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503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Clonal Hematopoiesis and Inflammation in the Vasculature (CHIVE), a Prospective, Longitudinal Clonal Hematopoiesis Cohort and Biorepository

Jonathan Heimlich, MDPhD[1], Morgan Shannon, MD[2], Sydney Olson, BS[1], Alexander J Silver, BA[2,3], Ariana Debevec, BS[2], Zachary Copeland, MPH[1], Caitlyn Vlasschaert, MD PhD[4], Christina Snider, MD[2], Ashwin Kishtagari, MBBS[5], Donovan J Brown, BS[1], Travis Spaulding, MD[1], Manasa R Bhatta, MD[6], Kelly Pugh, MD[1], Shannon S Stockton, MD[1], Jessica Ulloa, BS[2], Yaomin Xu, PhD[7,8], Muhamed Baljevic, MD[1], Sanjay Mohan, MD MSCI[1], Javid J. Moslehi, MD[9], Eiman Jahangir, MD MPH[1], Brent Ferrell Jr., MD[10,11,1,3], David Slosky, MD[1], Alexander G. Bick, MD PhD[3,1,11,10], Michael R. Savona, MD[12,10,11,1]

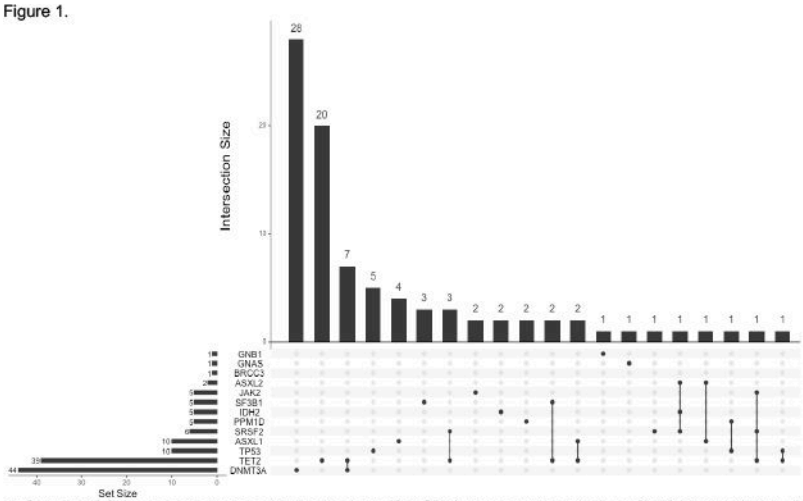
[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[2]Vanderbilt University School of Medicine, Nashville, TN
[3]Program in Cancer Biology, Vanderbilt University School of Medicine, Nashville, TN
[4]Department of Medicine, Queen's University, Kingston, Canada
[5]Department of Internal Medicine, Division of Hematology, Vanderbilt University School of Medicine; Ingram Cancer Center, Nashville, TN
[6]Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN
[7]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN
[8]Department of Bioinformatics, Vanderbilt University Medical Center, Nashville, TN
[9]Section of Cardi-Oncology & Immunology, Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA
[10]Center for Immunobiology, Vanderbilt University School of Medicine, Nashville, TN
[11]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN
[12]Program in Cancer Biology, Vanderbilt University Medical Center, Nashville, TN

Introduction
Clonal hematopoiesis (CH), the expansion of a clonal population of hematopoietic cells, is an age-associated phenomenon leading to increased risk of both hematologic malignancy and non-malignant organ dysfunction. There have been significant advances in our understanding of the underlying pathophysiology of CH in recent years. However, additional studies are needed to better understand clinical trajectories and optimal care of patients with CH. To address this gap, the prospective, longitudinal CHIVE (Clonal Hematopoiesis and Inflammation in the VasculaturE) registry and biorepository was created to support multidisciplinary CH clinics.
Methods
Adults without active hematological malignancy who were clinically identified to have CH or who were at risk for CH were sequentially enrolled utilizing a multidisciplinary referral approach between October 2020 to April 2023 at Vanderbilt University Medical Center (VUMC). Research samples were procured at the time of routine clinical blood draws or bone marrow biopsies and stored in a newly established biorepository, equipped to store DNA, plasma, and viably cryopreserved cells to enable a spectrum of downstream applications. Specimens were sequenced on a highly cost efficient (~$6/sample) targeted next generation sequencing capture panel that identified mutations residing in the 24 most frequently mutated CHIP genes.The VUMC CH clinic, which serves as a referral pool, were included in Arm A of CHIVE (n=57). We also sought out a population at risk for CH which included patients over 18 years of age with a history of solid tumor, cardiovascular disease, renal disease, rheumatologic disease, or diabetes, who were included in Arm B (n=122). Patients from Arm A or B were included in the CH-positive (CH+) group if they met criteria for CH on the research assay at any time during their enrollment in the study. All other genotyped patients who were not found to have CH by the research assay, regardless of their clinical CH status at study enrollment, were included in the CH-negative (CH-) group.Anthropometric data and clinical assessments, including laboratories and cardiovascular studies obtained in the course of routine clinical care were extracted from the electronic health record, and recorded and maintained in the CHIVE database.

Results
261 patients were approached for consent to enroll in CHIVE and 179 were ultimately enrolled. More than one half (54%) of all participants had a CH mutation (CH+) and of those, 49.5% were female. Median age of CH+ patients was 71.9 (IQR 64.0-77.5). DNMT3A (n=44) and TET2 (n=39) were the most commonly mutated genes, while variant allele fractions (VAF) ranged from 2.1 - 79.8% (Figure 1). 246 samples were serial samples collected from 89 patients at regular intervals. Significantly more CH+ patients had a diagnosis of coronary artery disease compared to CH- patients (55.7% vs 32.9%, p=0.004). CH+ patients also had increased rates of hypertension and heart failure compared to the CH- group ($p<0.001$, 0.035, respectively). Laboratory evaluation showed CH+ patients to have a lower median white blood cell count, hemoglobin, and platelets, and elevated blood urea nitrogen values compared to CH- patients, differences that did not meet statistical significance. 8.2% of the CH+ patients progressed to frank hematologic malignancy over the course of the 2.5-year study (Table 1). Eight of the 97 CH+ and 2 of the 82 CH- patients died over the course of the study period resulting in a trend toward decreased survival in CH+ patients (p=0.112).
Conclusions
We demonstrate the feasibility of a prospective, observational study of CH patients utilizing a robust referral network to support both clinical care and translational research. A well-genotyped and phenotyped cohort of CH patients will be critical to future translational research efforts and clinical trials - a key function of our study design. Early clinical findings from our cohort recapitulate large scale retrospective datasets where CH patients are at an increased risk of development of hematologic malignancy, end organ damage, and all-cause mortality. Scaling this resource in collaboration with other centers is underway and will ultimately enable the development of clinical guidelines and treatment strategies for this increasingly recognized patient population.

Disclosures Kishtagari: *Servier Pharmaceuticals:* Consultancy; *Geron Corporation:* Membership on an entity's Board of Directors or advisory committees; *CTI BioPharma Corp., a Sobi company:* Speakers Bureau. **Baljevic:** *AbbVie:* Consultancy; *Janssen Biotech:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees; *BMS/Celgene:* Membership on an entity's Board of Directors or advisory committees; *Parexel:* Membership on an entity's Board of Directors or advisory committees; *Cardinal Health:* Consultancy. **Mohan:** *Karyopharm, Astex, Incyte, Kartos, Ichnos, NCCN:* Research Funding. **Moslehi:** *Pfizer:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *Teva:* Consultancy; *BitterRoot Bio:* Consultancy; *Regeneron:* Consultancy; *Bristol-Myers Squibb:* Research Funding; *Takeda:* Consultancy; *Cytokinetics:* Consultancy; *Janssen:* Consultancy; *Beigene:* Consultancy; *Repare:* Consultancy. **Ferrell:** *Novartis:* Research Funding. **Bick:** *TenSixteen Bio:* Membership on an entity's Board of Directors or advisory committees. **Savona:** *Karyopharm Therapeutics Inc.:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Ryvu Therapeutics:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Sierra Oncology, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Taiho:* Membership on an entity's Board of Directors or advisory committees; *Takeda Pharmaceutical Company:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *TG Therapeutics, Inc.:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Boehringer Ingelheim:* Patents & Royalties; *ALX Oncology:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *Incyte Corporation:* Research Funding; *Geron Corporation:* Membership on an entity's Board of Directors or advisory committees; *Forma Therapeutics Inc.:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *CTI BioPharma Corp.:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees; *AbbVie Inc.:* Membership on an entity's Board of Directors or advisory committees.

Figure 1.



UpSet plot of CH-associated genes. Horizontal bars (Set Size) represent the number of individual mutations in each gene present within our cohort of CH+ patients (n = 97). Vertical bars (Intersection Size) represent the number of CH+ patients with a given mutational landscape. Connecting dot plot displays the specific gene or combination of genes that are mutated in each patient group.

Table 1.

Patient ID	Number of Mutations	Mutation	Maximum VAF	High Risk Gene	Average VAF	Type of Malignancy
0004	4	TET2 R1516X	0.398	No	0.217	MDS
		TET2 Q695X	0.369	No		
		SRSF2 P95H	0.177	Yes		
		JAK2 V617F	0.02	Yes		
1014	2	TET2 L957Lfs*15	0.505	No	0.365	CMML
		SRSF2 P95R	0.402	Yes		
1017	3	DNMT3A R882H	0.198	No	0.098	MDS
		IDH2 R140Q	0.104	No		
		TP53 R273C	0.049	Yes		
1060	1	SF3B1 R625C	0.241	Yes	0.236	MDS
1073	4	TET2 Q742X	0.422	No	0.237	CMML
		SRSF2 P95R	0.330	Yes		
		TET2 Y1245Lfs*22	0.270	No		
		TET2 N535Kfs*6	0.033	No		
1096	1	TET2 G1288D	0.796	No	0.758	CMML
2026	1	TP53 Y220C	0.676	Yes	0.676	AML
2038	1	TET2 Q749Rfs*15	0.021	No	0.021	MDS

Clone features of CH patients that developed hematologic malignancy over the course of the study. High-risk features include total number of mutations, variant allele fraction (VAF), and mutations in high-risk genes.

Figure 1

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