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In this edition of the Leukemia Insights newsletter, written by Kelly Chien, M.D., Danielle Hammond, M.D., Courtney DiNardo, M.D., Guillermo Garcia-Manero, M.D., we provide a summary of our approach to CHIP/CCUS and an overview of the clonal hematopoiesis and Leukemia Prevention Clinic. Learn more about our Leukemia program.

New updates in clonal hematopoiesis

Introduction

As we age, our hematopoietic stem cells sporadically can acquire genetic mutations without evidence of a hematologic malignancy, a phenomenon called clonal hematopoiesis (CH). Clonal hematopoiesis (Figure 1) encompasses the terms clonal hematopoiesis of indeterminate potential (CHIP), where patients have mutations but normal blood counts, and clonal cytopenias of undetermined significance (CCUS), which refers to mutations in the setting of a World Health Organization (WHO)-defined cytopenia (anemia: hemoglobin < 12 g/dL in females or < 13 g/dL in males; thrombocytopenia: platelet count < 150 x 10^9 cells/L; neutropenia: absolute neutrophil count < 1.8 x 10^9 cells/L)[1,2]. These mutations have been detected in healthy individuals with a rise in frequency with increasing age and are present in the peripheral blood of more than 10% of people aged 65 or older[3,4]. While most of these genetic aberrations are of little consequence, certain changes in the right context can lead to the development of hematologic malignancies, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)[5]. Clonal hematopoiesis is also associated with therapy-related myeloid neoplasms in those who receive cytotoxic therapy for another cancer diagnosis,[6,7] and is now a recognized risk factor for and causally implicated in the development of several chronic disease of aging and/or inflammation, especially atherosclerotic cardiovascular disease[8,9]. Furthermore, there have been several population studies linking specific clonal hematopoiesis mutations to environmental exposures, such as smoking and certain antineoplastic agents[10].

Studying clonal hematopoiesis not only provides the opportunity to test early-intervention preventive strategies for people at the highest risk of developing hematologic malignancies, but also allows for a better understanding of the origins of MDS and related myeloid neoplasms. We provide a summary of our approach to CHIP/CCUS and an overview of the Clonal Hematopoiesis and Leukemia Prevention Clinic, which is a part of the MDS section in the Leukemia Department at the University of Texas MD Anderson Cancer Center.

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The MD Anderson Experience with Clonal Hematopoiesis

We evaluated 78 patients with 1 myeloid somatic mutation on next generation sequencing from 2015 to 2021[11]. Of those, 46 patients had concurrent cytopenias. As expected in a cohort from a tertiary cancer center, 76% had a previous cancer diagnosis and 56% had received cytotoxic therapy for another primary malignancy. More than 75% of patients had moderate or severe comorbidities by the ACE-27 score[12,13], with 73% suffering from cardiovascular comorbidities. A total of 58 patients were observed, and all 20 treated patients had CCUS. Therapies received include growth factors, non-steroidal immunosuppressive therapies, corticosteroids, iron supplementation, intravenous immunoglobulin, and rituximab. Twelve patients (15%) transformed to MDS or AML. With a median follow-up time of 27 months, 20 patients (26%) died of various causes, including primary malignancy (35%), complications from other comorbidities (20%), MDS/AML (20%), or infections (15%). Therefore, close monitoring of CHIP/CCUS patients for not only progression to MDS/AML but also extra-hematologic manifestations is paramount.

This retrospective review demonstrated that most individuals with clonal hematopoiesis will not develop a hematologic malignancy. It is crucial to identify the types of clonal hematopoiesis that lead to clonal expansion and malignant progression, with the goal of early intervention to prevent malignant transformation.

Clonal Hematopoiesis and Leukemia Prevention at MD Anderson

There are no consensus guidelines regarding the optimal screening, monitoring, and management of individuals with CH, but there is a growing need for multidisciplinary guidance. The increasing frequency with which individuals with clonal hematopoiesis are identified, and the growing knowledge about the potential clinical implications of CH has led to the recent development of specialized hematologic precursor clinics, including ours. The aims of our Clonal Hematopoiesis and Leukemia Prevention Clinic are:

1. Natural History Study: to advance our understanding about the natural history of CH and the determinants of clonal progression.

2. Health Maintenance: to screen and facilitate appropriate specialist care for associated extra-hematologic toxicities and consequences, especially cardiovascular disease.

3. Leukemia Prevention: to identify individuals with CH at highest risk of progression to hematologic malignancies and offer precision monitoring and prevention strategies.

Figure 2 outlines our clinic framework. There is no evidence to support screening the general population for CH. The main referral streams for our clinic are below, but we also see referrals for CH detected in prospective donors for allogeneic stem cell transplantation and in individuals who have undergone sequencing to evaluate for potential inherited cancer predispositions.

Most frequent referrals are:

•Individuals with cytopenias and suspicion of an underlying hematologic malignancy. This includes both healthy individuals and those with non-hematologic tumors experiencing excessive cytopenias with antineoplastic therapy. A mutation on peripheral blood next generation sequencing does not confirm the presence of a myeloid neoplasm[14]. On bone marrow evaluation, these patients do not meet diagnostic criteria for a myeloid neoplasm but have myeloid somatic mutation(s). A comprehensive laboratory and clinical evaluation are critical to exclude more common etiologies for the patient's cytopenias.

•Patients who undergo bone marrow evaluation for an established non-myeloid hematologic cancer such as chronic lymphocytic leukemia or multiple myeloma, and in whom myeloid somatic mutations are discovered.
•Those with non-hematologic cancers, such as solid tumors, who have undergone sequencing. At MD Anderson, matched blood and solid tumor DNA is routinely sequenced in parallel. If CHIP is identified, the patient's primary oncologist is notified and invited to refer the patient to Clonal Hematopoiesis and Leukemia Prevention clinic. CH in non-hematologic cancers has been shown to have adverse clinical outcomes, such as increased risk of hematologic malignancies and shorter survival[15].

We aim to provide an individualized risk assessment to inform diagnostic and monitoring recommendations. However, there are currently neither evidence-based management guidelines nor established preventative interventions. Individuals are counseled according to their downstream risk profile of future myeloid malignancies, cardiovascular disease, and autoinflammatory disease. The following sections will review the current framework to achieve our objectives.

Natural History Study

We perform a complete blood count with differential every 3-6 months with or without a bone marrow evaluation every 6-12 months. All clinic referrals are approached regarding permission for banking of de-identified blood and bone marrow samples for future research. If the patient provides informed consent, we store the blood and bone marrow samples in our tissue bank for scientific investigation in collaboration with basic science researchers in the Leukemia Department.

Health Maintenance

Cardiovascular Screening

CH is strongly associated with an increased risk of atherosclerotic cardiovascular disease due to the generation of proinflammatory cytokines and endovascular interaction with circulating clonal macrophage progenitor cells[4,8,9]. The use of existing anti-inflammatory therapies is a promising approach for reducing CH-related cardiovascular risk, as shown by the CANTOS trial in which a preferential reduction in secondary cardiovascular events was observed in patients with *TET2*-mutated clonal hematopoiesis treated with canakinumab, an anti-IL-1β antibody[16,17]. Given the increased risk of atherosclerotic cardiovascular disease, all patients with CH should undergo cardiovascular screening, and a clinical algorithm for the primary prevention of cardiovascular disease in these patients was previously proposed[18]. Generally, all patients undergo a baseline echocardiogram (if not already available) and laboratory testing every 6-12 months, including lipid panel, hemoglobin A1c, and thyroid function tests. If the individual has anginal symptoms, urgent cardiology clinic referral is warranted for a stress test or left heart catheterization. However, if the patient has no anginal symptoms, the risk of cardiovascular disease is calculated by the atherosclerotic cardiovascular disease (ASCVD) 10-year score[19], a risk stratification tool validated for those over 40 years of age. In younger patients, a coronary CT angiogram should be considered. Recently, the use of coronary CT scans to calculate the coronary artery calcium (CAC) score has been advocated to add additional risk stratification to the standard ASCVD score[20]. If needed, aspirin 81 mg and an appropriate statin can then be initiated.

Mitigation of Autoimmune Conditions

Less is established about the mechanistic link between CH and other comorbidities, but there is a growing body of evidence implicating certain forms in the development of inflammatory conditions such as gout, arthritis, vasculitis, and adult-onset hemophagocytic lymphohistiocytosis. There is thought that patients with *TET2* or *IDH1/2*-mutated CH may be at an increased risk due to T-cell dysregulation[21]. Additionally, there has been great interest in VEXAS syndrome, a

life-threatening autoimmune condition with relapsing polychondritis involving a rare form of CH with mutations in the *UBA1* gene[22,23]. Individuals with CH and unexplained autoimmune conditions are co-managed with rheumatologists in our clinic.

Routine Health Maintenance

Similar to the general population, individuals with CH should undergo routine cancer screening and vaccinations according to the Centers for Disease Control and Prevention. The table below summarizes the current US Preventive Services Task Force guidelines for cancer screening.

Cancer	Age	Testing
Cervical Cancer	21-29	Pap smear every 3 years
	30-65	HPV ± pap smear every 5 years
Breast Cancer	25-39	Breast exam every 1-3 years
	40-75	Mammogram + breast exam every year
Colon Cancer	45-75	Colonoscopy every 10 years
		Virtual colonoscopy every 5 years
		Stool testing every 1-3 years
Prostate Cancer*	45+	Baseline PSA and DRE
Lung Cancer**	50-80	Low-dose CT chest every year

*optional
**those with 20-pack-year smoking history and who currently smoke or have quit within past 15 years

Leukemia Prevention and Clinical Trial Options

In addition to the standard hematologic monitoring, as described in our natural history study, we aim to identify individuals at highest risk of evolution to overt myeloid neoplasms. The risk of developing a myeloid malignancy from CHIP/CCUS is gene-specific; healthy individuals with somatic mutations in spliceosome genes (e.g. *U2AF1*, *SRSF2*), *IDH1/2*, *JAK2*, and *TP53* have an increased risk of developing AML[24-26]. Various factors, including increased variant allelic frequency (VAF) ≥ 0.1-0.2, 2 or more mutations, and adverse mutational profiles, have also been implicated in transformation to myeloid malignancies[27-29].

The Clonal Hematopoiesis Risk Score (CHRS) was recently published as a personalized prediction tool for the risk of progression to myeloid neoplasms in healthy adults with CHIP/CCUS based on specific mutations, VAF, age, and several peripheral blood laboratory values, including peripheral blood counts, red cell distribution width, and mean corpuscular volume[30]. However, there is no standard approach to risk stratification for cancer patients in the setting of therapy-related CH. Our approach to identifying high-risk patients is:

•Causally attributed cytopenias
•High-risk mutations (e.g. *TP53,* splicing mutations)
•Higher mutation burden (higher VAF and/or multiple mutations)

There are currently no Food and Drug Administration (FDA)-approved strategies for the prevention of myeloid neoplasms in the setting of CHIP/CCUS. However, we have available clinical trial options.

1. Canakinumab (NCT04239157): an anti-IL-1β antibody with limited efficacy in high-molecular-complexity MDS patients who had undergone multiple lines of prior treatment but yielded sustained long-term responses in patients with single *DNMT3A* or *TET2* mutations[31]. We have expanded the MDS clinical trial to include frontline lower-risk transfusion-dependent MDS, lower-risk transfusion-independent MDS, and CCUS.

2. Luspatercept (NCT06113302): binds TGFβ ligand to reduce SMAD2/SMAD3 signaling, which is increased in diseases with ineffective erythropoiesis. Based on the phase III trials MEDALIST[32] (luspatercept vs placebo for lower-risk transfusion-dependent MDS with ringed sideroblasts

who were refractory to or unlikely to respond to erythropoietin stimulating agents [ESA]) and COMMANDS[33] (luspatercept vs ESA in frontline lower-risk transfusion-dependent MDS), it is FDA-approved as frontline therapy for lower-risk MDS patients who require transfusions. We have expanded an investigator-initiated trial to include lower-risk transfusion-independent MDS and are working on the addition of CCUS patients. We are also participating in ELEMENT-MDS, a randomized phase III trial with luspatercept vs ESA in frontline lower-risk transfusion-independent MDS[34].

3. Olutasidenib (pending): an oral, selective potent inhibitor of the IDH1 mutant protein with no significant off-target activity, which received FDA approval as monotherapy in relapsed/refractory *IDH1*-mutated AML[35]. Observational studies have demonstrated that CCUS patients with mutations in high-risk genes, including *IDH1*, are more likely to transform to acute myeloid leukemia (AML)[25,30,36], with one study showing a progression rate of 100% in *IDH1/2*-mutated patients after 5 years of follow-up[24]. Additionally, *IDH1/2* mutations are also detected in chronic myeloid neoplasms, with studies showing their prevalence in approximately 5% of patients with MDS/chronic myelomonocytic leukemia (CMML), though some publications note up to 12%, and roughly 9% of patients with myeloproliferative neoplasms (MPNs)[37-39]. Mutations of *IDH1* have also been associated with shortened leukemia-free survival and overall survival and increased rates of transformation to AML in patients with MDS, and potentially those with MPN[40-42]. We are pending activation of 2 clinical trials: olutasidenib monotherapy in *IDH1*-mutated CCUS or lower-risk MDS/CMML and olutasidenib + hypomethylating agents in *IDH1*-mutated higher-risk MDS/CMML or advanced MPN.

4. Decitabine/cedazuridine (pending): a DNA methyltransferase inhibitor with the addition of cedazuridine, a cytidine deaminase inhibitor in the gastrointestinal tract that increases systemic exposure of decitabine after oral administration, that is FDA-approved in MDS[43,44]. As part of a multicenter collaboration via Break Through Cancer, we are pending activation of a feasibility study investigating low-dose decitabine/cedazuridine in patients with high-risk CCUS.

Figure 1. Definition of terms in clonal hematopoiesis
HSC, hematopoietic stem cell; VAF, variant allele frequency

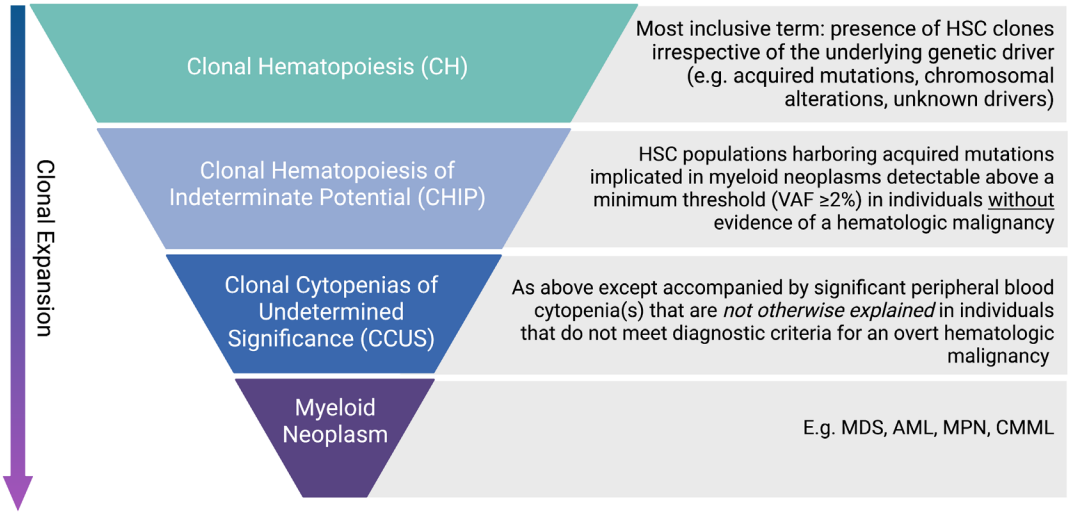
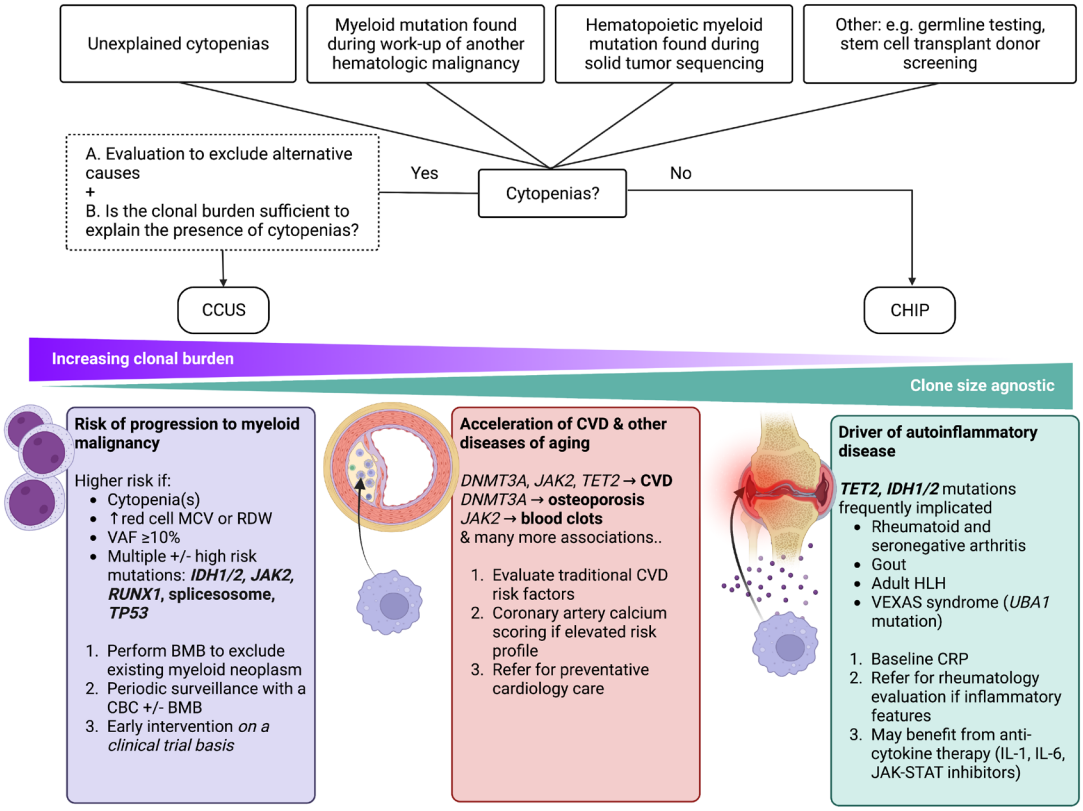


Figure 2. Current clinical approach to clonal hematopoiesis and its downstream implications

BMB, bone marrow; CVD, cardiovascular disease; HLH, hemophagocytic lymphohistiocytosis; VAF, variant allele frequency.



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