Pre-MDS states: CHIP, CCUS, ICUS – How to manage in the clinic?

08 Dec 2023

MDS Foundation Breakfast Symposium
Annual American Society of Hematology Meeting, San Diego, CA

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George and Beverly Rawlings Director of Hematology Research and the Early Therapy Program
Professor of Medicine and Cancer Biology
Vanderbilt University School of Medicine

Disclosures

I have the following financial relationships to disclose:

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The Patients
The Families
The Mice

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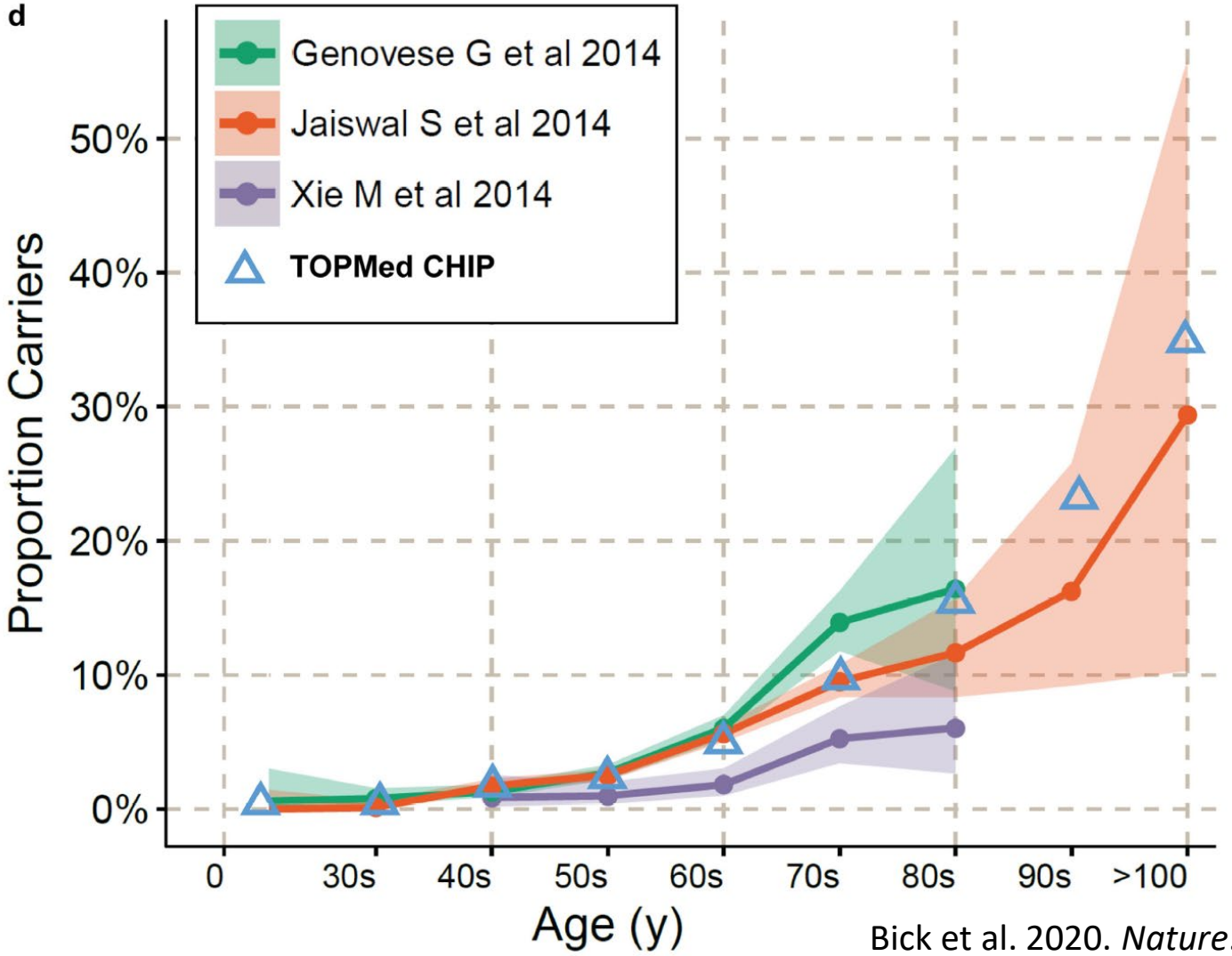
Clonal Hematopoiesis of Indeterminate Potential (CHIP) is 3-6% at 60yo

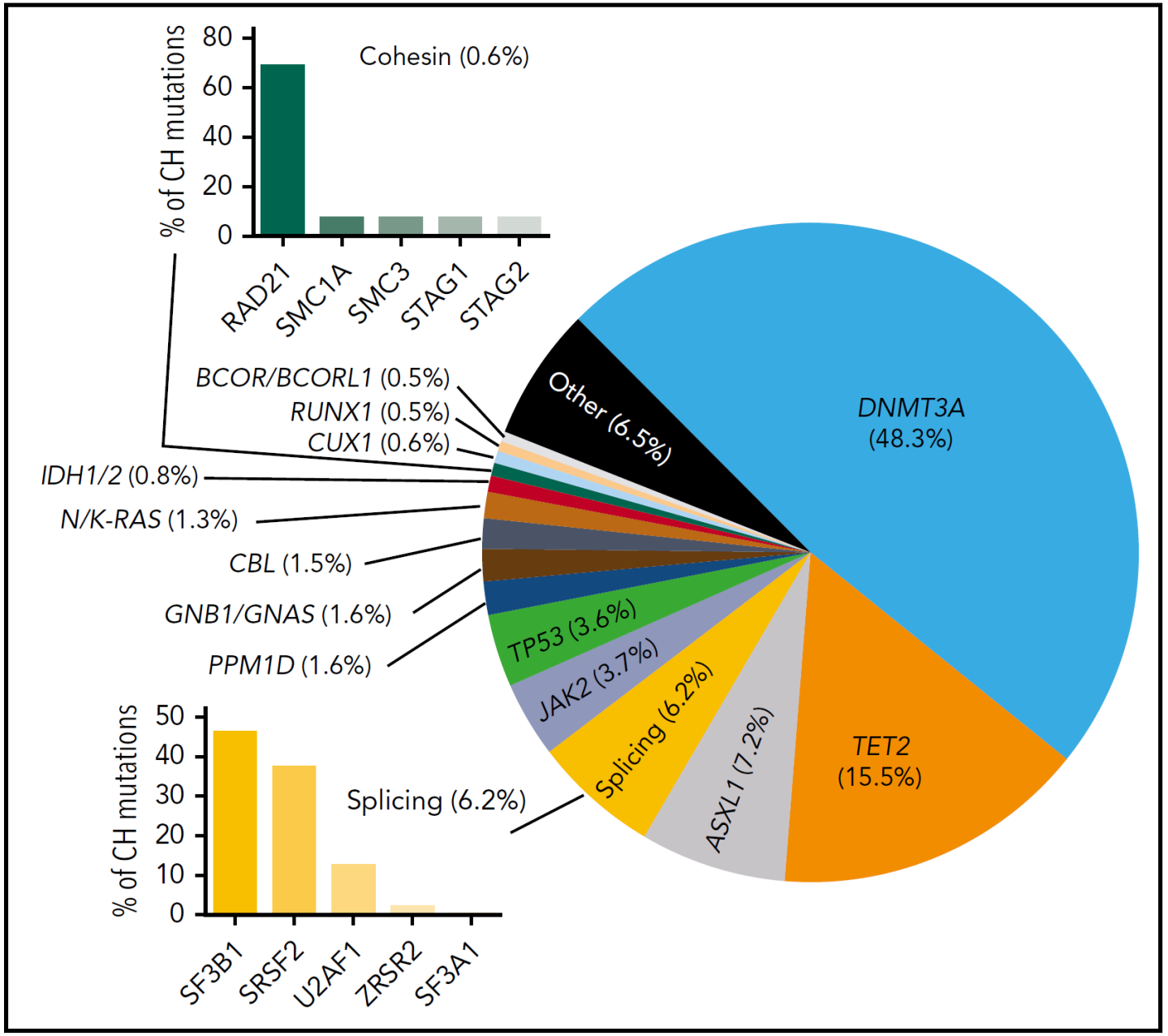
While CH in small variant allele fractions are ubiquitous, the term of CHIP refers to clones present in a substantial number of cells (usually >2% VAF), and repeatedly occur in genes related to epigenetic function, splicing, and DNA damage repair



Bick et al. 2020. *Nature*.

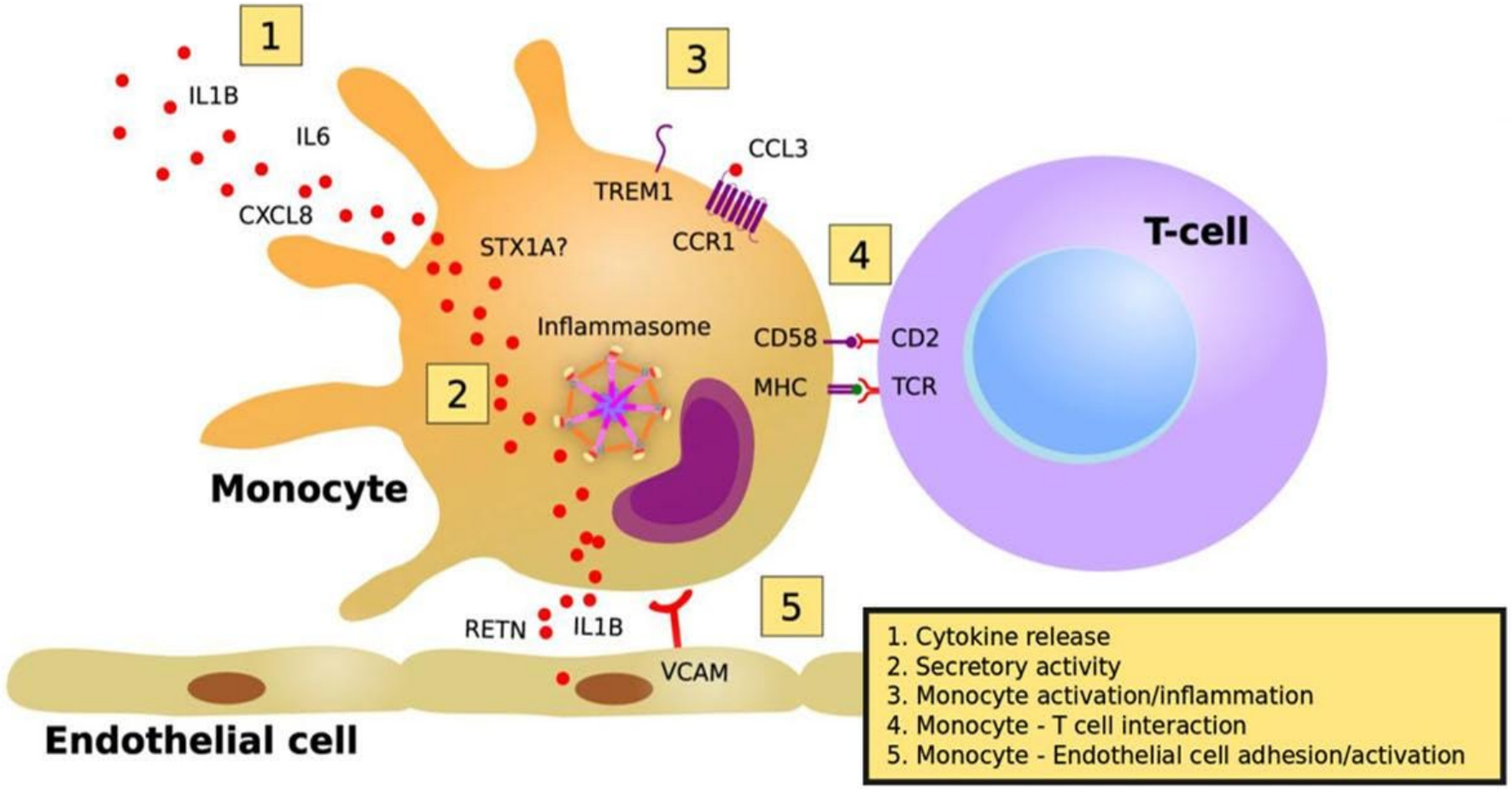
“CHIP Genes” = Commonly mutated Genes in Myeloid Disease

- *Though incidence is different than what is seen in myeloid disease*
- Many of the genes are implicated in one of the following roles:
  1. Epigenetic regulation
  2. Splicing
  3. DNA damage response



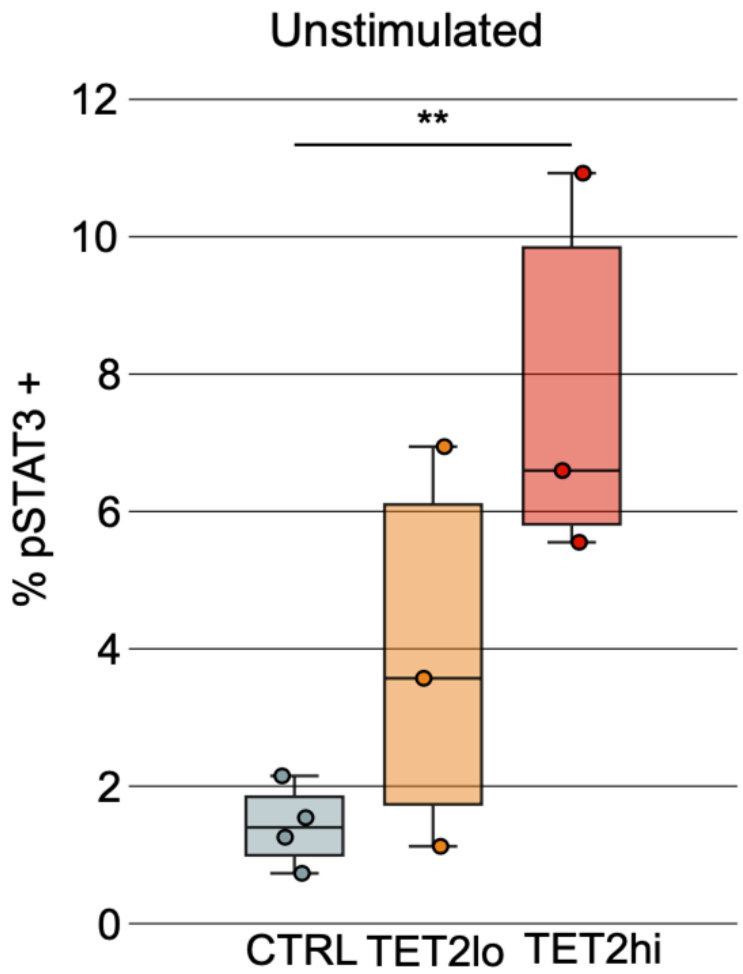
Challen and Goodell. 2020. *Blood*.

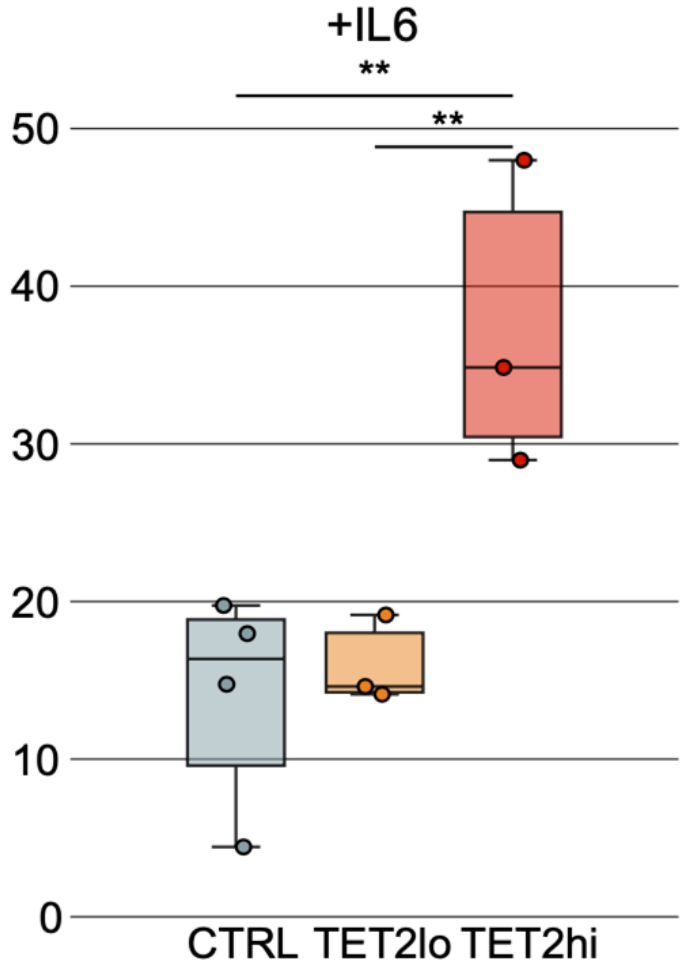
DNMT3A-mutant monocytes display robust inflammatory signatures



Abplanalp et al., Circ. Res., 2021

Mutant TET2 boosts inflammatory signaling in primary monocytes





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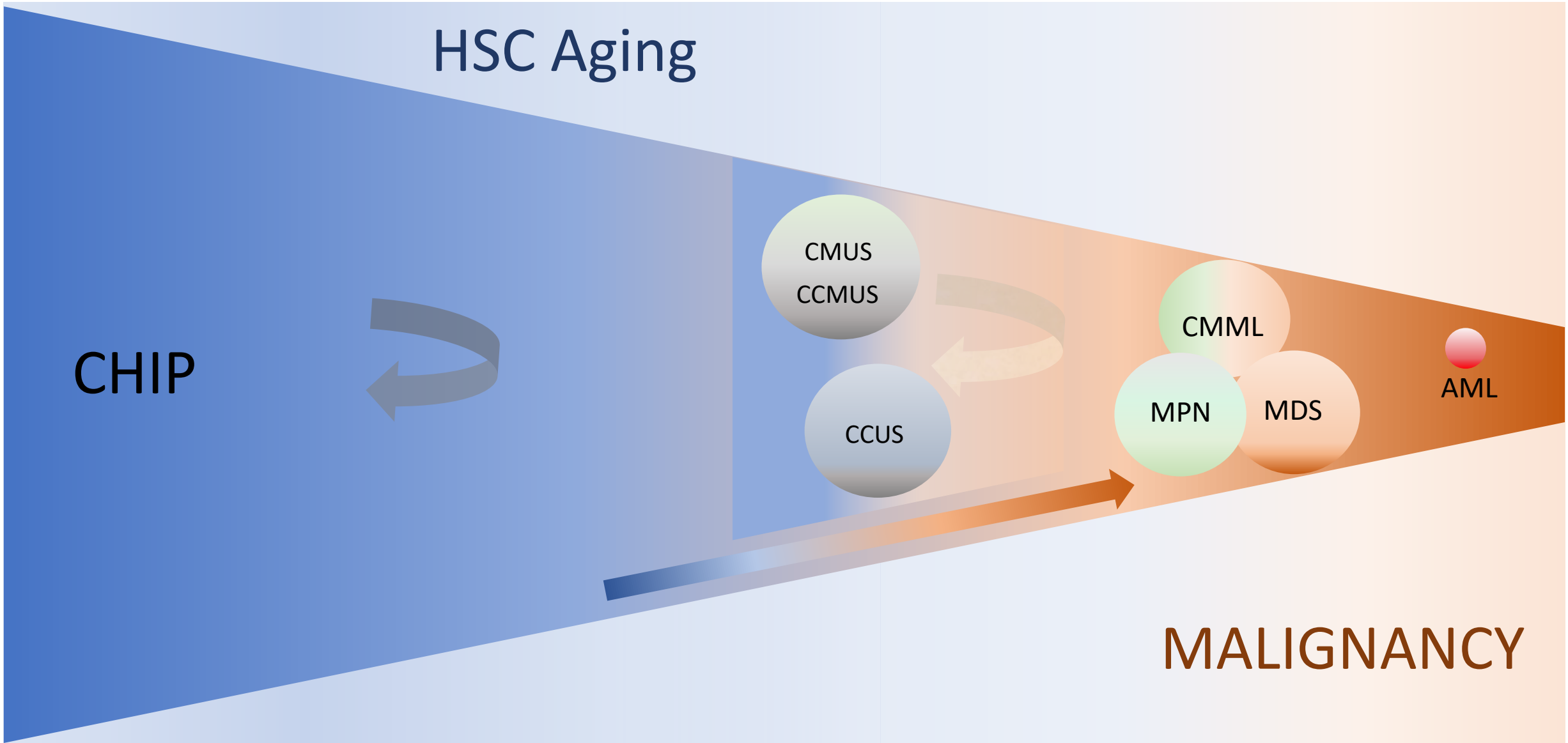
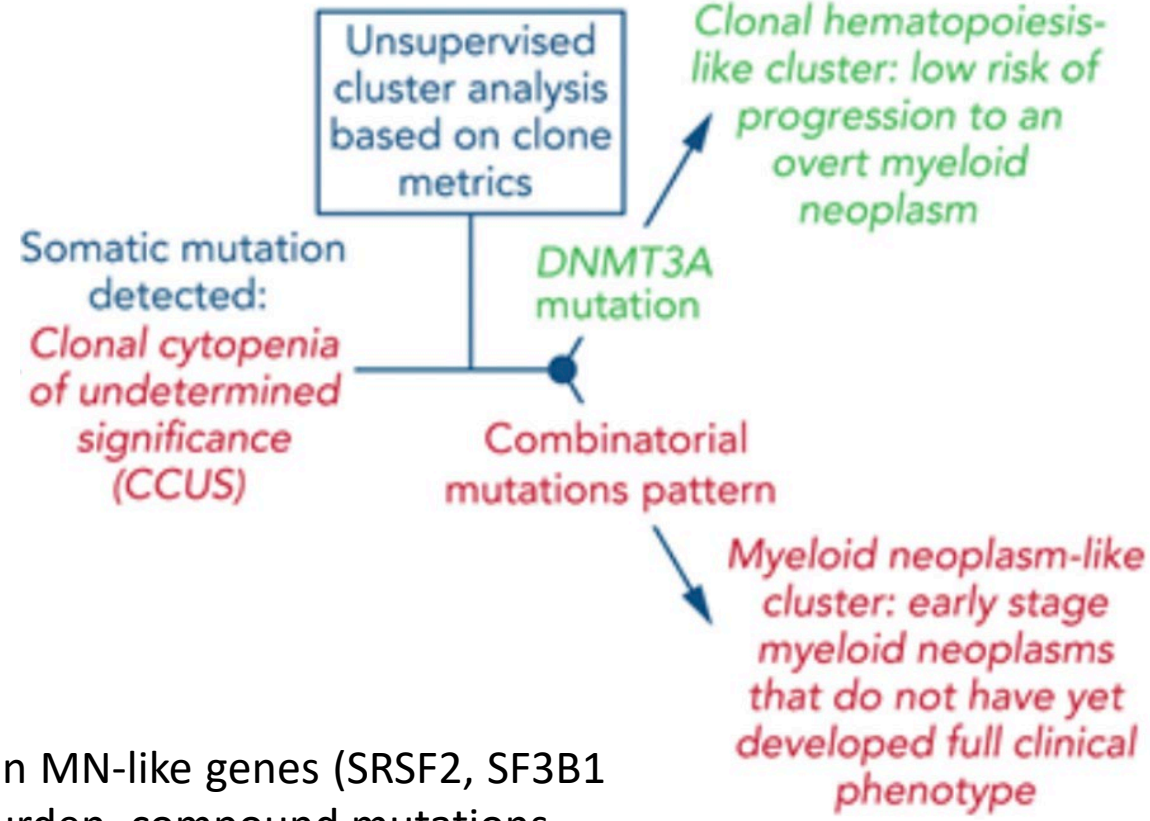
Heimlich et al., bioRxiv, 2022

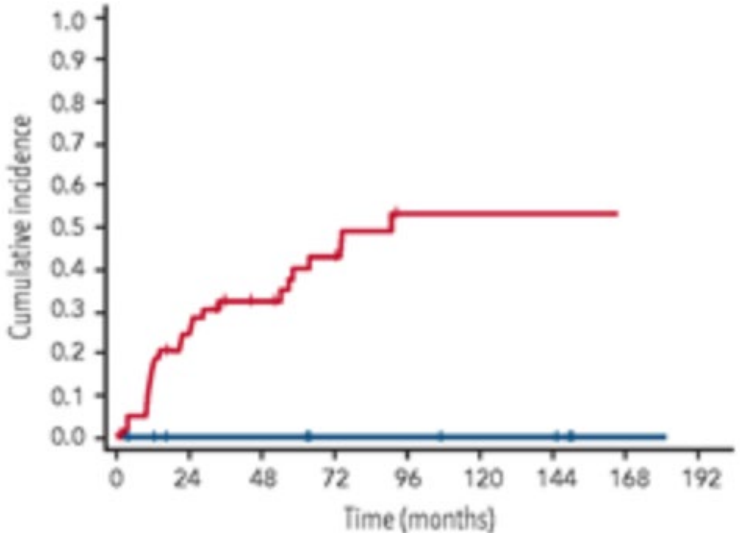
Age associated CH and a model of malignant transformation



Risk of Transforming to MDS is…

1. Specific *Mutation* Dependent





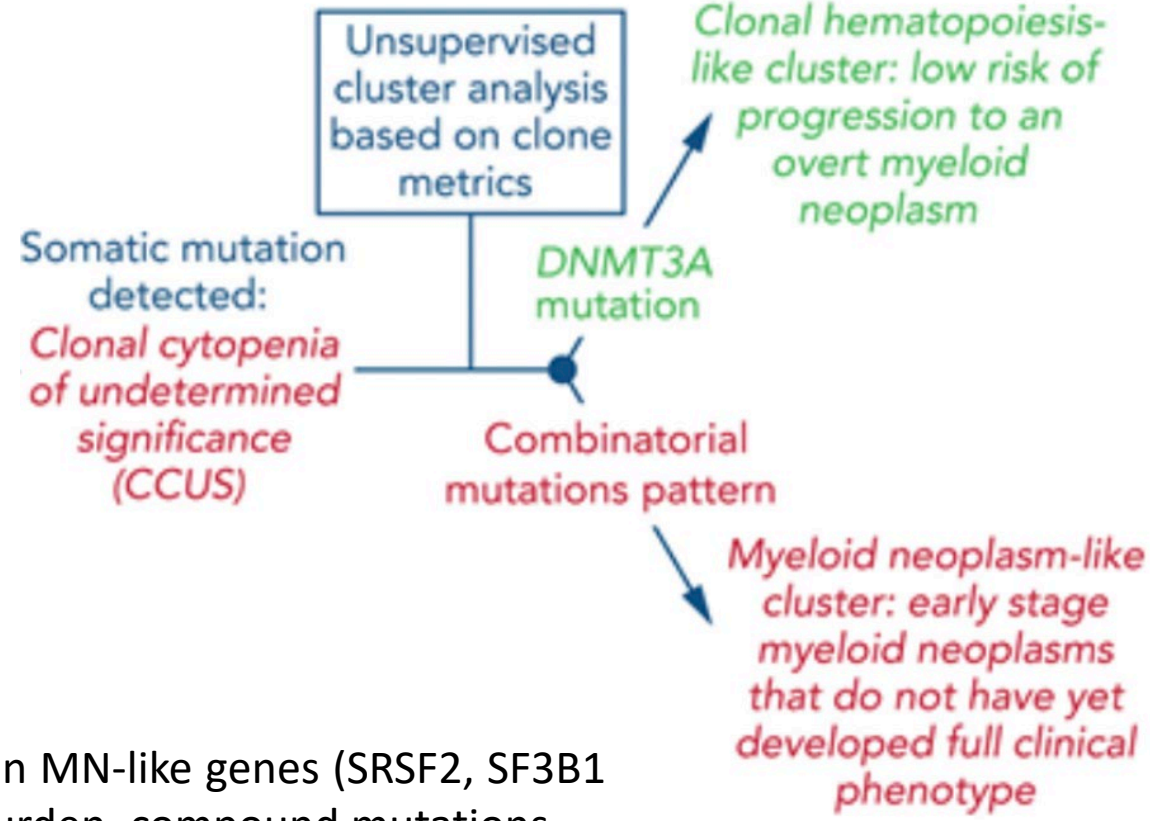
Red – mutations in MN-like genes (SRSF2, SF3B1 etc), high allele burden, compound mutations

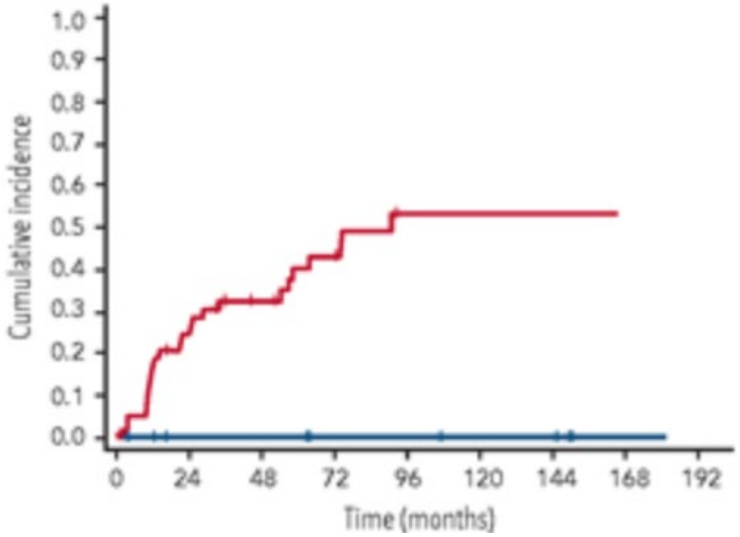
Blue – DTA mutations, lower allele fractions, and single mutations.

Galli et al, Blood, 2021; 138(11),965-976.

Risk of Transforming to MDS is…

2. *VAF* Dependent





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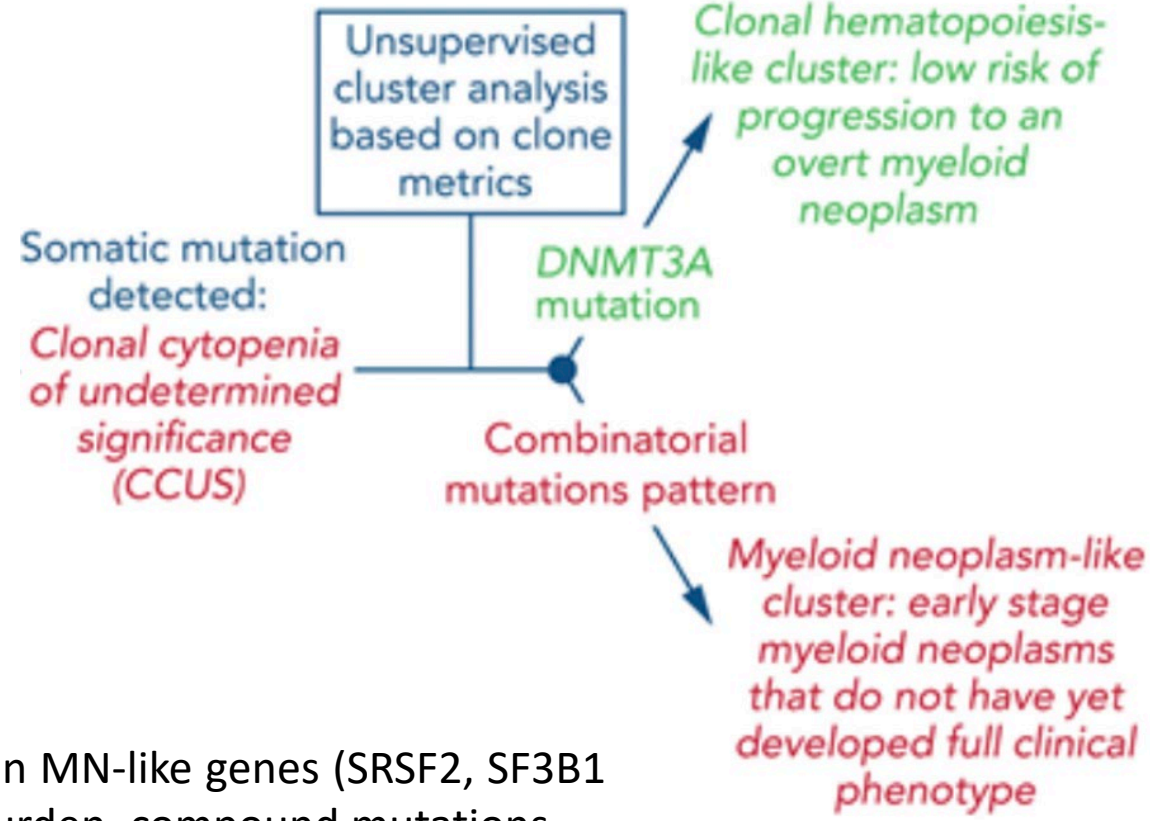
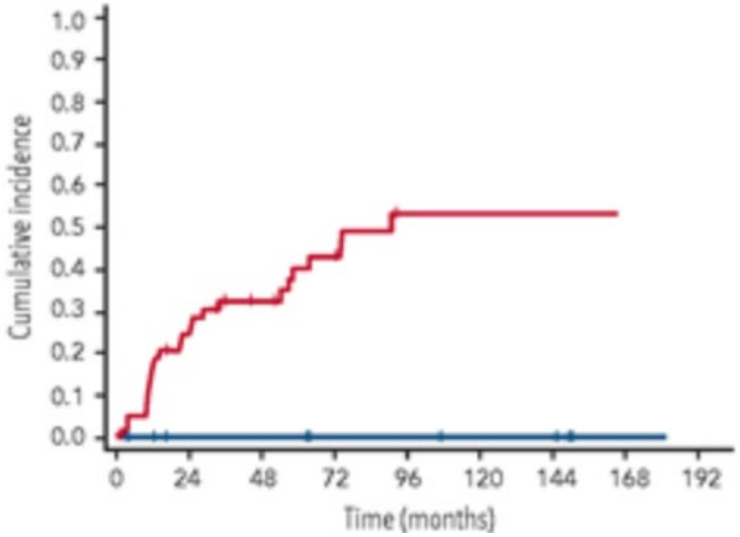
Risk of Transforming to MDS is…

3. Combination/*Signature* Dependent





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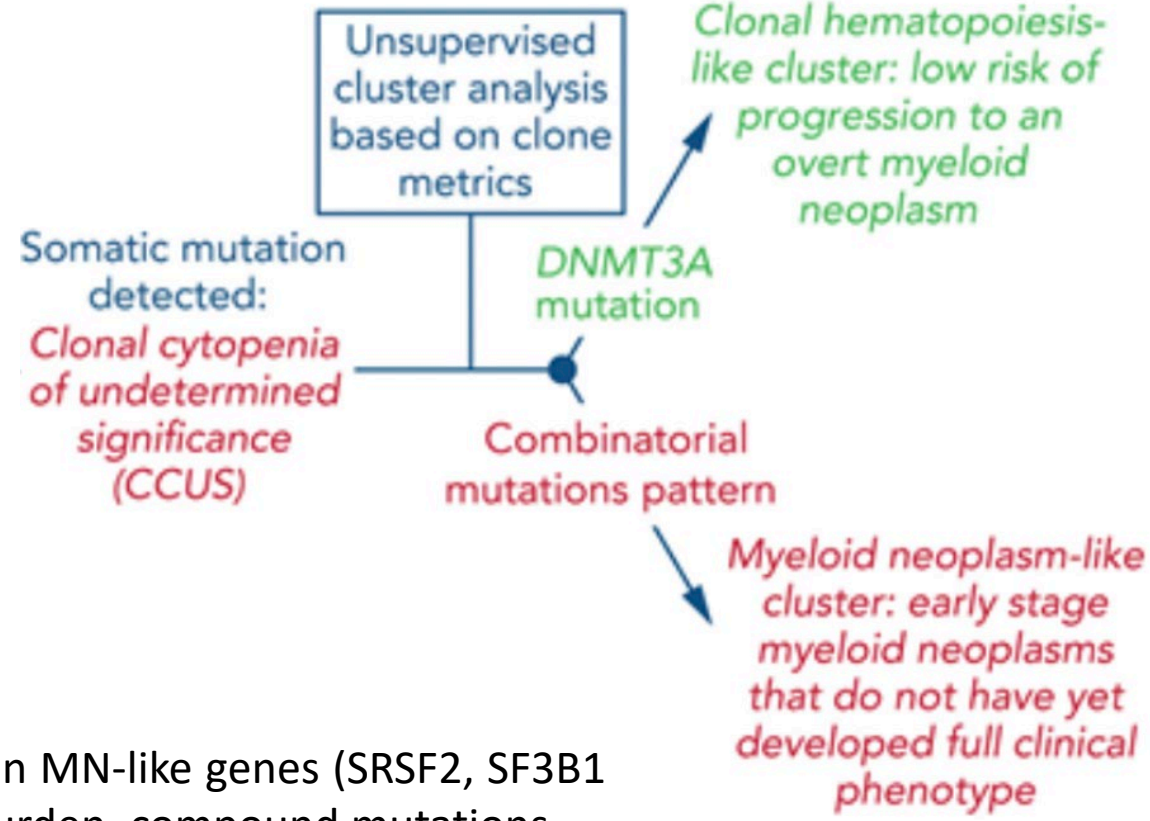
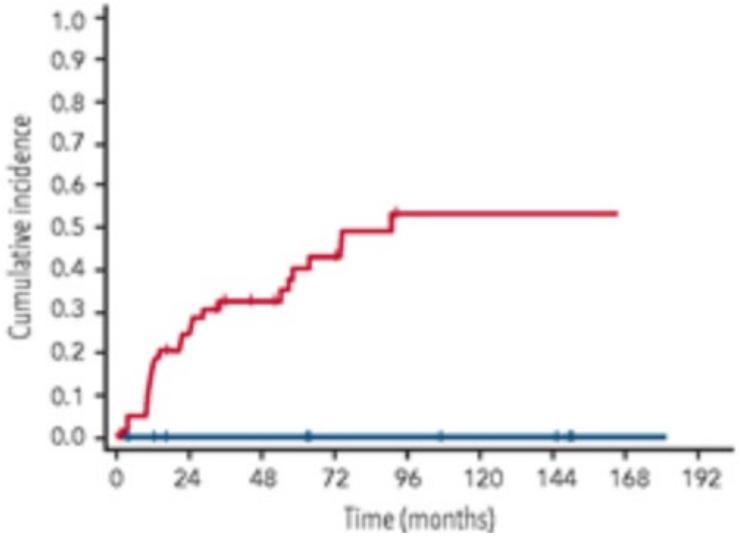
Risk of Transforming to MDS is…

4. **Probably *variant* dependent**





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Risk of Transforming to MDS is…

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815 DNMT3A R882H Exhibits Greater Inflammatory Potential Than R882C in Primary Hematopoietic Stem and Progenitor Cell Knock-in Model and Population Data

Program: Oral and Poster Abstracts
Type: Oral
Session: 503. Clonal Hematopoiesis, Aging and Inflammation: From Omics to Discoveries
Hematology Disease Topics & Pathways:
Research, Translational Research, CHIP, genomics, hematopoiesis, Biological Processes, Technology and Procedures, gene editing, Study Population, Human, omics technologies

Monday, December 11, 2023: 3:45 PM

Alexander Silver
MSTP Student
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NEJM Evidence

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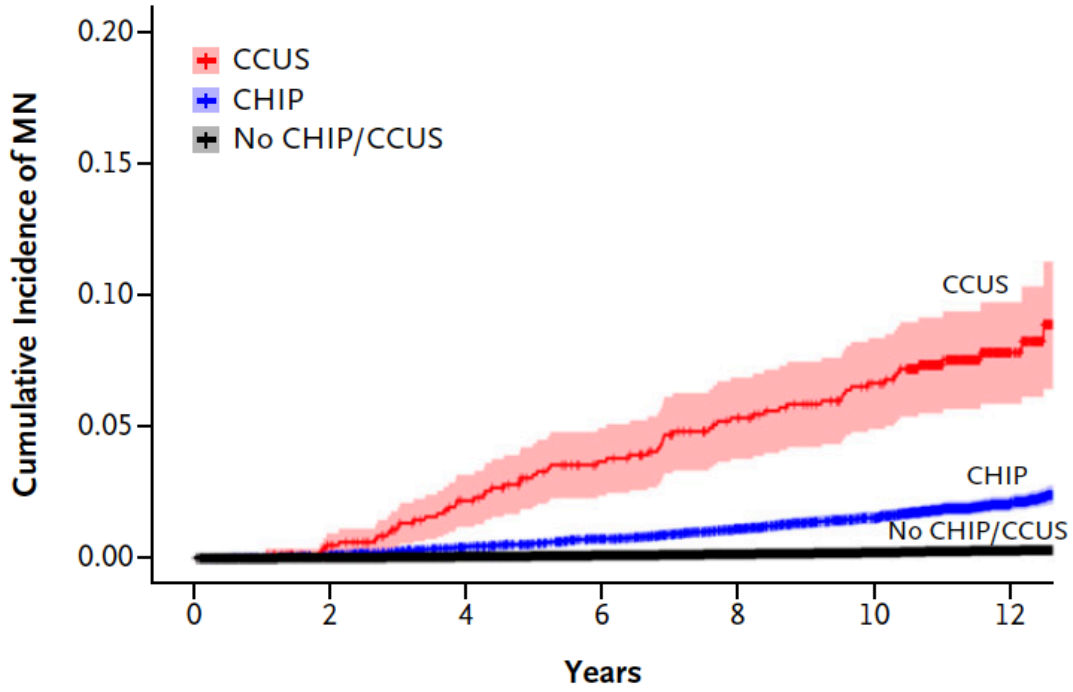
ORIGINAL ARTICLE

Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis

Lachelle D. Weeks, M.D., Ph.D.,[1,2,3] Abhishek Niroula, Ph.D.,[4,5] Donna Neuberg, Sc.D.,[6] Waihay Wong, M.D., Ph.D.,[7] R. Coleman Lindsley, M.D., Ph.D.,[1,2] Marlise R. Luskin, M.D., M.S.C.E.,[1,2] Nancy Berliner, M.D.,[2,8] Richard M. Stone, M.D.,[1,2] Daniel J. DeAngelo, M.D., Ph.D.,[1,2] Robert J. Soiffer, M.D.,[1,2,3] Md Mesbah Uddin, M.Sc., Ph.D.,[9,10] Gabriel Griffin, M.D.,[6,7] Caitlyn Vlasschaert, M.D., M.Sc.,[11] Christopher J. Gibson, M.D.,[1,2] Siddhartha Jaiswal, M.D., Ph.D.,[12] Alexander G. Bick, M.D., Ph.D.,[13] Luca Malcovati, M.D.,[14,15] Pradeep Natarajan, M.D., M.M.S.C.,[2,9,10] and Benjamin L. Ebert, M.D., Ph.D.[1,2,3,4,16]

CHRS edifies earlier conclusions on CCUS

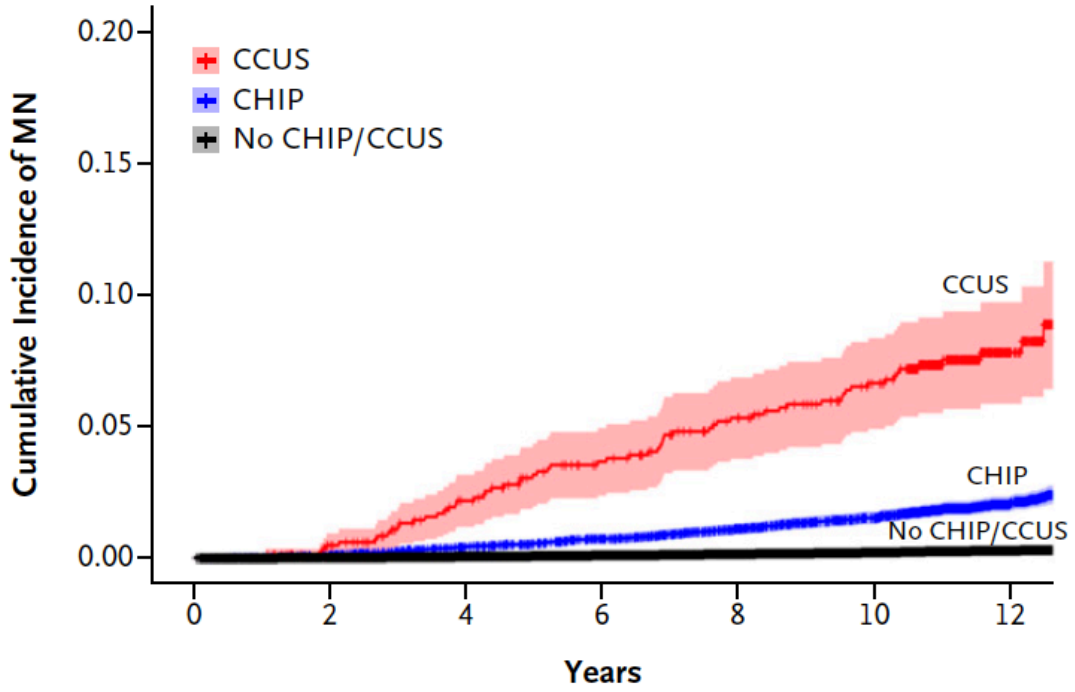


Number at Risk

Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254

Weeks et al. NEJM Evid. 2023

Objective hematologic parameter and mutational testing informs model



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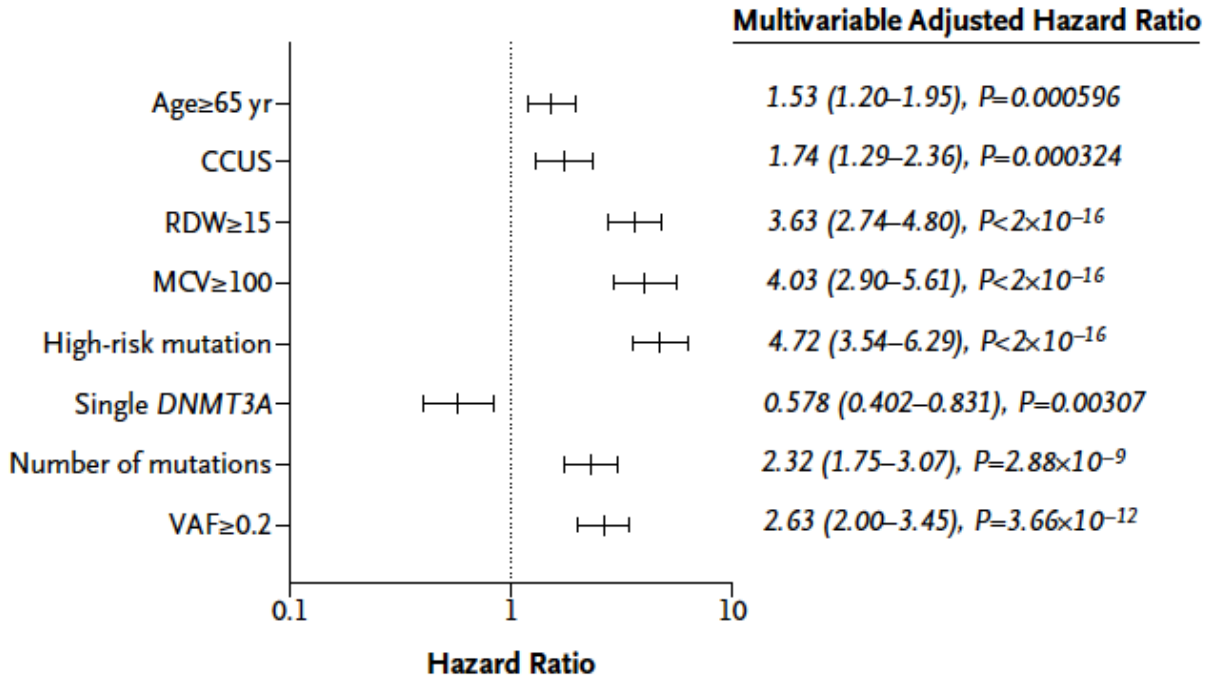
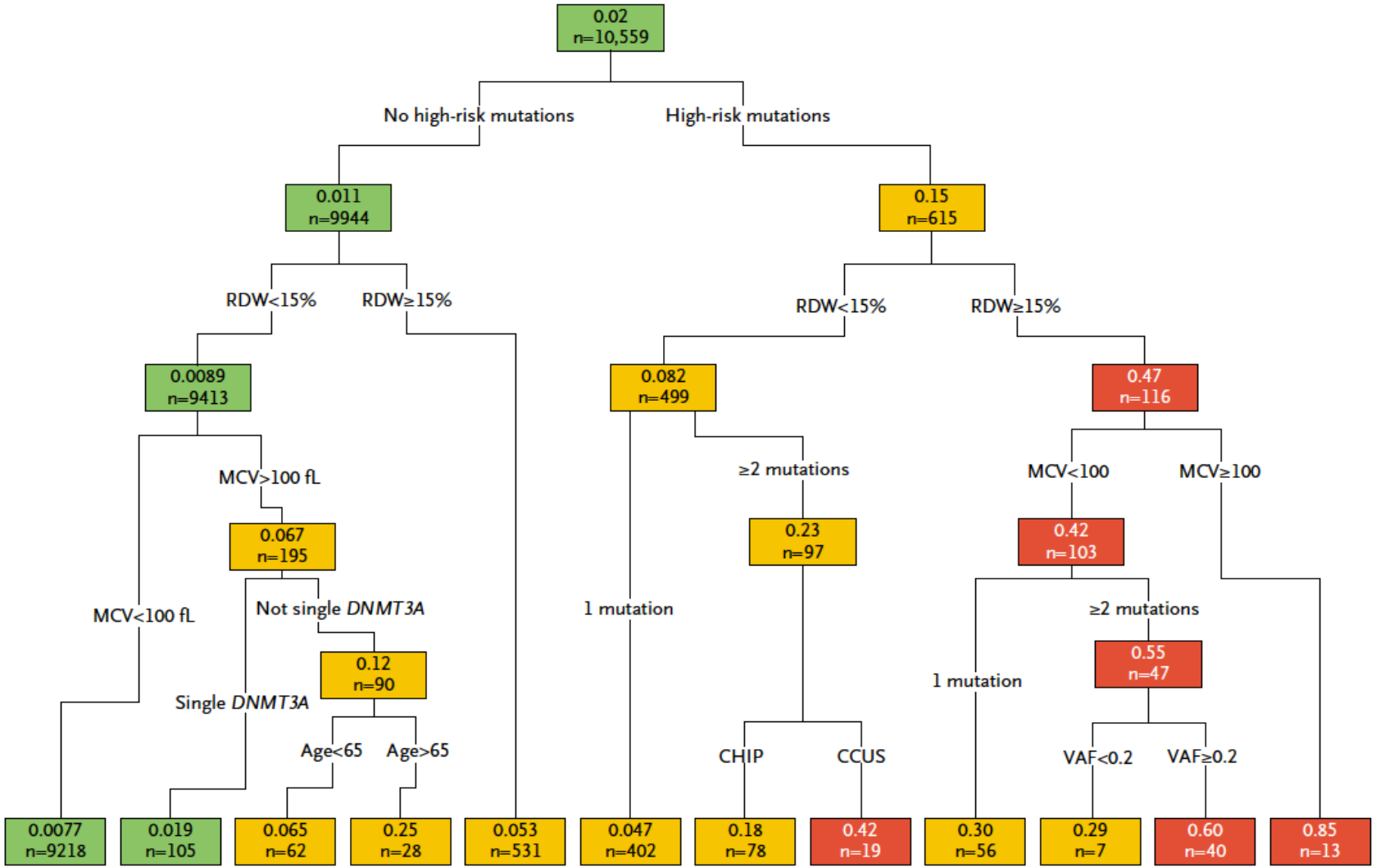


Weeks et al. NEJM Evid. 2023

Recurvise partitioning based on incidence of MN



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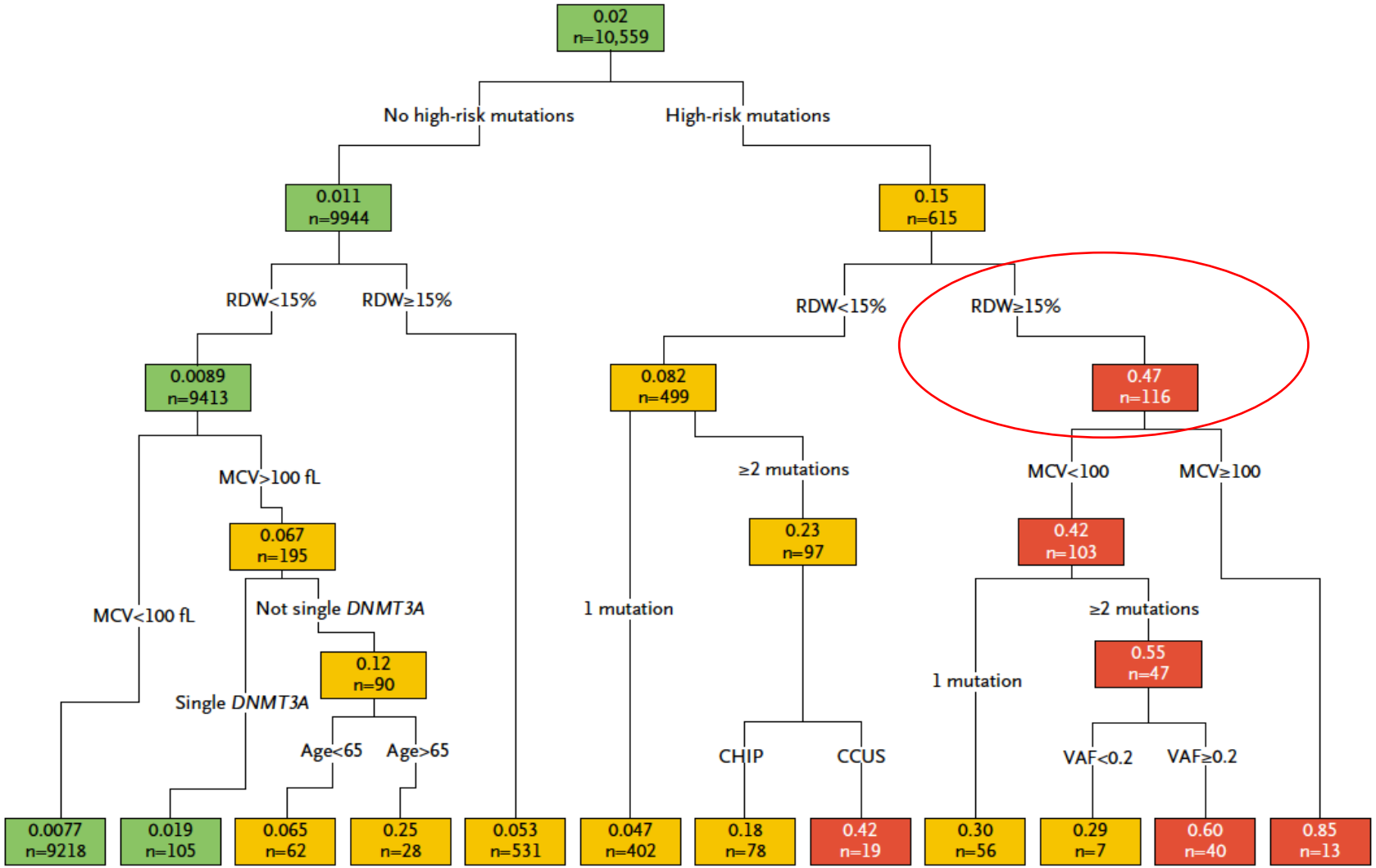
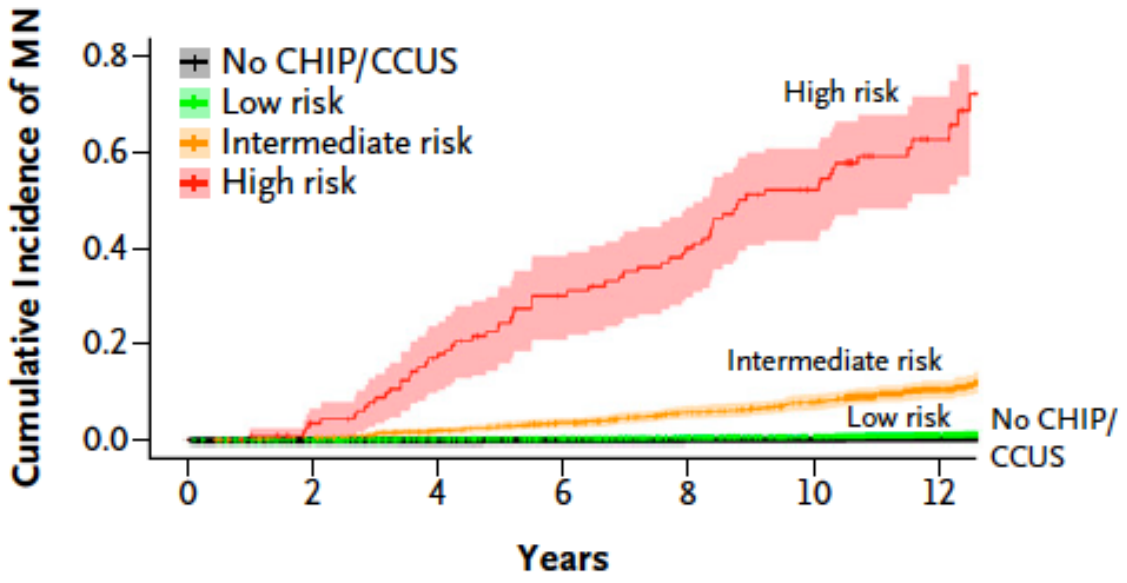


Weeks et al. NEJM Evid. 2023

Model partitions well by CHRS risk of transformation



Number at Risk

Time (yr)	0	2	4	6	8	10	12
High risk	123	109	90	72	60	43	15
Int. risk	1,196	1,174	1,125	1,080	1,016	961	336
Low risk	10,018	9,958	9,821	9,699	9,540	9,348	3,772
No CHIP/CCUS	182,406	181,674	180,407	178,734	176,174	174,455	72,254

www.chrsapp.com

Weeks et al. NEJM Evid. 2023

Clonal Hematopoiesis and Inflammation in the VasculaturE (CHIVE)

Cooperative Biorepository and Registry for CH

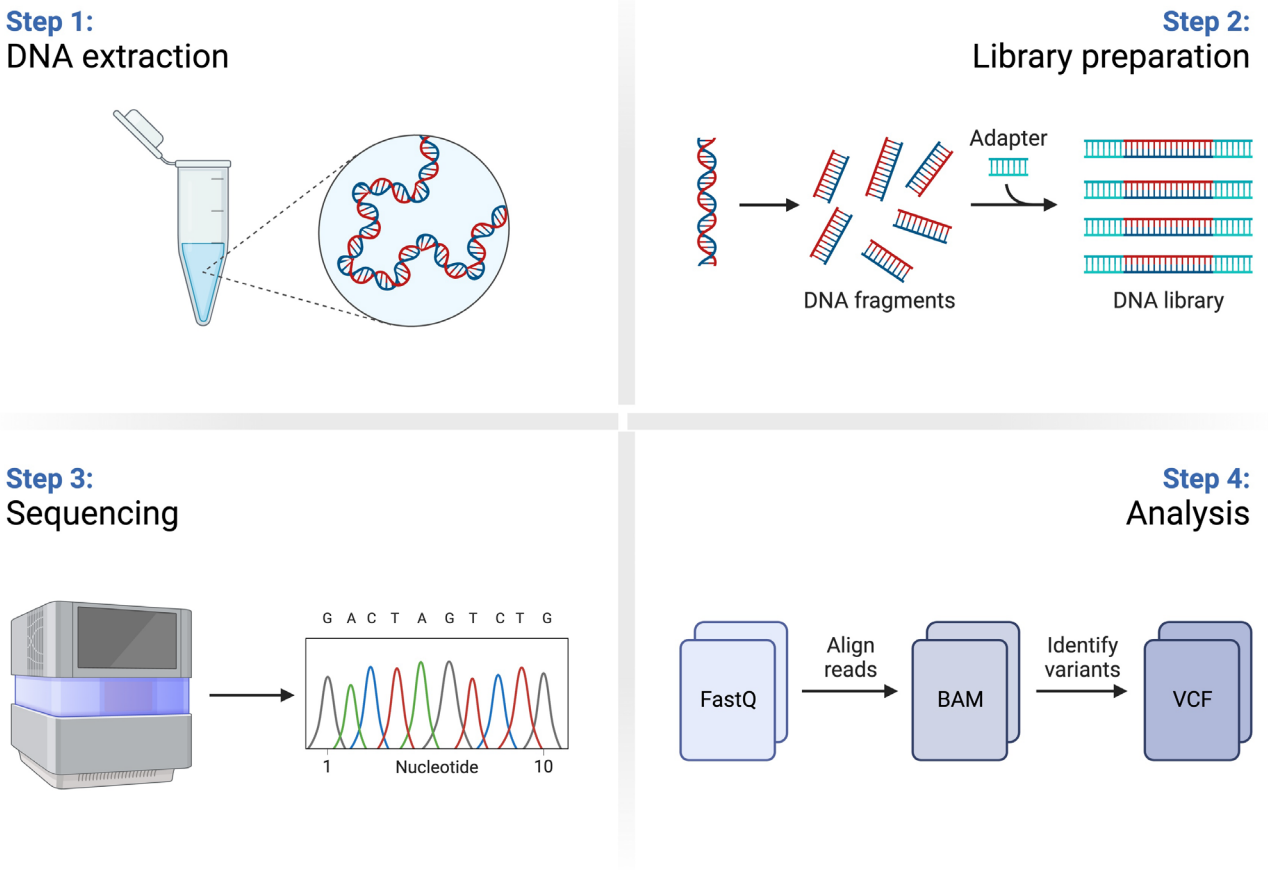
09 Dec 2023
MDS Foundation Breakfast Symposium - Annual American Society of Hematology Meeting, San Diego, CA

What is *CHIVE*?

- Registry following the natural history of CH
  - CH and *at risk* for CH
  - dB with clinical features captured
- Biorepository for storing samples for patients at risk/with CH
  - *Sequential* sample collection of peripheral blood, bone marrow (when available)
  - IRB approval for a variety of cellular assays and genotyping to further understand the pathophysiology of CH

*CHIVE*seq: Twist CH Assay

- This assay uses Twist bioscience hybrid capture technology to sequence coding sequences of **24 CHIP genes** (or portions of genes) known to cause CHIP at >500x depth.
- The genes include: ASXL1, ASXL2, BRCC3, CBL, DNMT3A, ETNK1, GNAS, GNB1, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NRAS, PPM1D, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, ZBTB33, ZNF318.
- The assay can be run for **as low as** 1/10th cost of commercial sequencing panels



CHIVE

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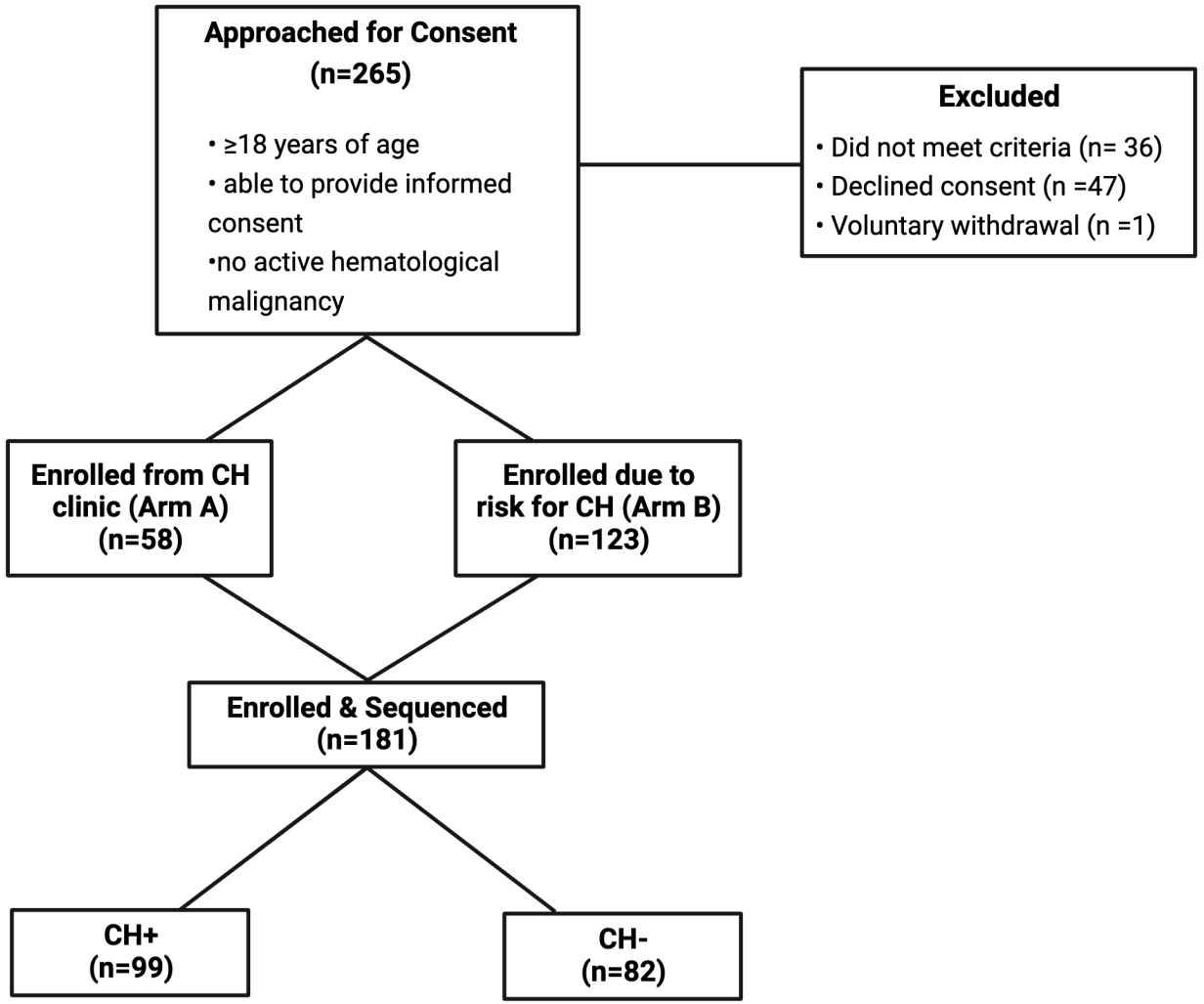
CHIVE (ver1.0) Schema



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	CH - (n=82)	CH + (n=99)	p value
Sex			
Male	24 (29.3)	50 (50.5)	**0.009**
Female	58 (70.7)	49 (49.5)	
Age			
18-29	3 (3.7)	0 (0.0)	
30-49	14 (17.1)	1 (1.0)	
50-64	27 (32.9)	24 (24.8)	
65+	38 (46.3)	73 (74.2)	
Median +/- IQR	62.9 (51.5 - 72.7)	71.9 (64.0 - 77.5)	**<0.001**
Body Mass Index (BMI)			
<18.5	3 (3.7)	1 (1.0)	
18.5 - 24.9	23 (28.0)	22 (22.7)	
25.0 - 29.9	28 (34.2)	34 (35.1)	
30.0 - 34.9	17 (20.7)	23 (23.7)	
>35	11 (13.4)	17 (17.5)	
Median +/- IQR	27.4 (24.1 - 32.4)	28.9 (25.4 - 32.1)	0.253

Background Demographics

- More male
- Older
- Trend to higher BMI

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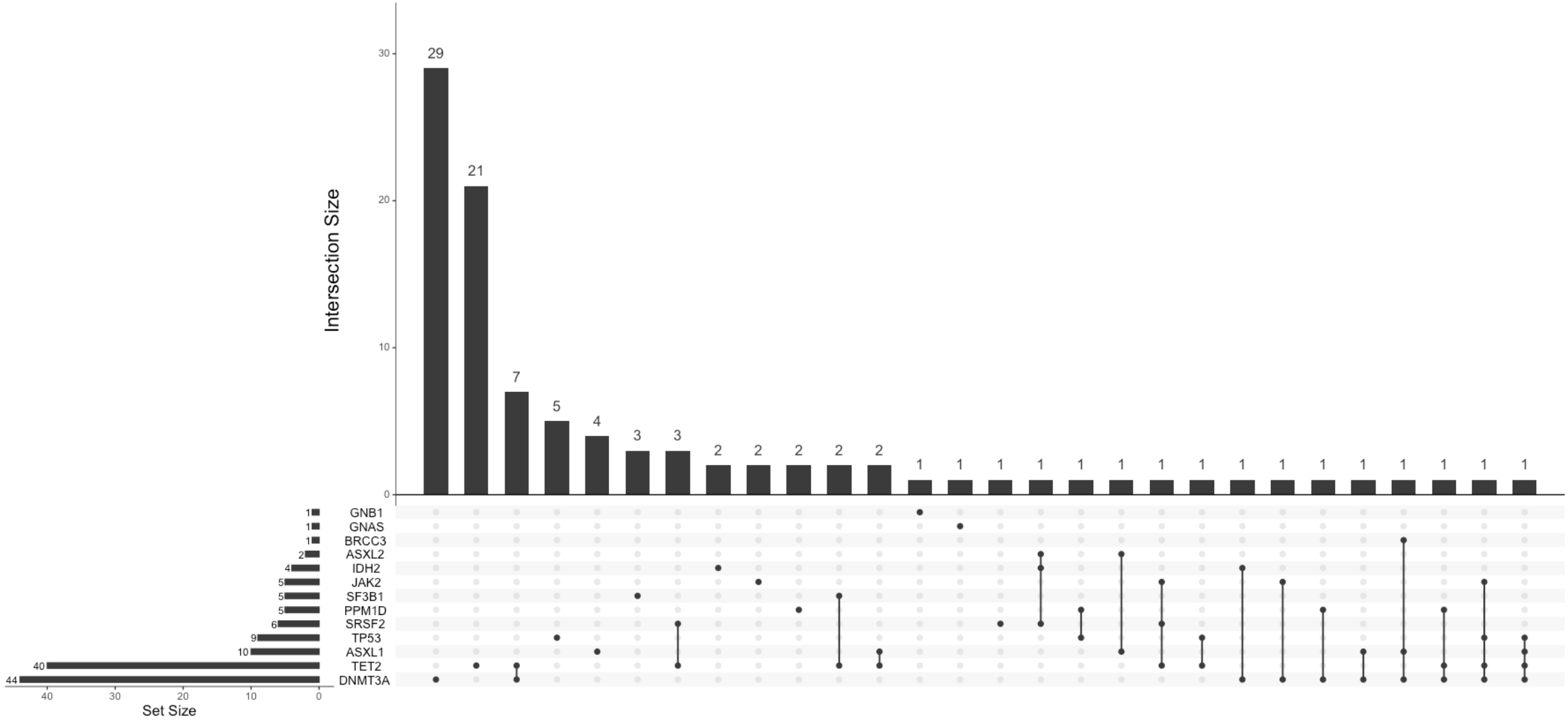
CHIVE – Gene Variant Frequencies similar to retrospective analyses



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CHIVE – Clinical features among CH^+ and CH^- patients

	CH -	CH +	Unit	p value
Blood Counts				
White Blood Cells	6.8 (5.2 - 8.4)	6.2 (4.5 - 8.1)	$x10^3$/mcL	0.455
Hemoglobin	13.3 (12.3 - 14.6)	12.9 (11.4 - 14.1)	gm/dL	0.136
Hematocrit	42.0 (37.0 - 44.0)	39.0 (35.0 - 43.0)	%	0.134
Platelet	245.0 (198.0 - 284.0)	203.0 (163.0 - 262.0)	$x10^3$/mcL	0.093
Kidney Function				
BUN	16.0 (12.0 - 21.0)	18.0 (14.0 - 23.0)	mg/dL	0.168
Creatinine	0.90 (0.76 - 1.11)	0.97 (0.84 - 1.29)	mg/dL	**0.015**
CKD Diagnosis, n(%)	15 (18.3)	41 (41.2)		**0.002**
Blood Glucose				
Glucose	97.0 (88.0 - 117.0)	106.0 (91.0 - 121.0)	mg/dL	0.210
HbA1c	6.0 (5.4 - 6.8)	5.8 (5.3 - 6.4)	%	0.450
Diabetes Mellitus Diagnosis, n(%)	22 (26.8)	32 (30.9)		0.522
Inflammatory Markers				
ESR	16.0 (6.0 - 33.0)	20.0 (15.0 - 32.0)	mm/hr	0.670
CRP	3.2 (1.2 - 13.1)	8.2 (2.3 - 37.3)	mg/L	0.183

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CHIVE – Clinical features among CH^+ and CH^- patients indicate increased risk of vascular disease

	CH -	CH +	Unit	p value
Cardiovascular Measurements				
Systolic Blood Pressure	125 (117 - 134)	129 (118 - 139)	mmHg	0.249
Diastolic Blood Pressure	75 (68 - 82)	72 (66 - 78)	mmHg	0.177
Coronary Artery Disease Diagnosis, n(%)	27 (32.9)	55 (55.7)		**0.004**
Hypertension Diagnosis, n(%)	43 (52.4)	77 (79.4)		**<0.001**
Clinical Heart Failure Diagnosis, n(%)	8 (9.8)	24 (22.7)		**0.035**
Brain Natriuretic Peptide	79 (47 - 110)	56 (34 - 184)	pg/mL	0.908
Ejection Fraction	60 (55 - 63)	61 (54 - 68)	%	0.424

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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		
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

High Risk Variants and progression to MDS/AML in *CHIVE* –

Validation of ‘Big Data’ restrospective reports with new prospective analysis

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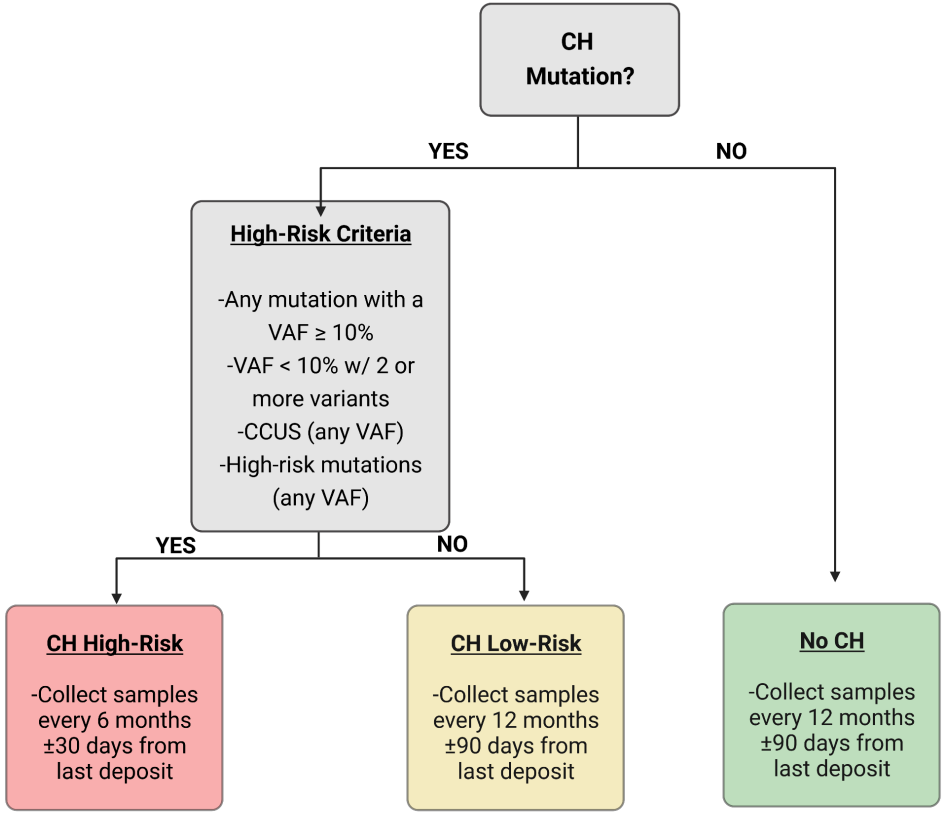
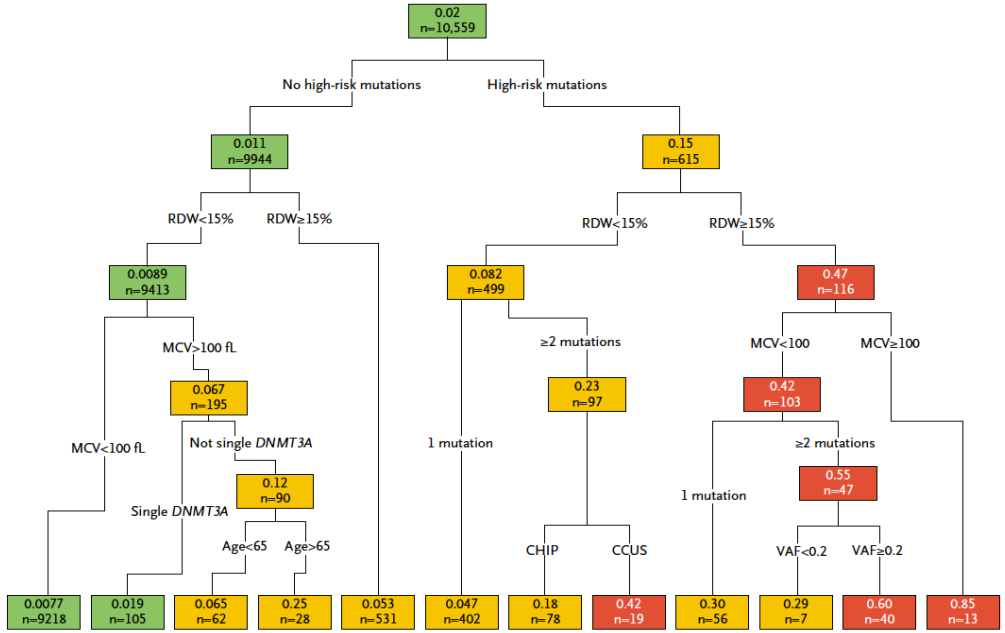
CHIVE Rubric for testing





Weeks et al. *NEJM Evid*. 2023
Shannon M, Heimlich B, et al. *Under Revision*.

Summary and next steps

- Clonal hematopoiesis (CH) is an age-associated phenomenon and one of the most impactful conceptual discoveries across disciplines in medicine – we need to understand how to risk assess CHIP.
- Early prospective analysis (200 patients) illustrates similar patterns seen in retrospective data and in CHRS analysis
- Large prospective international, multicenter participation is needed to properly understand risk

3rd Annual Meeting of Somatic Mutations and Predisease
Addressing high risk clones

Nashville: October 25-26, 2024