Supplementary Materials

Supplementary Methods

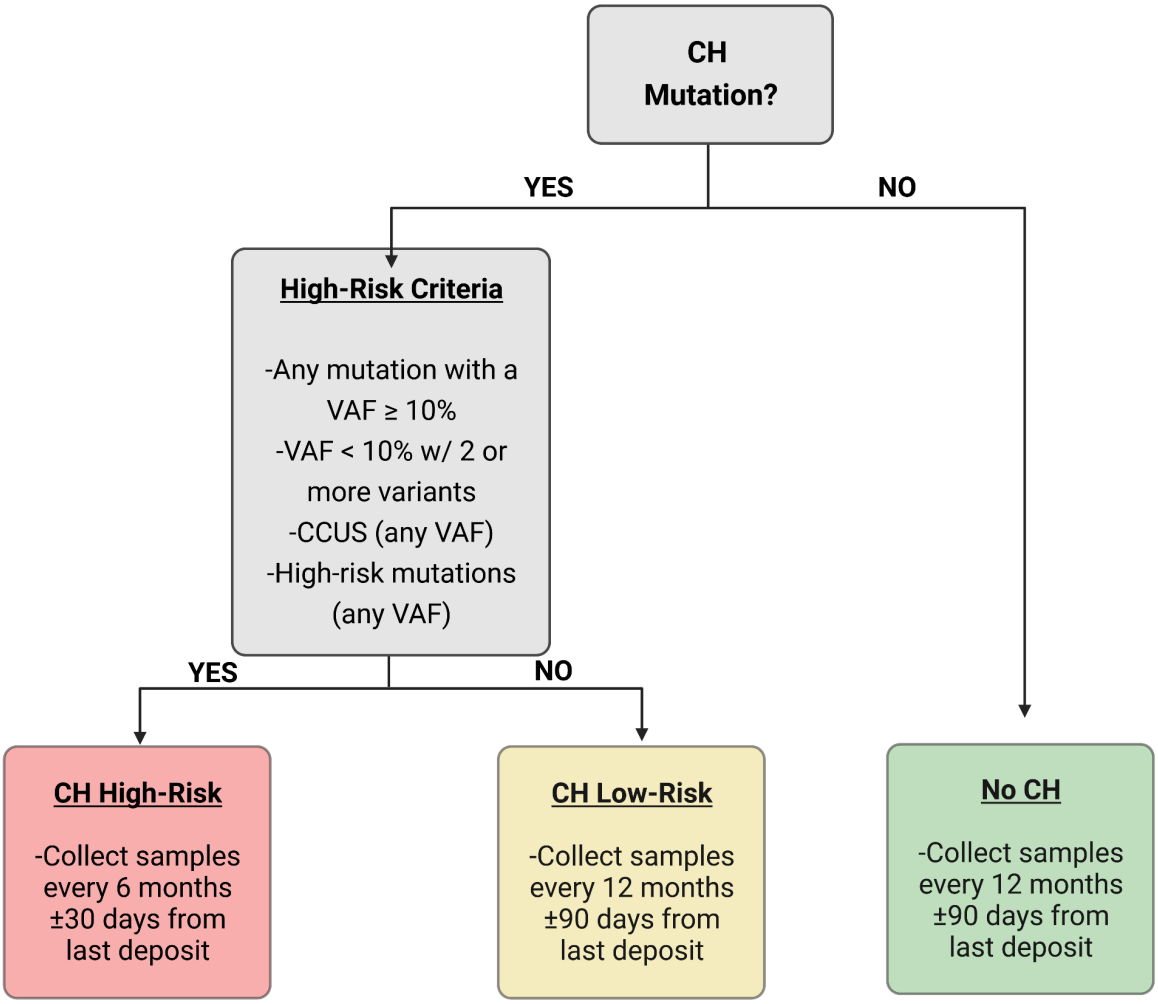
Development of a Biorepository

After participants gave informed consent, clinical data available from standard clinical care was collected, including demographic data, medical histories, vital signs, laboratory studies, imaging studies, data from bone marrow biopsies, and clinically ordered genotyping. Genetic data included germline testing, clinical next generation sequencing mutation analyses, and chromosome analyses. Additional cardiovascular studies including electrocardiogram data, and echocardiogram data were collected when available. Upon study enrollment, initial research samples from peripheral blood draws were obtained at the time of planned, routine, clinical sample collection. Similarly, aliquots from bone marrow aspirate and biopsies were procured when available.

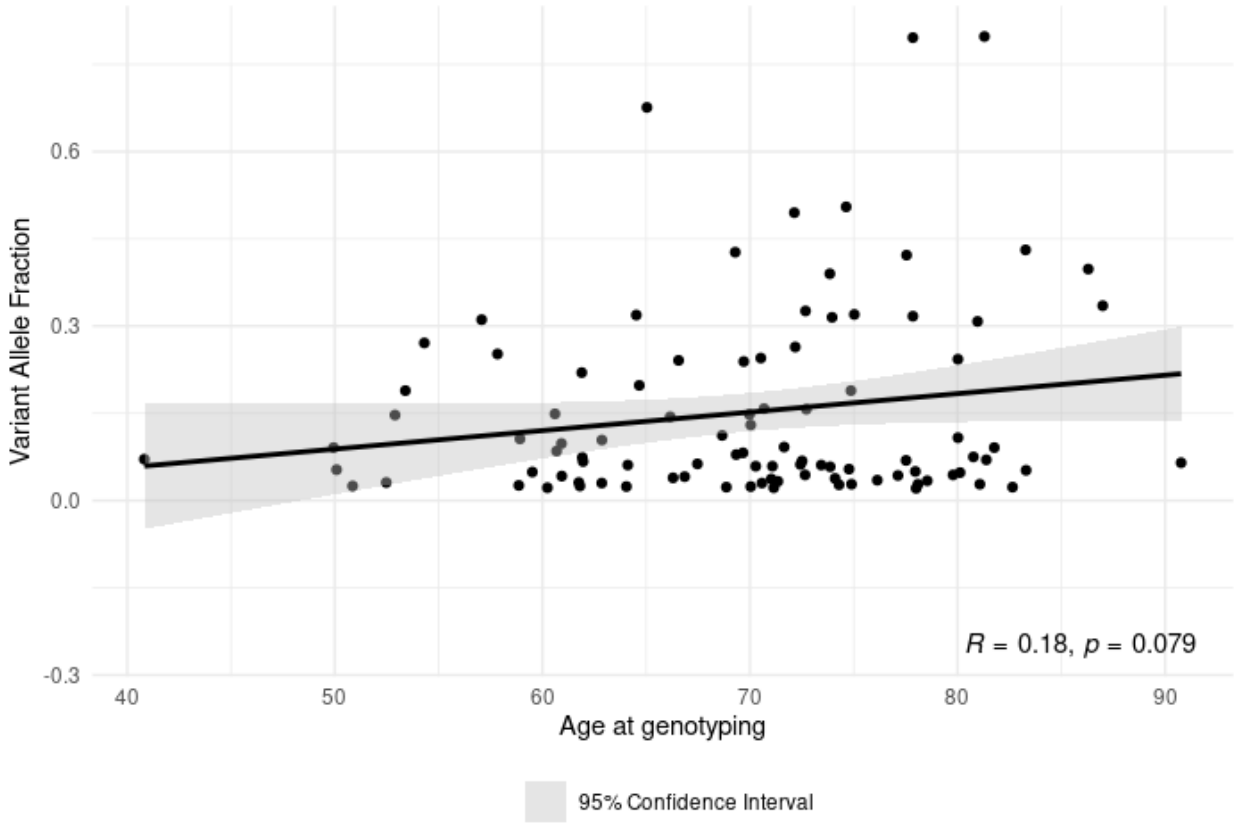
Blood samples collected at 6- to 12-month intervals were stored within the *CHIVE* biorepository, a dedicated space with capacity to store peripheral blood and bone marrow samples. Specimens were maintained in a liquid nitrogen freezer with a password protected lock, which was housed in a dedicated laboratory space under supervision. Specimens were assigned a de-identified participant number for archiving to prevent subject identification; patient identifiers were separately stored in a REDcap database, accessible only with secure ID and password.

Supplementary Figures and Tables

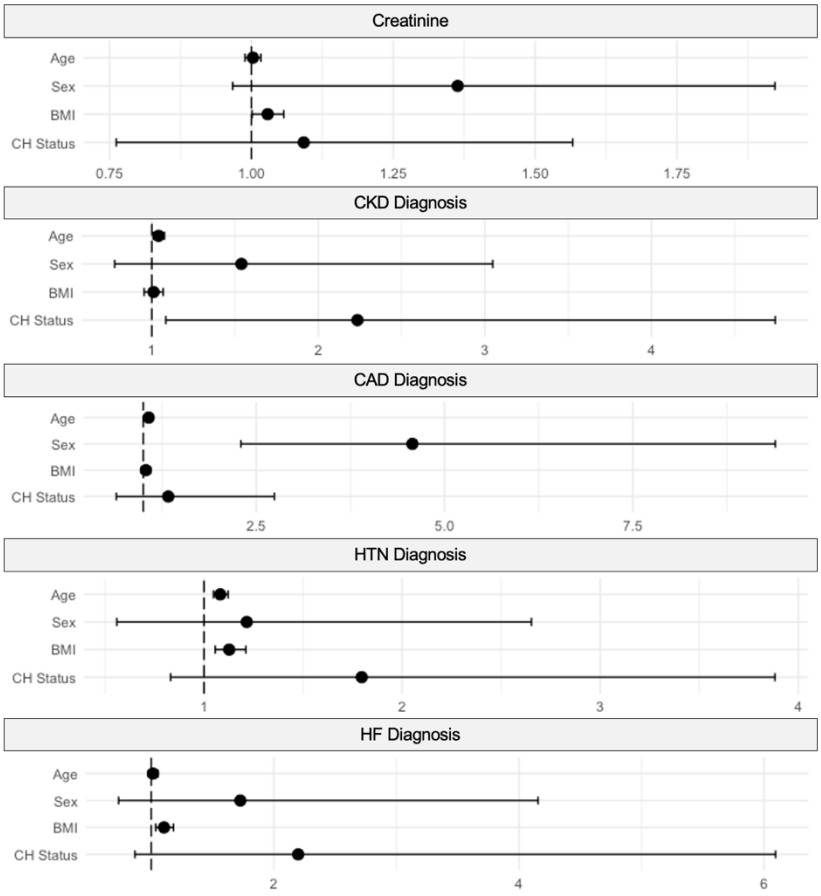
Supplementary Figures



Supplementary Figure 1. Rubric used to determine frequency of sample collection for CHIVEseq based on patient risk assessment. Samples were collected approximately every 12 months from patients without CH and from patients with CH but without high-risk clone features. Samples were collected approximately every 6 months from CH patients whose clone met one or more high-risk criteria.

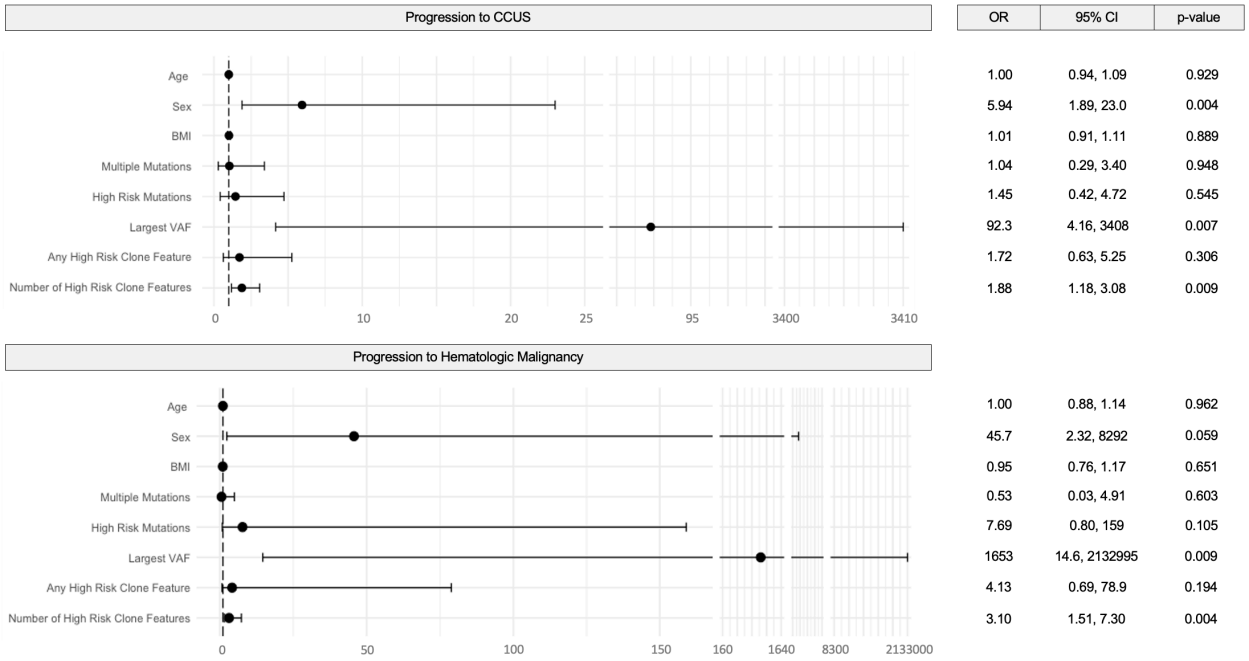


Supplementary Figure 2. Scatter plot of the correlation between maximum variant allele fraction (VAF) and age at time of genotyped sample collection. Each dot represents a single CH patient. If a patient had multiple mutated genes and/or multiple samples genotyped, the highest VAF across all genes and time points was selected. A weakly positive but insignificant correlation between age and VAF is shown, p =0.079.



OR	95% CI	p-value
1.00	0.99, 1.02	0.717
1.36	0.97, 1.92	0.079
1.03	1.00, 1.07	0.043
1.09	0.76, 1.57	0.632
1.04	1.01, 1.08	0.015
1.54	0.78, 3.05	0.215
1.01	0.95, 1.07	0.711
2.23	1.08, 4.74	0.032
1.07	1.04, 1.11	6.71×10^{-5}
4.57	2.30, 9.39	2.18×10^{-5}
1.03	0.98, 1.09	0.238
1.33	0.64, 2.74	0.437
1.08	1.05, 1.12	5.79×10^{-6}
1.22	0.56, 2.65	0.621
1.13	1.06, 1.21	5.53×10^{-4}
1.80	0.83, 3.88	0.134
1.01	0.98, 1.06	0.473
1.73	0.73, 4.16	0.213
1.10	1.04, 1.18	0.003
2.20	0.87, 6.09	0.109

Supplementary Figure 3. Forest plots depicting the odds ratio and 95% confidence interval for each covariable included in multivariate regression for those clinical outcomes determined to be significantly different between CH+ and CH- groups. Outcomes for which multivariate regression was performed include creatinine, chronic kidney disease (CKD) diagnosis, coronary artery disease (CAD) diagnosis, hypertension (HTN) diagnosis, and heart failure (HF) diagnosis. For each outcome; age, sex, body mass index (BMI), and CH status were included as variables in multivariate regression.



Supplementary Figure 4. Forest plots depicting the odds ratio and 95% confidence interval for each covariable included in regression for progression to CCUS and progression to malignancy outcomes. For each outcome, age, sex body mass index (BMI), presence of high-risk mutations, presence of multiple mutations, and largest variant allele fraction (VAF) were included as covariables in the multivariate regression. Association between progression to CCUS or progression to malignancy and presence of any high-risk mutation or number of high-risk mutations were independently assessed via univariate regressions.

Supplementary Tables

Supplementary Data Table 1: Genomic regions included in CHIVEseq assay as CH-associated mutations

Gene	Chromosome	Base Pairs
ASXL1	20	32358770-32358837; 32359741-32359796; 32366378-32366472; 32369006-32369128; 32428122-32428253; 32428319-32428427; 32429332-32429436; 32429895-32430058; 32431315-32431489; 32431577-32431684; 32432874-32432990; 32433278-32433922; 32434426-32437343
ASXL2	2	25749689-25750420; 25753532-25753640
BRCC3/MTCP1	X	155071527-155071650; 155072326-155072343; 155073376-155073431; 155077169-155077289; 155078615-155078703; 155089262-155089351; 155090783-155090839; 155099314-155099389; 155116056-155116188; 155116710-155116754

CBL	11	119278160-119278302; 119278504-119278718
DNMT3A	2	25234273-25234425; 25235701-25235830; 25236930-25237010; 25239124-25239220; 25239484-25239518; 25240296-25240455; 25240634-25240735; 25241556-25241712; 25243892-25243987; 25244149-25244343; 25244534-25244657; 25245247-25245337; 25246014-25246069; 25246154-25246314; 25246614-25246781; 25247045-25247163; 25247585-25247754; 25248031-25248257; 25249651-25249729; 25251906-25252099; 25252188-25252202; 25274935-25275092; 25275494-25275548; 25282382-25282716; 25300133-25300248; 25313907-25313989
ETNK1	12	22671265-22671359
GNAS	20	58909344-58909428; 58909515-58909584; 58909678-58909809; 58909945-58910086; 58910328-58910406; 58910677-58910834
GNB1	1	1806469-1806543; 1815750-1815867
IDH1	2	208243524-208243601; 208248358-208248421
IDH2	15	90088655-90088758
JAK2	9	5073683-5073800
KIT	4	54727415-54727542; 54727822-54727927; 54728010-54728121; 54729334-54729485; 54731327-54731419; 54731870-54731998; 54736497-54736609
KRAS	12	25225612-25225772; 25227220-25227424; 25245270-25245384
MPL	1	43349257-43349363
NRAS	1	114713799-114713978; 114716047-114716162
PPM1D	17	60662989-60663557
SETBP1	18	44951903-44952002
SF3B1	2	197400049-197400171; 197400246-197400439; 197400709-197400941; 197401394-197401530; 197401736-197401893; 197401979-197402135; 197402550-197402831; 197402943-197403040; 197403579-197403769; 197405070-197405182; 197405269-197405477; 197407992-197408124; 197408363-197408586; 197409764-197410012; 197416735-197416916
SRSF2/MFSD11	17	76736785-76736983
TET2	4	105233891-105237445; 105241333-105241438; 105242828-105242932; 105243564-105243783; 105259613-105259774; 105261753-105261853; 105269604-105269752; 105272558-105272923; 105275042-105276524
TP53	17	7669603-7669695; 7670603-7670720; 7673213-7673271; 7673301-7673344; 7673529-7673613; 7673695-7673842; 7674175-7674295; 7674814-7674976; 7675047-7675243; 7675988-7676277; 7676376-7676408; 7676515-7676627
U2AF1	21	43093096-43093254; 43094461-43094568; 43094649-43094793; 43095432-43095541; 43095688-43095748; 43100447-43100524; 43101274-43101437; 43104309-43104407; 43107445-43107499
ZBTB33	X	120253410-120255439
ZNF318	6	43340784-43340913; 43342106-43342216; 43342670-43342884; 43348318-43348630; 43352371-43352481; 43354658-43356150; 43357120-43357770; 43365286-43365445; 43368961-43369370

Supplementary Data Table 2: Recruitment sources for all patients in CH+ and CH- groups

Recruitment Source	No CH (n = 82)	CH (n = 99)
Hematology/Oncology	22	40
Cardiology	23	45
Hereditary Cancer	35	10
Rheumatology	2	4

Supplementary Data Table 3. Germline Mutations in CH Genes Among CHIVE Patients

Sample	Chr	Start	End	Ref	Alt	Region	Gene	Mutation Type	RefSeq	AA Change	Gnomad AF	ClinVar
6517-AB-221	chr4	105237193	105237193	A	C	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.Q1084P,TET2	0.0033	Benign/Likely Benign
6517-AB-231	chr4	105275843	105275843	A	G	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.H1778R	0.0389	Benign
6969-NH-20	chr20	32434666	32434666	G	A	exonic	ASXL1	Nonsynonymous SNV	NM_001363734	p.G591S,ASXL1	0.0067	Benign/Likely Benign
6969-NH-20	chr4	105234028	105234028	C	G	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.P29R,TET2	0.0319	Benign
6969-NH-36	chr6	43339661	43339661	G	A	exonic	ZNF318	Nonsynonymous SNV	NM_014345	p.P1446L	0.0101	Benign
6969-NH-8	chr4	105235030	105235030	C	T	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.P363L,TET2	0.0529	Benign
8412-NH-111	chr4	105234042	105234042	C	T	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.L34F,TET2	0.0168	Benign
8412-NH-111	chr4	105234594	105234594	G	A	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.V218M,TET2	0.0390	Benign
8618-NH-005	chr4	54733102	54733103	CC	TA	exonic	KIT	nonframeshift substitution	NM_000222	p.L799I,KIT	0.0282	Benign/Likely Benign
8618-NH-020	chr20	32436018	32436018	G	T	exonic	ASXL1	Nonsynonymous SNV	NM_001363734	p.E1041D,ASXL1	0.0105	Benign/Likely Benign
8618-NH-062	chr2	25749709	25749709	A	G	exonic	ASXL2	Nonsynonymous SNV	NM_001369347	p.V356A,ASXL2	0.0000	NA
8618-NH-080	chr4	105234042	105234042	C	T	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.L34F,TET2	0.0168	Benign
9077-NH-0074	chr4	105236541	105236541	T	C	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.Y867H,TET2	0.0106	Benign
9077-NH-0074	chr4	105275843	105275843	A	G	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.H1778R	0.0389	Benign
9077-NH-0074	chr6	43339632	43339632	G	C	exonic	ZNF318	Nonsynonymous SNV	NM_014345	p.P1456A	0.0002	NA
9077-NH-0076	chr6	43339907	43339907	G	A	exonic	ZNF318	Nonsynonymous SNV	NM_014345	p.S1364L	0.0041	NA
9532-NH-0032	chr4	105235030	105235030	C	T	exonic	TET2	Nonsynonymous SNV	NM_001127208	p.P363L,TET2	0.0529	Benign

Supplementary Data Table 4. Non hematologic cancer in CHIVE patients

Non-Hematologic Cancer in CHIVE Patients

	CH (N=30)	No CH (N=37)	Overall (N=67)
Cancer Type			
Bladder Cancer	2 (6.9%)	1 (2.7%)	3 (4.5%)
Breast cancer	6 (20.7%)	15 (40.5%)	21 (31.8%)
Colon cancer	1 (3.4%)	2 (5.4%)	3 (4.5%)
Large cell lung cancer	1 (3.4%)	0 (0%)	1 (1.5%)
MDS	1 (3.4%)	0 (0%)	1 (1.5%)
Non-hodgkin's lymphoma	1 (3.4%)	0 (0%)	1 (1.5%)
NSCLC	2 (6.9%)	1 (2.7%)	3 (4.5%)
Other	3 (10.3%)	6 (16.2%)	9 (13.6%)
Ovarian cancer	2 (6.9%)	2 (5.4%)	4 (6.1%)
Pancreatic cancer	2 (6.9%)	0 (0%)	2 (3.0%)
Peritoneal cancer	1 (3.4%)	0 (0%)	1 (1.5%)
Prostate cancer	5 (17.2%)	1 (2.7%)	6 (9.1%)
Thyroid Cancer	2 (6.9%)	2 (5.4%)	4 (6.1%)
Basal Cell Carcinoma	0 (0%)	3 (8.1%)	3 (4.5%)
CML	0 (0%)	1 (2.7%)	1 (1.5%)
Hepatic cancer	0 (0%)	1 (2.7%)	1 (1.5%)
Hodgkin's lymphoma	0 (0%)	1 (2.7%)	1 (1.5%)
Small cell lung cancer	0 (0%)	1 (2.7%)	1 (1.5%)

Supplementary Data Table 5: Deceased patients in CH+ and CH- groups and causes of death

Patient ID	CH Status	Cause of Death
006	CH	Pancreatic Cancer
007	CH	Peritoneal Cancer
009	CH	Septic Shock
012	CH	Breast Cancer
026	CH	AML
099	CH	Pancreatic Cancer
054	CH	Septic Shock
016	No CH	Renal Failure
028	No CH	Trauma