landscape and interference of clonal haematopoiesis mutations for liquid biopsy: A Chinese pan-cancer cohort. J Cell Mol Med. 2021;25(21):10279-10290.

79. Li BT, Janku F, Jung B, et al. Ultra-deep next-generation sequencing of plasma cell-free DNA in patients with advanced lung cancers: results from the Actionable Genome Consortium. Ann Oncol. 2019;30(4):597-603.

80. Leal A, Grieken NCT van, Palsgrove DN, et al. White blood cell and cell-free DNA analyses for detection of residual disease in gastric cancer. Nat Commun. 2020;11(1):525.

81. Razavi P, Li BT, Brown DN, et al. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. Nat Med. 2019;25(12):1928-1937.

82. Brannon AR, Jayakumaran G, Diosdado M, et al. Enhanced specificity of clinical high-sensitivity tumor mutation profiling in cell-free DNA via paired normal sequencing using MSK-ACCESS. Nat Commun. 2021;12(1):3770.

83. Arango-Argoty G, Haghighi M, Sun GJ, et al. An artificial intelligence-based model for prediction of clonal hematopoiesis variants in cell-free DNA samples. NPJ Precis Oncol. 2025;9(1):147.

84. Jensen K, Konnick EQ, Schweizer MT, et al. Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference. JAMA Oncol. 2021;7(1):107-110.

85. Magee D, Domenyuk V, Abraham J, et al. Characterization of Plasma Cell-Free DNA Variants as of Tumor or Clonal Hematopoiesis Origin in 16,812 Advanced Cancer Patients. Clin Cancer Res. 2025;31(13):2710-2718.

86. Huang F, Yang Y, Chen X, et al. Chemotherapy-associated clonal hematopoiesis mutations should be taken seriously in plasma cell-free DNA KRAS/NRAS/BRAF genotyping for metastatic colorectal cancer. Clin Biochem. 2021;92:46-53.

87. Zollinger DR, Rivers E, Fine A, et al. Analytical validation of a novel comprehensive genomic profiling informed circulating tumor DNA monitoring assay for solid tumors. PLoS One. 2024;19(5):e0302129.

88. Iranmanesh Y, Omar N, Rasouli A, et al. Inferred clonal hematopoiesis from tumor DNA sequencing among men with prostate cancer: correlation with somatic tumor alterations and outcomes. Oncolologist. 2025;30(4):oyaf049.

89. Severson EA, Riedlinger GM, Connelly CF, et al. Detection of clonal hematopoiesis of indeterminate potential in clinical sequencing of solid tumor specimens. Blood. 2018;131(22):2501-2505.

90. Menon A, Sukhanova M, Nocito KL, Gao J, Jennings LJ, Vormittag-Nocito ER. Detection and Interpretation of Clonal Hematopoiesis Variants during Routine Solid Tumor Next-Generation Sequencing A Single-Institution Experience. J Mol Diagn. 2024;26(12):1149-1158.

91. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. Lancet Oncol. 2017;18(1):112-121.

92. Takahashi K, Wang F, Kantarjian H, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. Lancet Oncol. 2017;18(1):100-111.

93. Kwan TT, Oza AM, Tinker AV, et al. Preexisting TP53-Variant Clonal Hematopoiesis and Risk of Secondary Myeloid Neoplasms in Patients With High-grade Ovarian Cancer Treated With Rucaparib. JAMA Oncol. 2021;7(12):1772-1781.

94. Musson EN, Miller RE, Mansour MR, Lockley M, Ledermann JA, Payne EM. Monitoring clone dynamics and reversibility in clonal haematopoiesis and myelodysplastic neoplasm associated with PARP inhibitor therapy-a role for early monitoring and intervention. Leukemia. 2024;38(1):215-218.

95. Singh A, Mencia-Trinchant N, Griffiths EA, et al. Mutant PPM1D- and TP53-Driven Hematopoiesis Populates the Hematopoietic Compartment in Response to Peptide Receptor Radionuclide Therapy. JCO Precis Oncol. 2022;6(6):e2100309.

96. Navitski A, Al-Rawi DH, Liu Y, et al. Baseline risk of hematologic malignancy at initiation of frontline PARP inhibitor maintenance for BRCA1/2-associated ovarian cancer. Gynecol Oncol Rep. 2021;38:100873.

97. Miller PG, Gibson CJ, Mehta A, et al. Fitness Landscape of Clonal Hematopoiesis Under Selective Pressure of Immune Checkpoint Blockade. JCO Precis Oncol. 2020;4(4):1027-1033.

98. Xie Z, Komrokji R, Ali NA, et al. Risk prediction for clonal cytopenia: multicenter real-world evidence. Blood. 2024;144(19):2033-2044.

99. Leveille E, Cheheyeb RJ, Matute-Martinez C, et al. Clonal Hematopoiesis Is Associated With Cardiomyopathy During Solid Tumor Therapy. JACC CardioOncol. 2024;6(4):605-607.

100. Chehayeb RJ, Singh J, Matute-Martinez C, et al. Clonal hematopoiesis of indeterminate potential is associated with increased risk of immune checkpoint inhibitor myocarditis in a prospective study of a cardio-oncology cohort. Cardiooncology. 2024;10(1):84.

101. Mammadova J, Colin-Leitzinger C, Nguyen D, et al. Clonal Hematopoiesis as a Molecular Risk Factor for Doxorubicin-Induced Cardiotoxicity: A Proof-of-Concept Study. JCO Precis Oncol. 2023;7(7):e2300208.

102. Steensma DP, Bolton KL. What to tell your patient with clonal hematopoiesis and why: insights from 2 specialized clinics. Blood. 2020;136(14):1623-1631.

103. Bolton KL, Gillis NK, Coombs CC, et al. Managing Clonal Hematopoiesis in Patients With Solid Tumors. J Clin Oncol. 2019;37(1):7-11.

104. Sella T, Fell GG, Miller PG, et al. Patient perspectives on testing for clonal hematopoiesis of indeterminate potential. Blood Adv. 2022;6(24):6151-6161.

105. Xie Z, Nanaa A, Saliba AN, et al. Treatment outcome of clonal cytopenias of undetermined significance: a single-institution retrospective study. Blood Cancer J. 2021;11(3):43.

106. Reed SC, Croessmann S, Park BH. CHIP Happens: Clonal Hematopoiesis of Indeterminate Potential and Its Relationship to Solid Tumors. Clin Cancer Res. 2022;29(8):1403-1411.

107. Buttigieg MM, Rauh MJ. Clonal Hematopoiesis: Updates and Implications at the Solid Tumor-Immune Interface. JCO Precis Oncol. 2023;7(7):e2300132.

108. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842-847.

109. Bick AG, Pirruccello JP, Griffin GK, et al. Genetic IL-6 Signaling Deficiency Attenuates Cardiovascular Risk in Clonal Hematopoiesis. Circulation. 2019;141(2):124-131.

110. Woo J, Zhai T, Yang F, et al. Effect of Clonal Hematopoiesis Mutations and Canakinumab Treatment on Incidence of Solid Tumors in the CANTOS Randomized Clinical Trial. Cancer Prev Res. 2024;17(9):429-436.

111. Garon EB, Lu S, Goto Y, et al. Canakinumab as Adjuvant Therapy in Patients With Completely Resected Non–Small-Cell Lung Cancer: Results From the CANOPY-A Double-Blind, Randomized Clinical Trial. J Clin Oncol. 2024;42(2):180-191.

Figures and Figure Legends

Figure 1. Tumor-infiltrating clonal hematopoiesis. Differentiated immune cells originating from clonally expanded hematopoietic stem cells (HSCs) infiltrate the tumor microenvironment and promote pro-tumorigenic cytokine signaling. CH mutations exert complex, context-dependent effects: mutated myeloid cells often foster an immunosuppressive niche that supports tumor growth, whereas certain T-cell mutations can preserve function and enhance immunotherapy efficacy. Created with BioRender.com. CH: Clonal Hematopoiesis; HSC: Hematopoietic Stem Cell.

Figure 2. Incidental detection of clonal hematopoiesis. Clonal hematopoiesis (CH)–associated mutations are often detected incidentally during routine clinical testing, including germline analysis, cell-free DNA (cfDNA) liquid biopsies, and tumor-only sequencing—particularly in older patients and at low variant allele frequencies (VAFs) that can mimic true germline or tumor variants. Misclassification can lead to inappropriate diagnosis or treatment. To prevent this, employ VAF thresholds, CH-specific bioinformatic filters, and, when feasible, paired blood or other tissue sequencing to confirm origin. Once validated, variants should be classified as germline, tumor-derived, or CH, guiding management toward genetic counseling, targeted therapy, or CH surveillance, respectively. Created with BioRender.com.

Figure 1

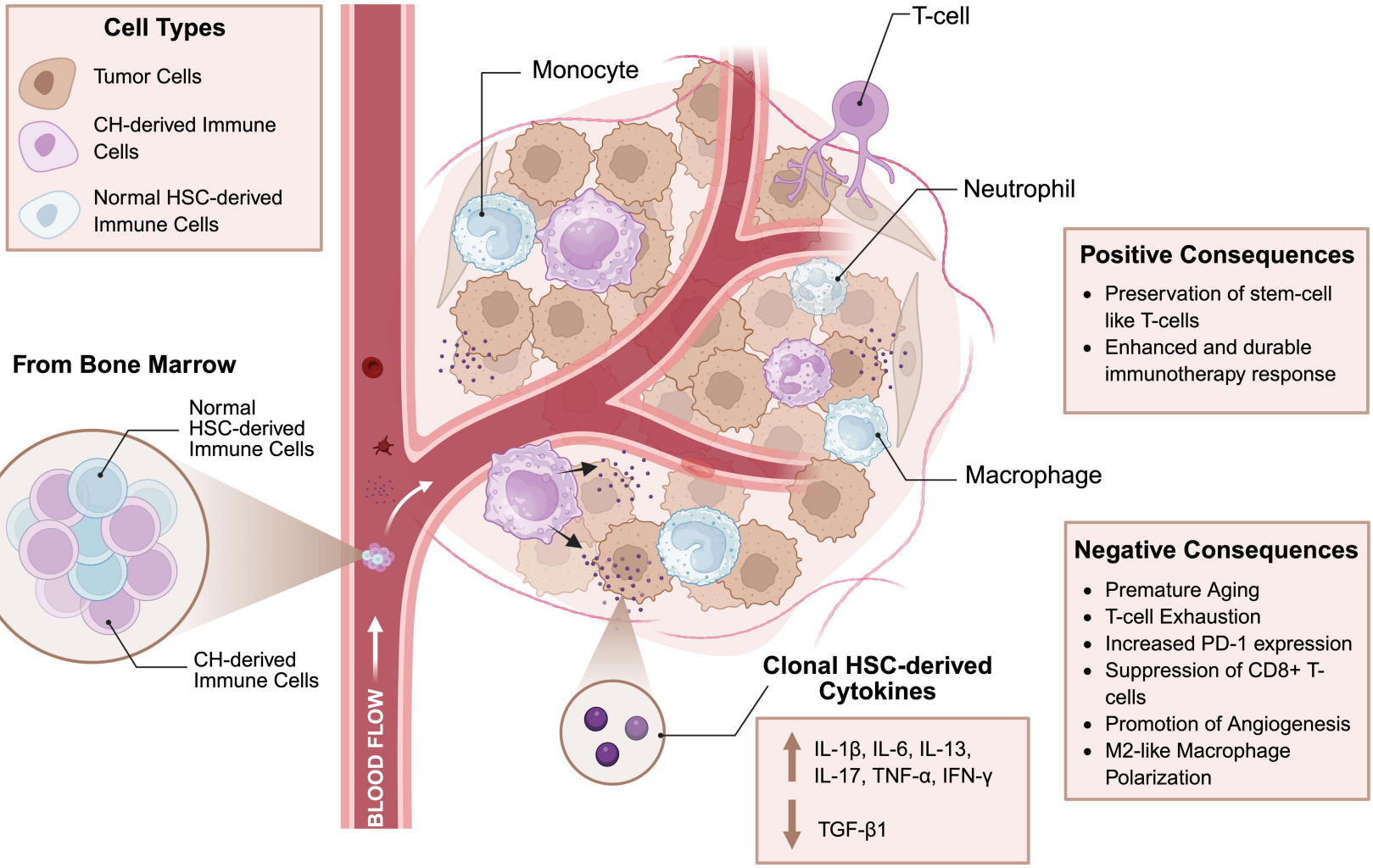
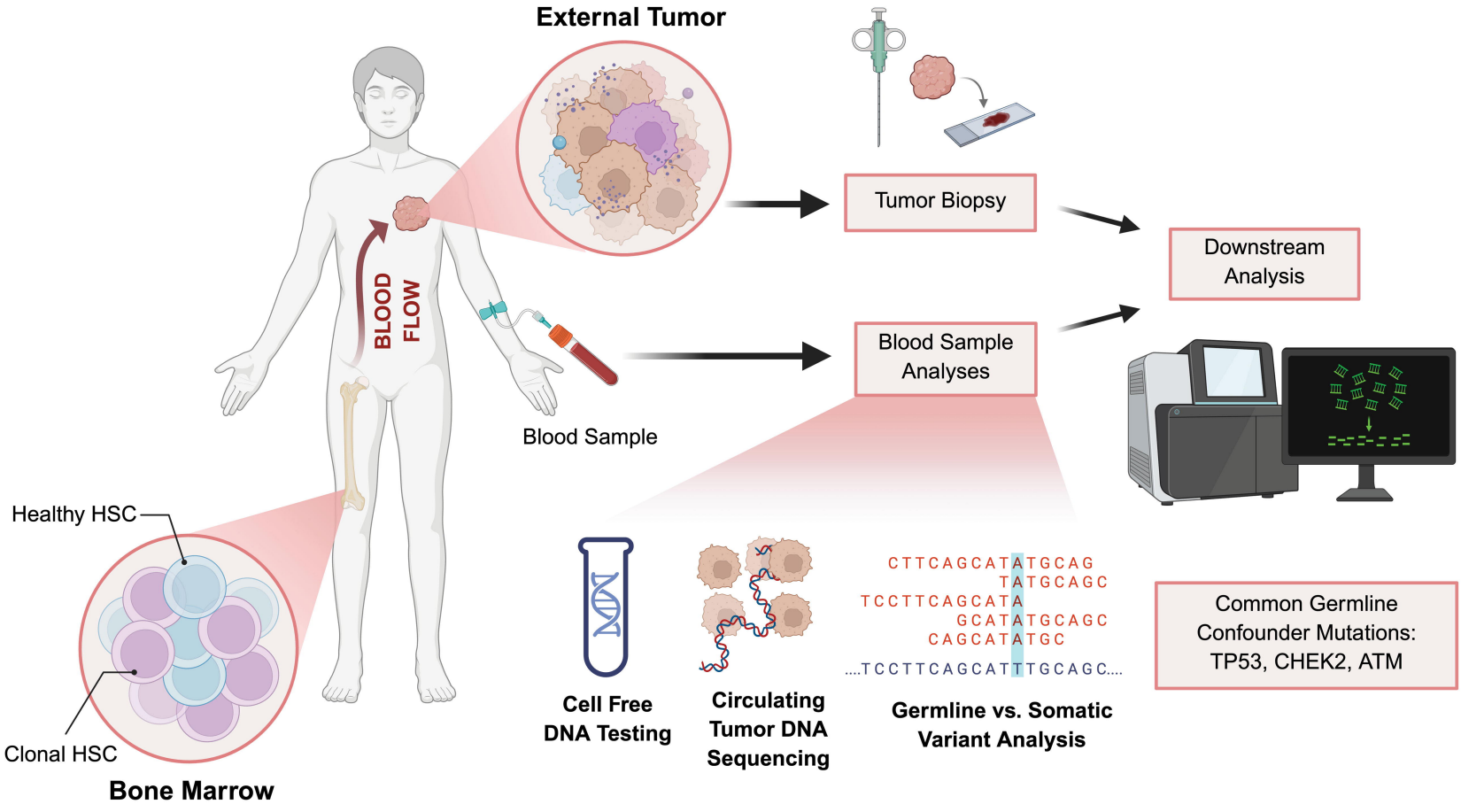

Cell Types
Tumor Cells
CH-derived Immune Cells
Normal HSC-derived Immune Cells
From Bone Marrow
Normal HSC-derived Immune Cells
CH-derived Immune Cells
BLOOD FLOW
Monocyte
T-cell
Neutrophil
Macrophage
Clonal HSC-derived Cytokines
IL-1β, IL-6, IL-13, IL-17, TNF-α, IFN-γ
TGF-β1
Positive Consequences
Preservation of stem-cell like T-cells
Enhanced and durable immunotherapy response
Negative Consequences
Premature Aging
T-cell Exhaustion
Increased PD-1 expression
Suppression of CD8+ T-cells
Promotion of Angiogenesis
M2-like Macrophage Polarization

Figure 2


External Tumor
BLOOD FLOW
Blood Sample
Tumor Biopsy
Blood Sample Analyses
Downstream Analysis
Healthy HSC
Clonal HSC
Bone Marrow
Cell Free DNA Testing
Circulating Tumor DNA Sequencing
CTTCAGCATATGCAG
TATGCAGC
TCCTTCAGCATA
GCATATGCAGC
CAGCATATGC
....TCCTTCAGCATTTGCAGC....
Germline vs. Somatic Variant Analysis
Common Germline Confounder Mutations: TP53, CHEK2, ATM