ICUS, CCUS AND CHIP

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Schulich
MEDICINE & DENTISTRY

Windsor
Cancer
Research
Group

What causes anemia in people aged ≥65 years?

Nutritional deficiency: *34.3%*

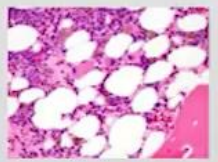


Iron only 16.6%,
Folate only 6.4%,
B_{12} only 5.9%,
Combined 5.4%

Endocrine renal insufficiency / anemia of chronic inflammation (ACI): *32.2%*


Renal anemia only 8.2%,
ACI only 19.7%,
Combined 4.3%

Unexplained anemia (UA): *33.6%*




Additional cytopenias or macrocytosis: 17% of UA

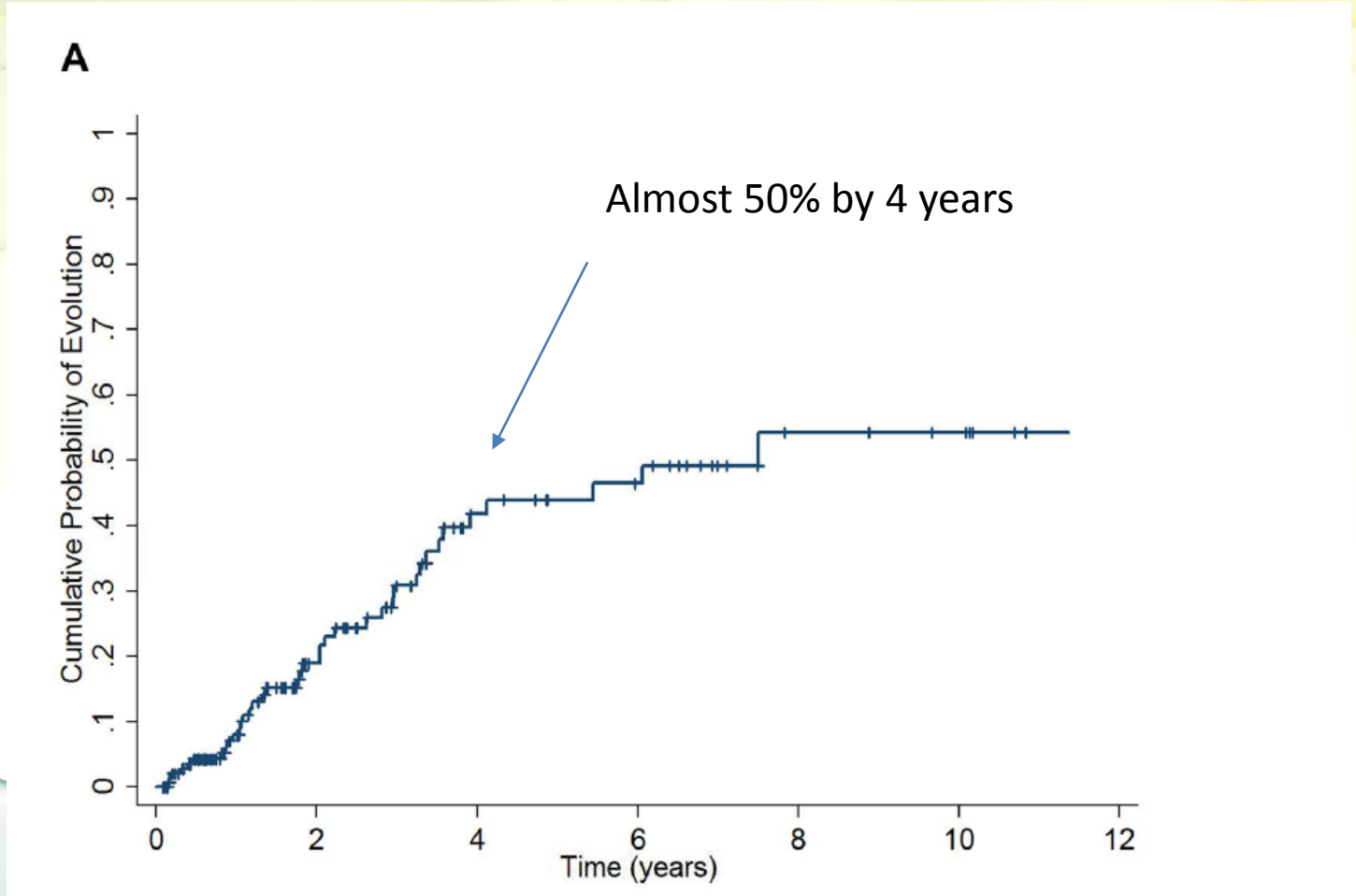
Theories:
Undiagnosed MDS
Immune-mediated cytopenia
Occult inflammation
Androgen depletion
Stem cell burnout/dropout

NHANES III data; Guralnik JM et al *Blood* 2004 104:2263-2268

Unexplained Cytopenias

- Prevalence of anemia rises sharply after age 50
  - 20% by age 85
  - **1/3 are never explained**
  - ? Myelodysplastic syndrome (MDS) – may be underdiagnosed

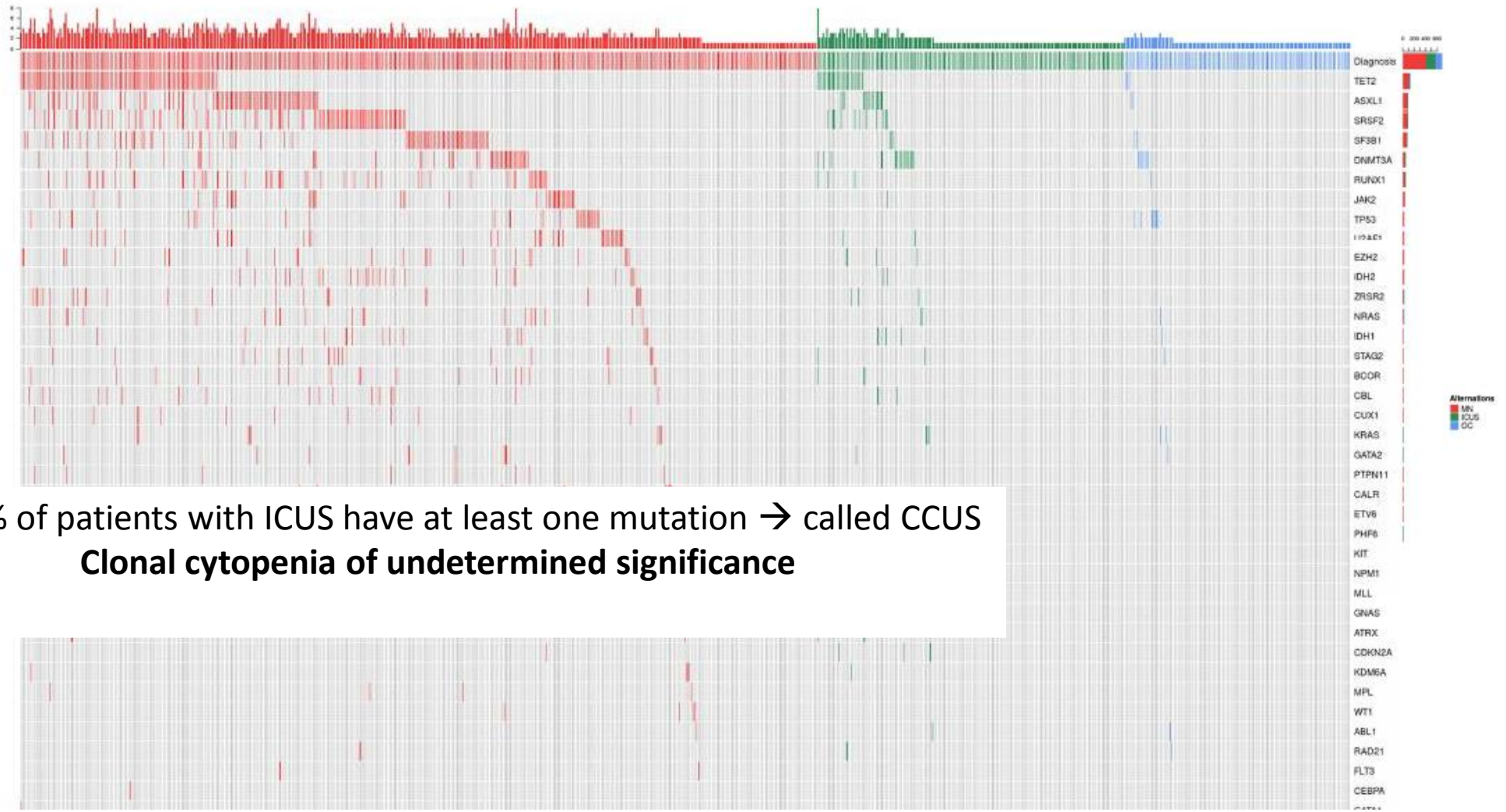
- ICUS was coined in 2007:
  - Idiopathic cytopenia of undetermined significance
  - Defined: cytopenias that don’t fit into MDS
  - No clone identified at that time



Overall likelihood of developing a myeloid neoplasm with the diagnosis of ICUS

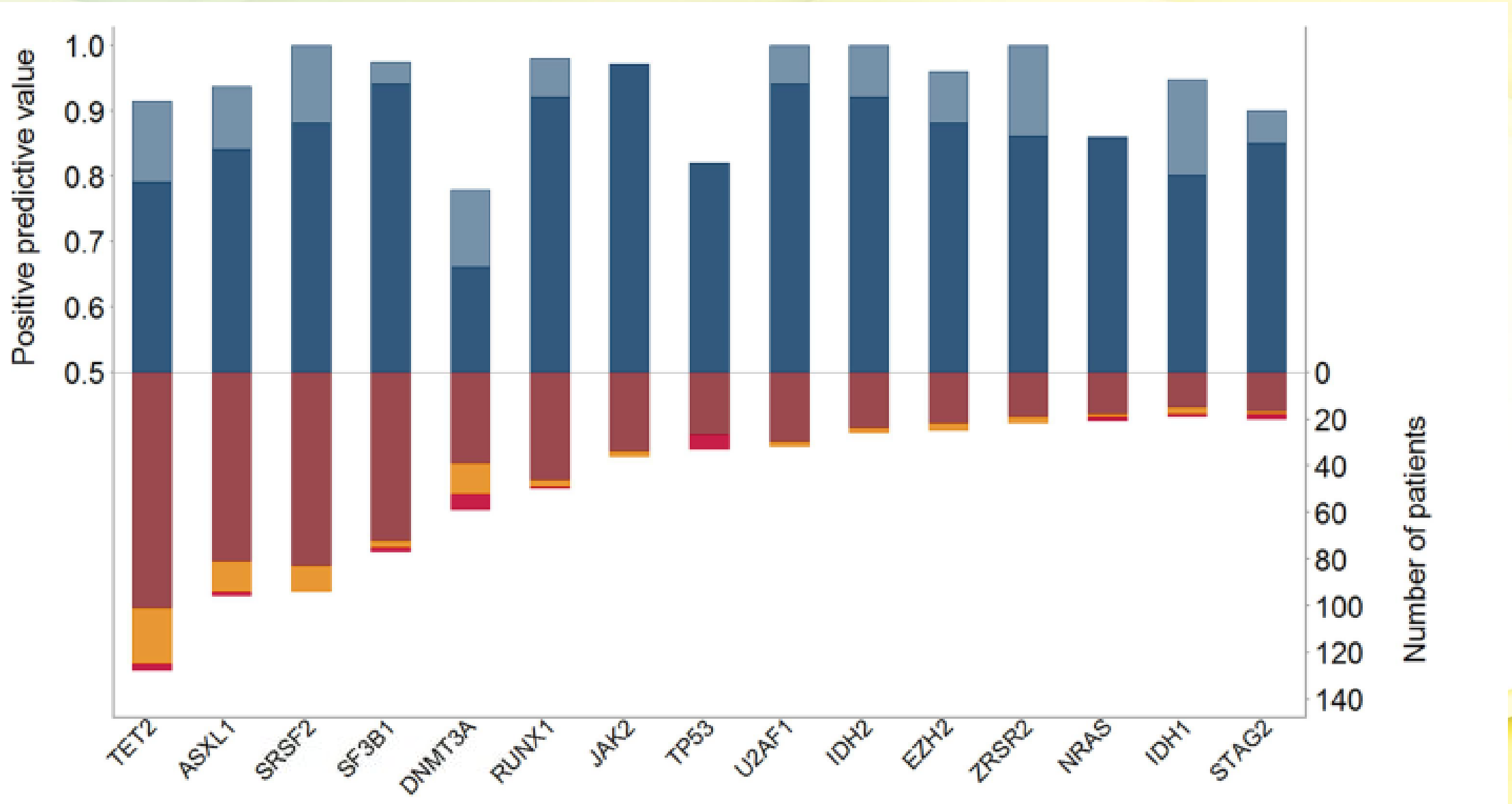
Malcovati et al Blood 2017

Molecular Profiling / Next Generation Sequencing by Peripheral Blood



36% of patients with ICUS have at least one mutation → called CCUS

Clonal cytopenia of undetermined significance



Positive Predictive Value of the most common mutations and frequency

AN EXTREME EXAMPLE OF SOMATIC MUTATIONS IN AN OLDER PERSON

Not all mutations are the same

Key findings:

-450 somatic mutations accumulated in the nonrepetitive genome within the healthy blood compartment (normal CBC/RDW/karyotype)

-Two dominant hematopoietic clones

-Extremely short leukocyte telomeres

-Died of metastatic gastric cancer

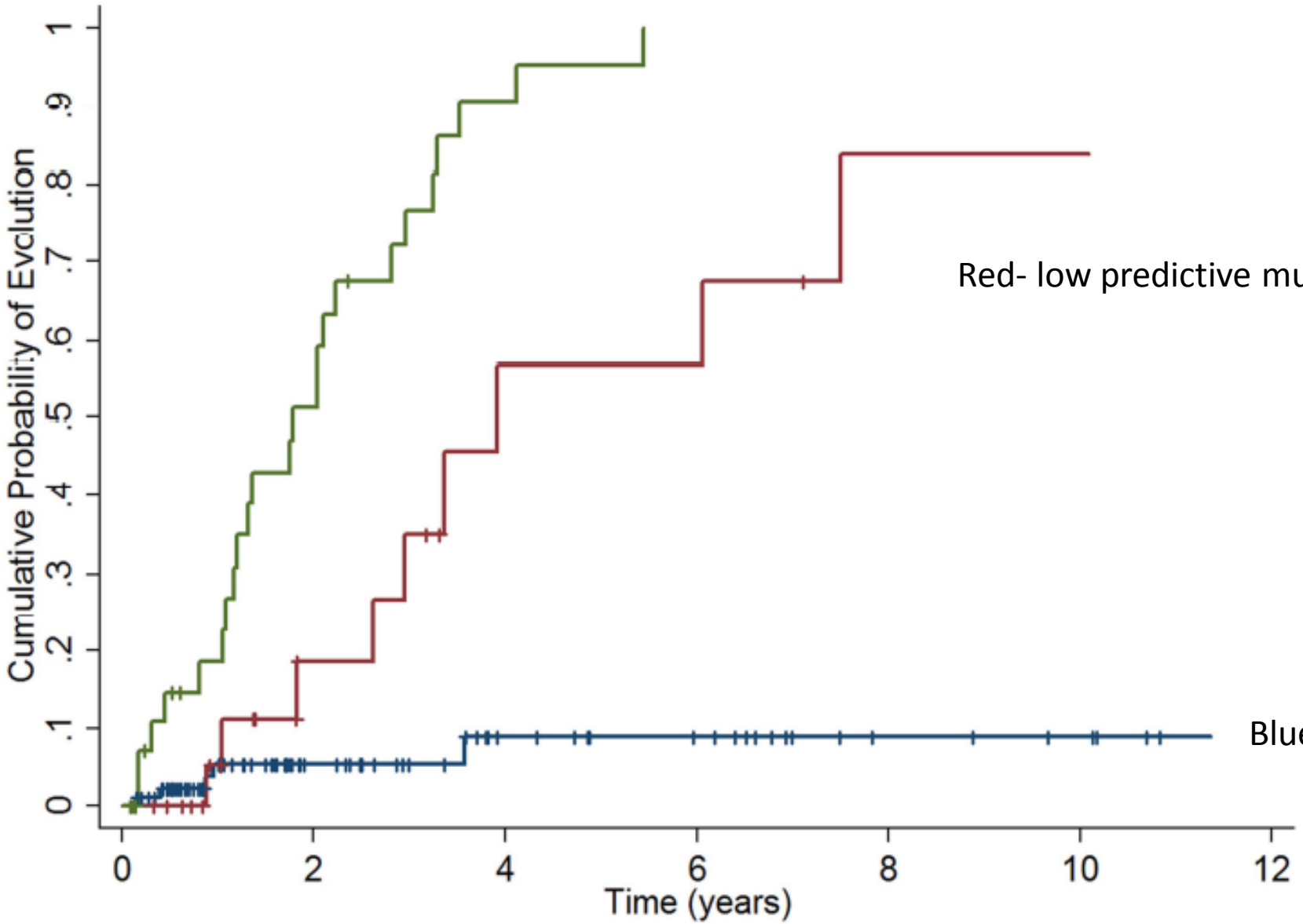
-No vascular or dementia related pathology

Hendrikje van Andel-Schipper (1890-2005)

Henne Holstege et al *Genome Res. 2014. 24: 733-742*

D

Green – have <u>mutations highly predictive of myeloid neoplasms</u>



Red- low predictive mutation pattern

Blue - No mutations

Malcovati Blood 2017

Are these tests available?

London Health Sciences Centre

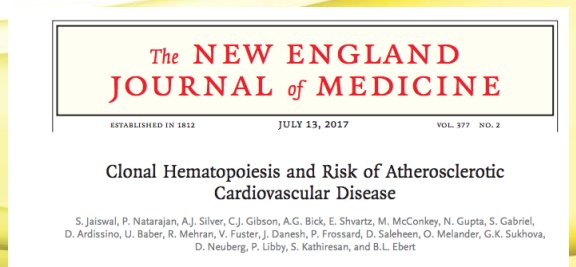
CCO Cancer Care Ontario

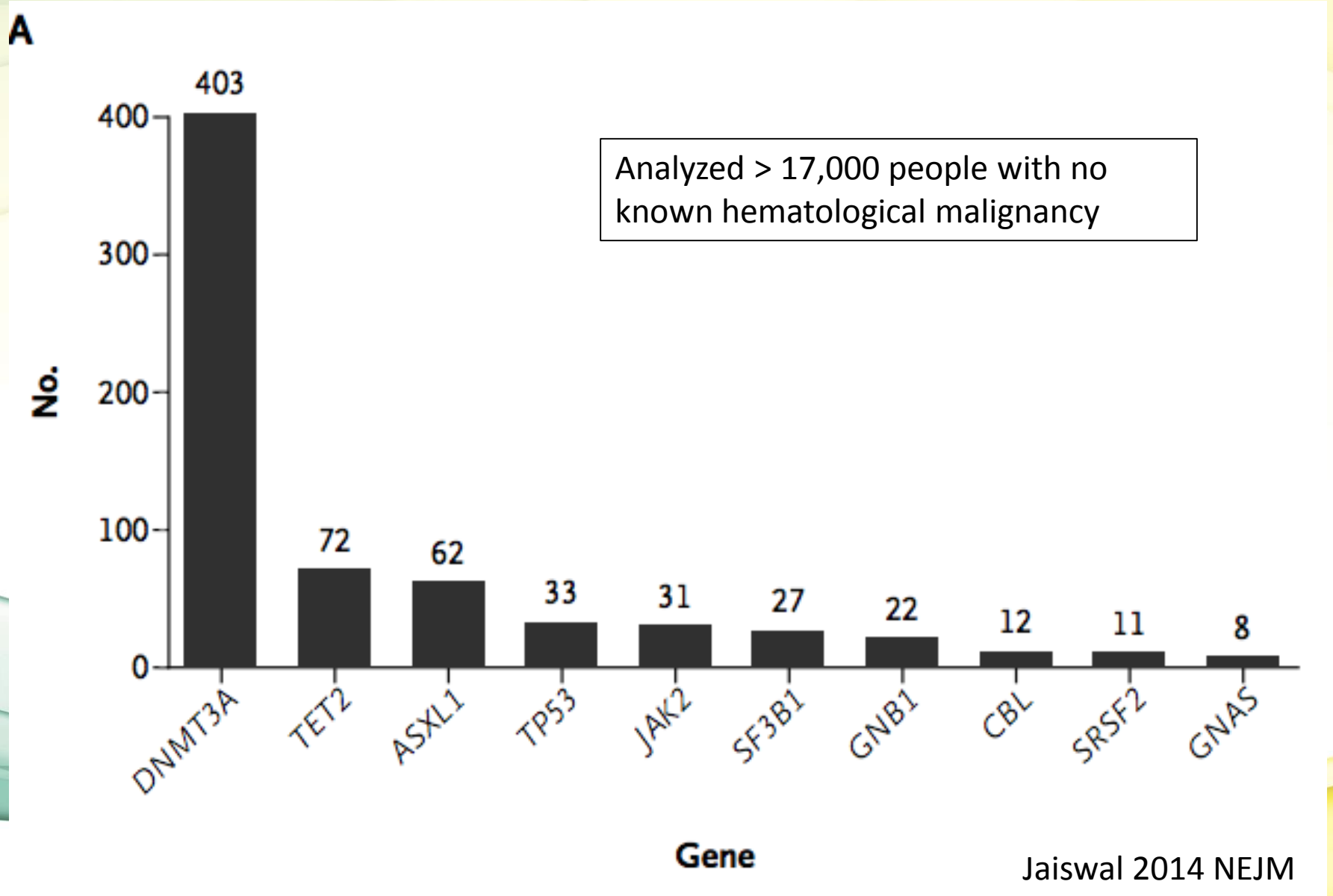
ITOS Oncology
It's the Oncogenes
Windsor

Yes - ? funding

CHIP
(Clonal hematopoieses of indeterminate potential)

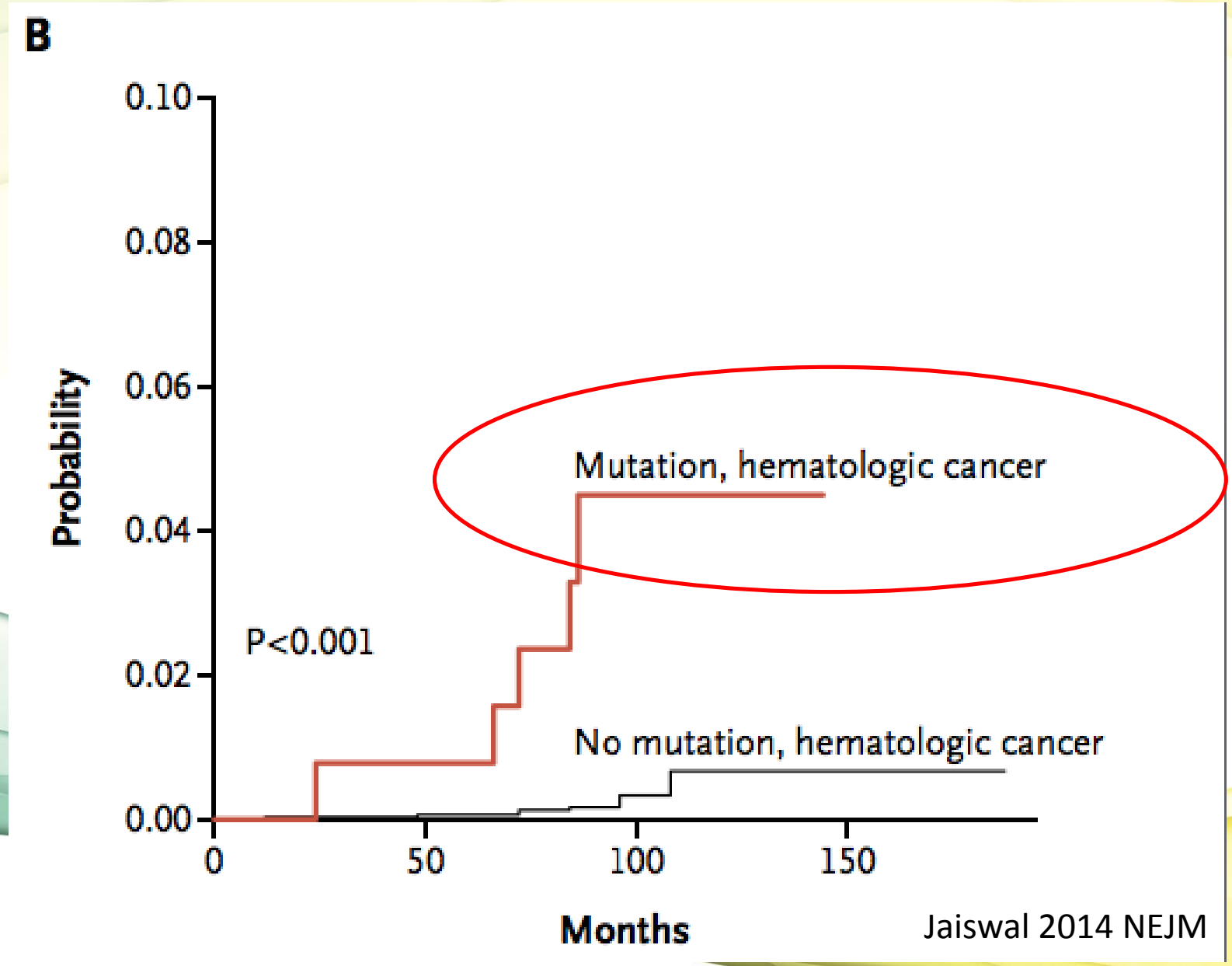
- Normal blood work, mutations associated with myeloid malignancies
- Identified by NGS molecular profiling
- Commonly found in the elderly, it may be found in up to 10 to 20 percent in those older than 70 years
- Associated with a rate of progression to a hematologic neoplasm of about 0.5 to 1 percent per year





Analyzed > 17,000 people with no known hematological malignancy

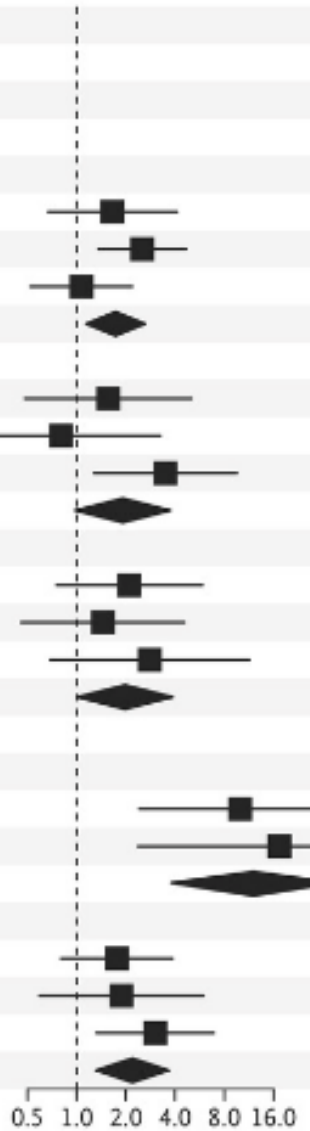
Jaiswal 2014 NEJM



Jaiswal 2014 NEJM

A CHIP and Coronary Heart Disease, According to Mutated Gene

Subgroup	No. of Participants with Myocardial Infarction/ No. at Risk	Hazard Ratio (95% CI)	P Value
No mutation			
BioImage	94/326		
MDC	299/607		
JHS/FUSION/FHS	169/3505		
DNMT3A			
BioImage	5/14	1.7 (0.7–4.1)	0.27
MDC	11/15	2.5 (1.4–4.7)	0.003
JHS/FUSION/FHS	8/99	1.1 (0.5–2.2)	0.90
Fixed-effects meta-analysis		**1.7 (1.1–2.6)**	**0.01**
TET2			
BioImage	3/7	1.6 (0.5–5.0)	0.46
MDC	2/6	0.8 (0.2–3.3)	0.76
JHS/FUSION/FHS	4/16	3.5 (1.3–9.6)	0.01
Fixed-effects meta-analysis		**1.9 (1.0–3.7)**	**0.06**
ASXL1			
BioImage	4/6	2.1 (0.7–5.8)	0.16
MDC	3/6	1.4 (0.5–4.6)	0.53
JHS/FUSION/FHS	2/10	2.8 (0.7–11.4)	0.15
Fixed-effects meta-analysis		**2.0 (1.0–3.9)**	**0.05**
JAK2			
BioImage	0/0		
MDC	2/2	10.0 (2.4–41.5)	0.001
JHS/FUSION/FHS	1/3	17.4 (2.4–127.6)	0.005
Fixed-effects meta-analysis		**12.0 (3.8–38.4)**	**<0.001**
Other			
BioImage	7/17	1.8 (0.8–3.9)	0.16
MDC	3/4	1.9 (0.6–6.0)	0.28
JHS/FUSION/FHS	6/35	3.0 (1.3–6.9)	0.009
Fixed-effects meta-analysis		**2.2 (1.3–3.7)**	**0.002**

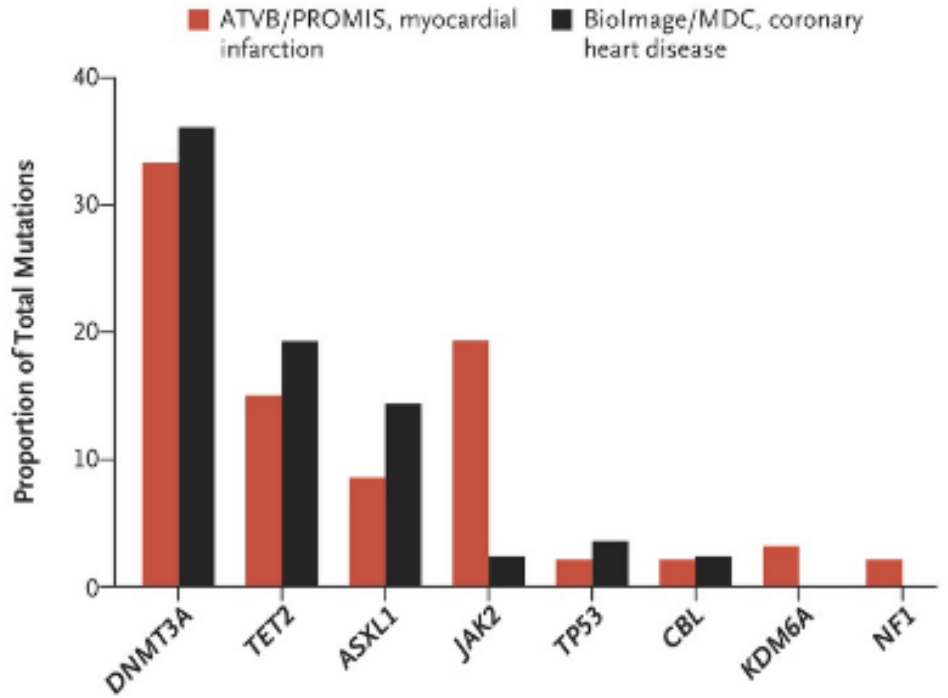


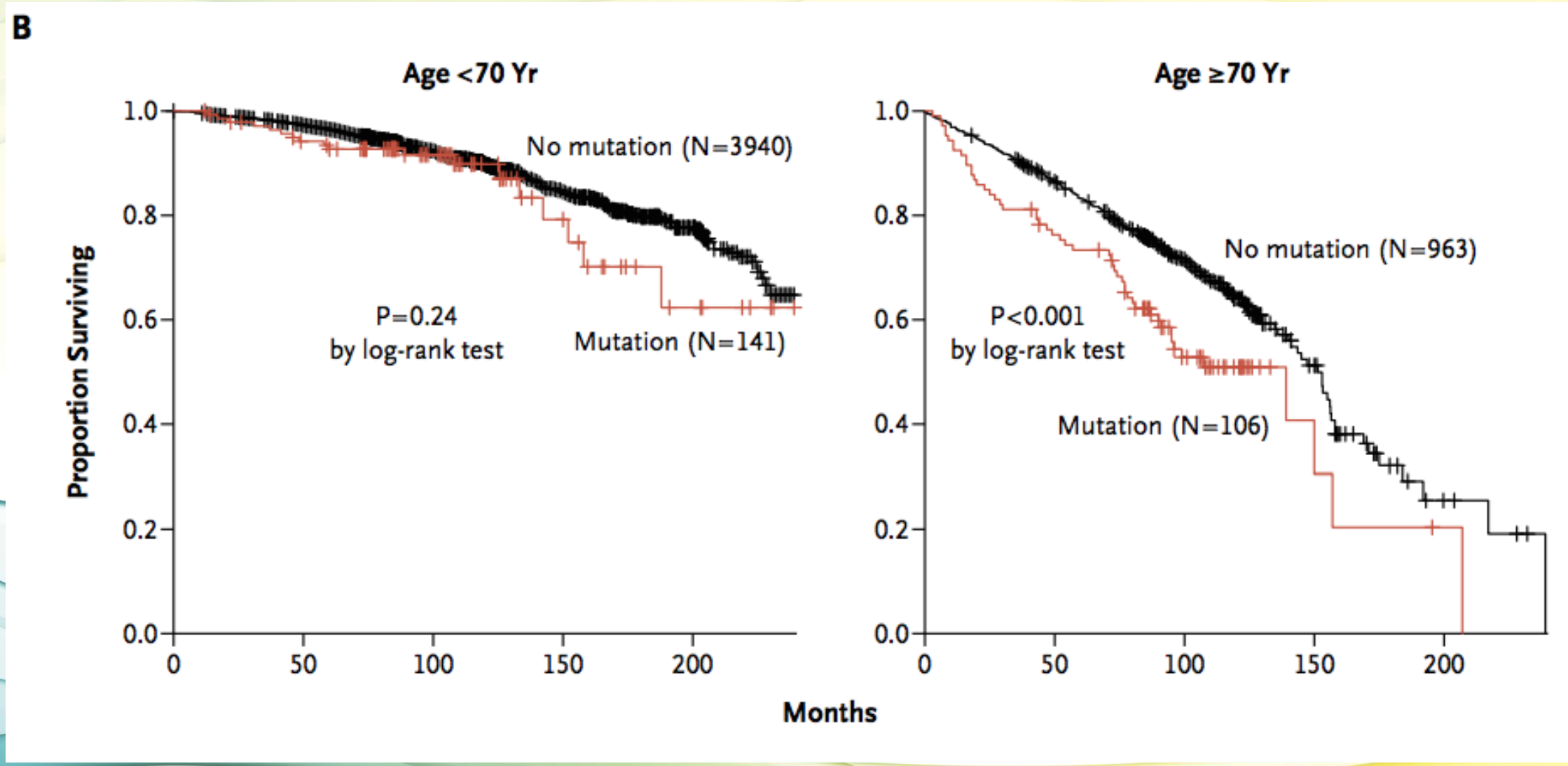
B CHIP and ... to Mutated Gene

Thought to be as high a risk factor as smoking and hyperlipidemia

ATVB and PROMIS		Odds Ratio (95% CI)	P Value
DNMT3A	31/46	1.4 (0.7–2.8)	0.29
TET2	12/13	8.3 (1.2–357.5)	0.02
ASXL1	8/8	Undefined	0.02
JAK2	16/16	Undefined	<0.001
Other	20/22	6.9 (1.7–61.6)	0.001

C Myocardial Infarction and Coronary Heart Disease, According to Mutated Gene





Jaiswal 2014 NEJM

CHIP

- Increased risk of Myeloid Neoplasms
- Increased risk of All Cause Mortality
- Increased risk of Cardiovascular disease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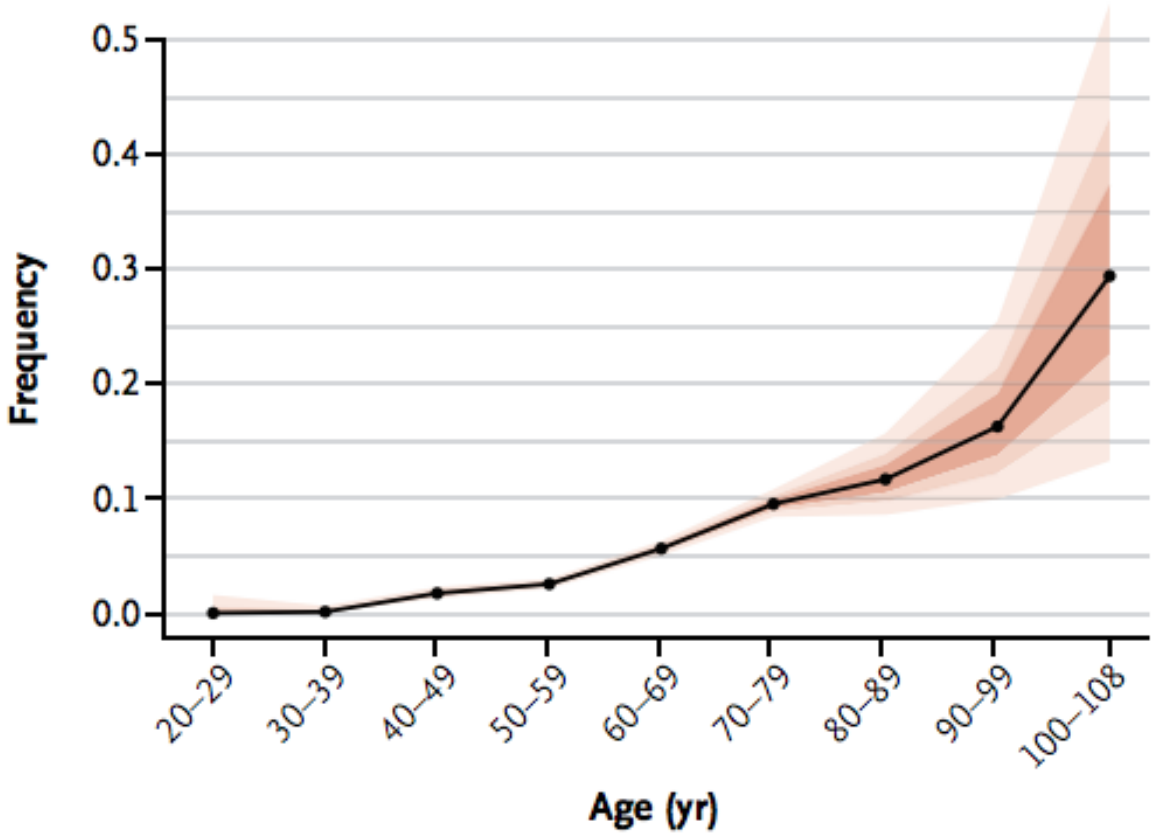
Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

S. Jaiswal, P. Natarajan, A.J. Silver, C.J. Gibson, A.G. Bick, E. Shvartz, M. McConkey, N. Gupta, S. Gabriel, D. Ardissino, U. Baber, R. Mehran, V. Fuster, J. Danesh, P. Frossard, D. Saleheen, O. Melander, G.K. Sukhova, D. Neuberg, P. Libby, S. Kathiresan, and B.L. Ebert



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.

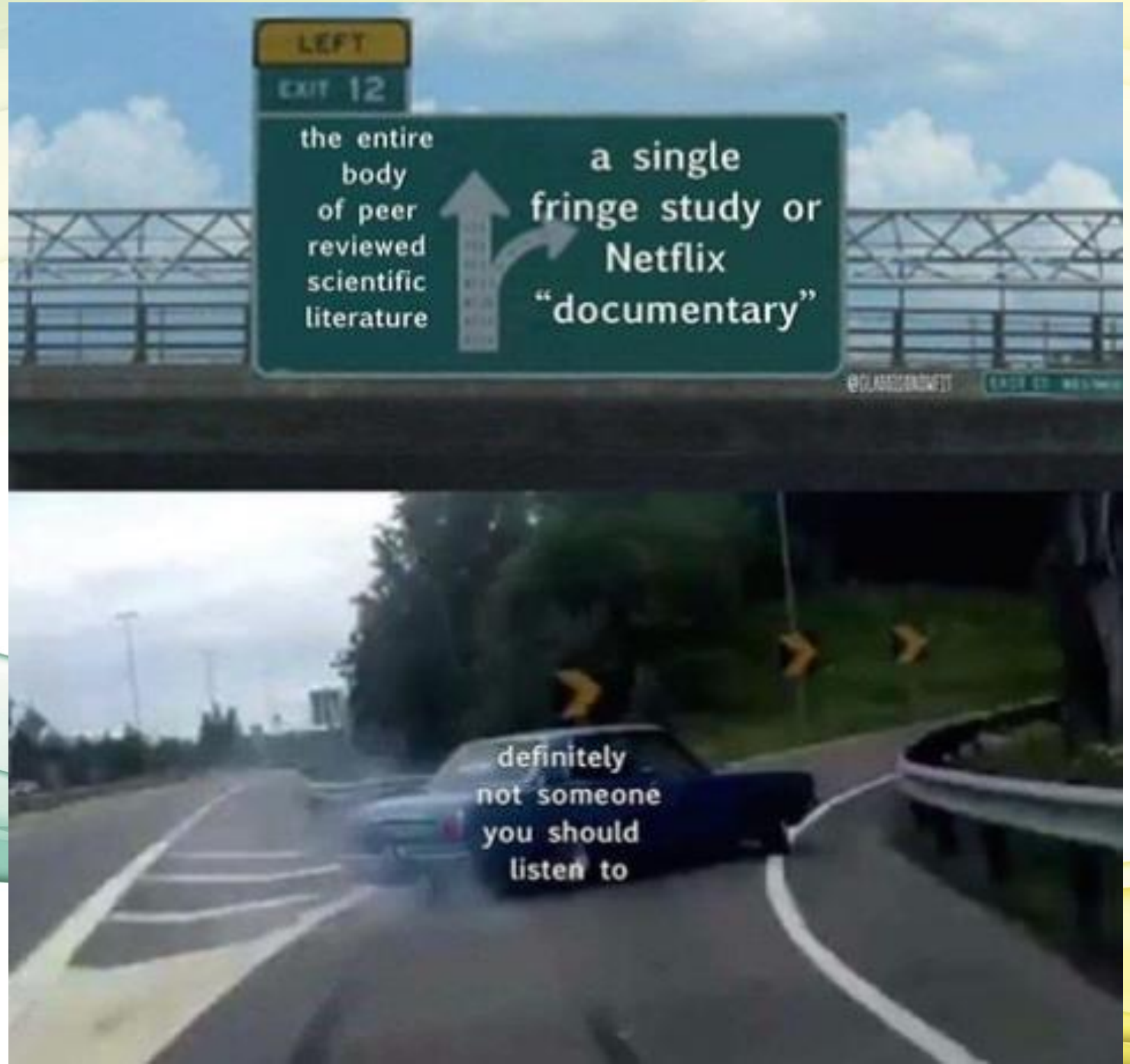
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Jaiswal 2014 NEJM

ICUS, CCUS AND CHIP

- Don’t start screening everyone / who should we test?
- Can we prevent cancer and cardiovascular deaths?
  - What do we do with the information when we find it?
  - Still don’t have great treatments for MDS

- Do we choose donors for allogeneic stem cell transplant differently?
- Cost – actually cheaper than current myeloid neoplasm workup?
- How do physicians keep up with the emerging data?



How do we translate this to the patient?