

Update on Diagnosis of Myelodysplastic Syndromes

Jay L. Patel, MD

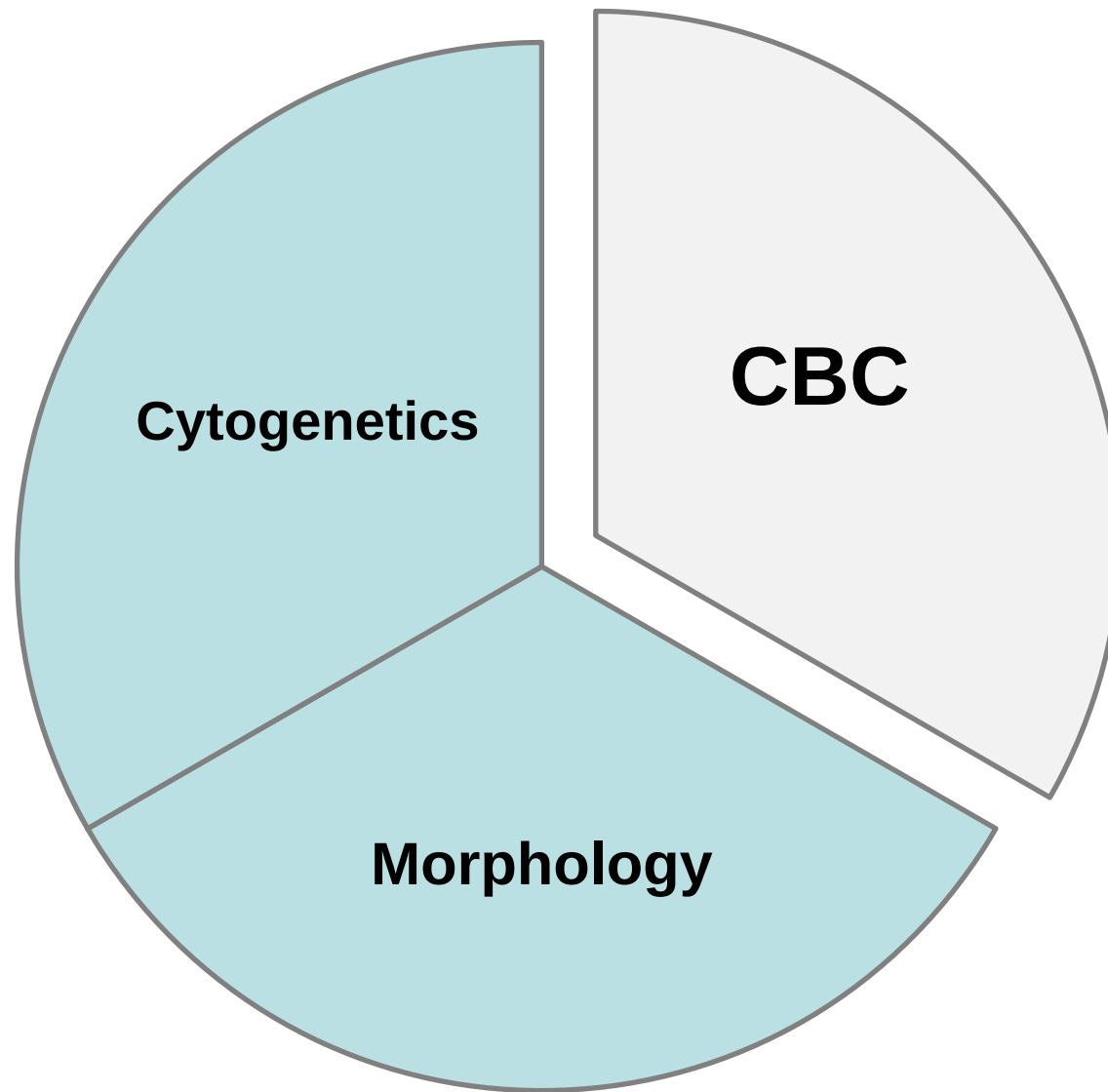
Disclosure

- None

Objectives

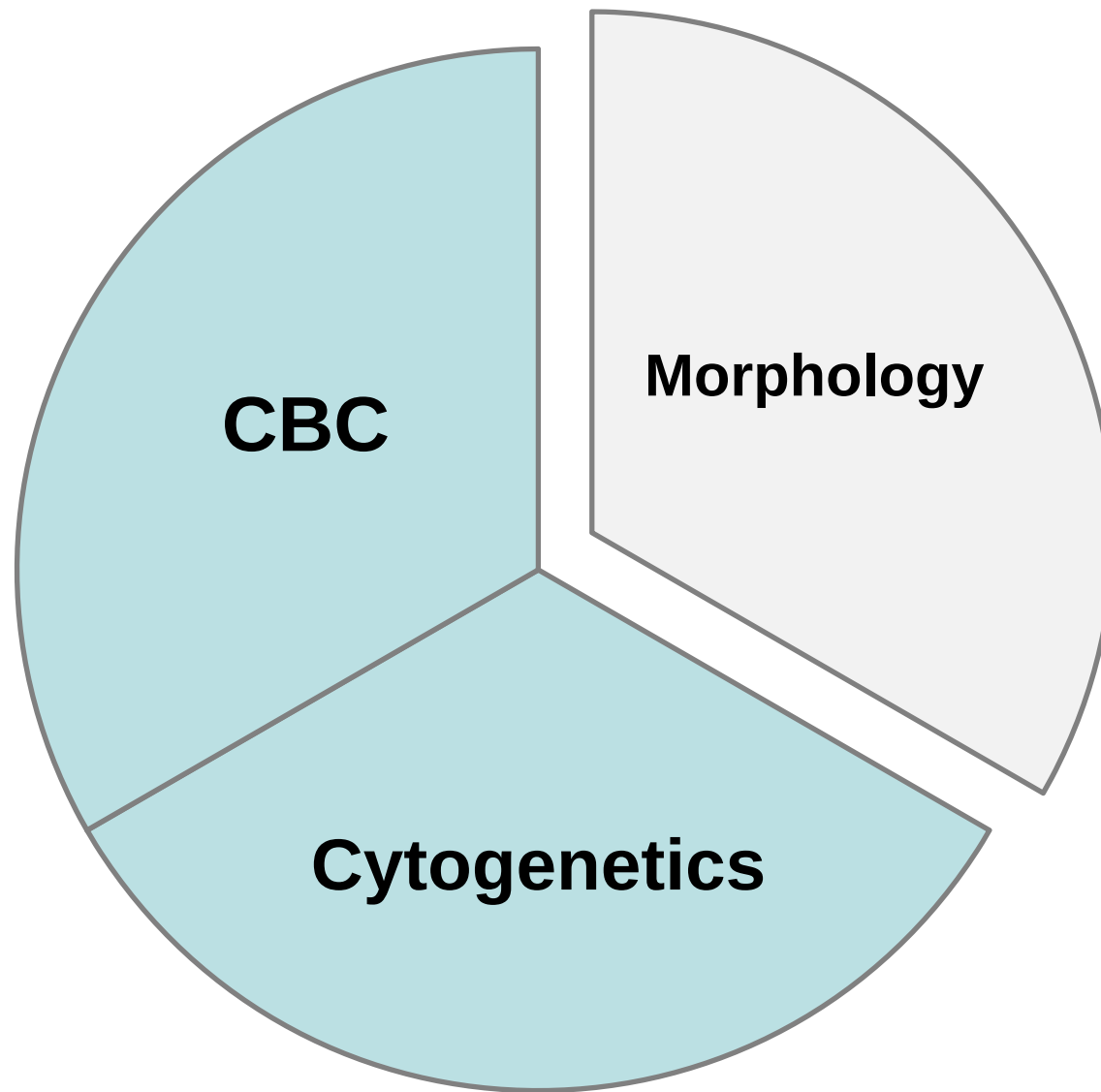
- Review current diagnostic criteria pertaining to myelodysplastic syndromes
- Understand the relevance of selected somatic gene mutations in the diagnosis and prognostication of myelodysplastic syndromes

WHO 2016	WHO 2008
MDS with single lineage dysplasia	Refractory cytopenia
MDS with multilineage dysplasia	Refractory cytopenia with multilineage dysplasia
MDS with ring sideroblasts* - Single lineage dysplasia - Multilineage dysplasia	Refractory anemia with ring sideroblasts
MDS with isolated del(5q)*	MDS with isolated del(5q)
MDS with excess blasts	Refractory anemia with excess blasts
MDS, unclassifiable	MDS, unclassifiable



Cytopenia?

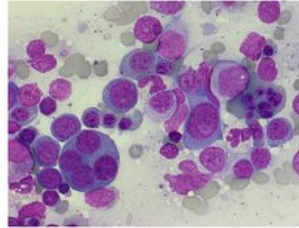
- Hemoglobin: <10 g/dL
- ANC: <1.8 x10⁹/L
- Platelets: <100 x10⁹/L



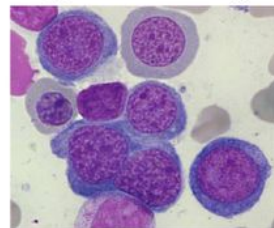
Representative examples of morphologic abnormalities in myelodysplasia

Erythroid lineage

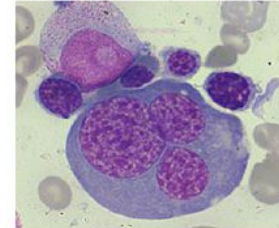
Erythroid hyperplasia



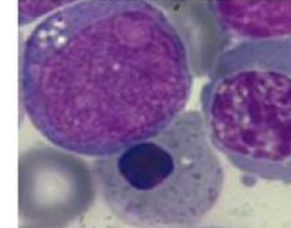
Megaloblastoid changes



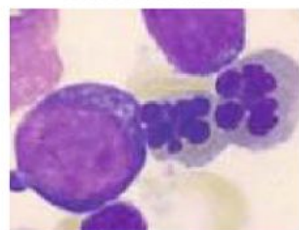
Multinuclearity



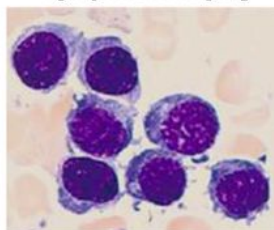
Nuclear pycnosis



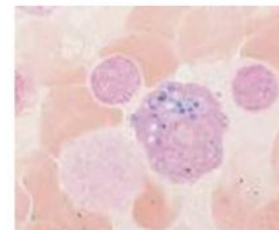
Nuclear lobulation



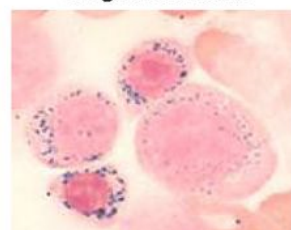
Cytoplasmic fraying



Ferritin sideroblast

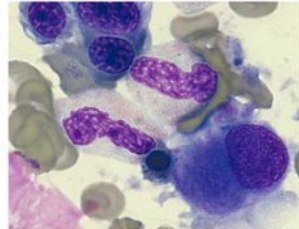


Ring sideroblasts

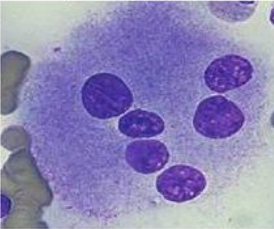


Megakaryocyte lineage

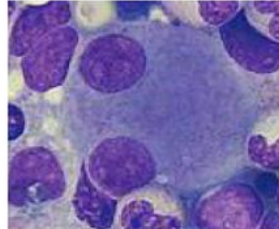
Micromegakaryocyte



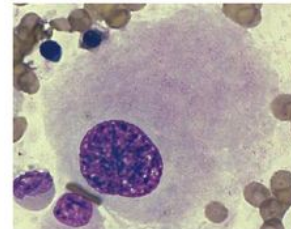
Multiple separated nuclei



Small binucleated cell

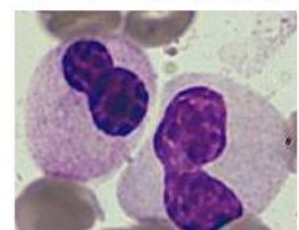


Monolobar cell

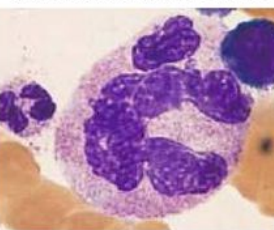


Granulocytic lineage

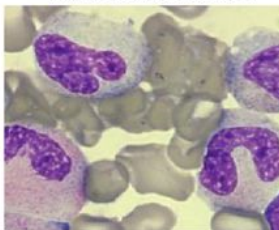
Pseudo-Pelger anomaly



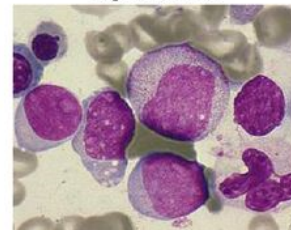
Abnormal nuclear shape



Hypo-degranulation

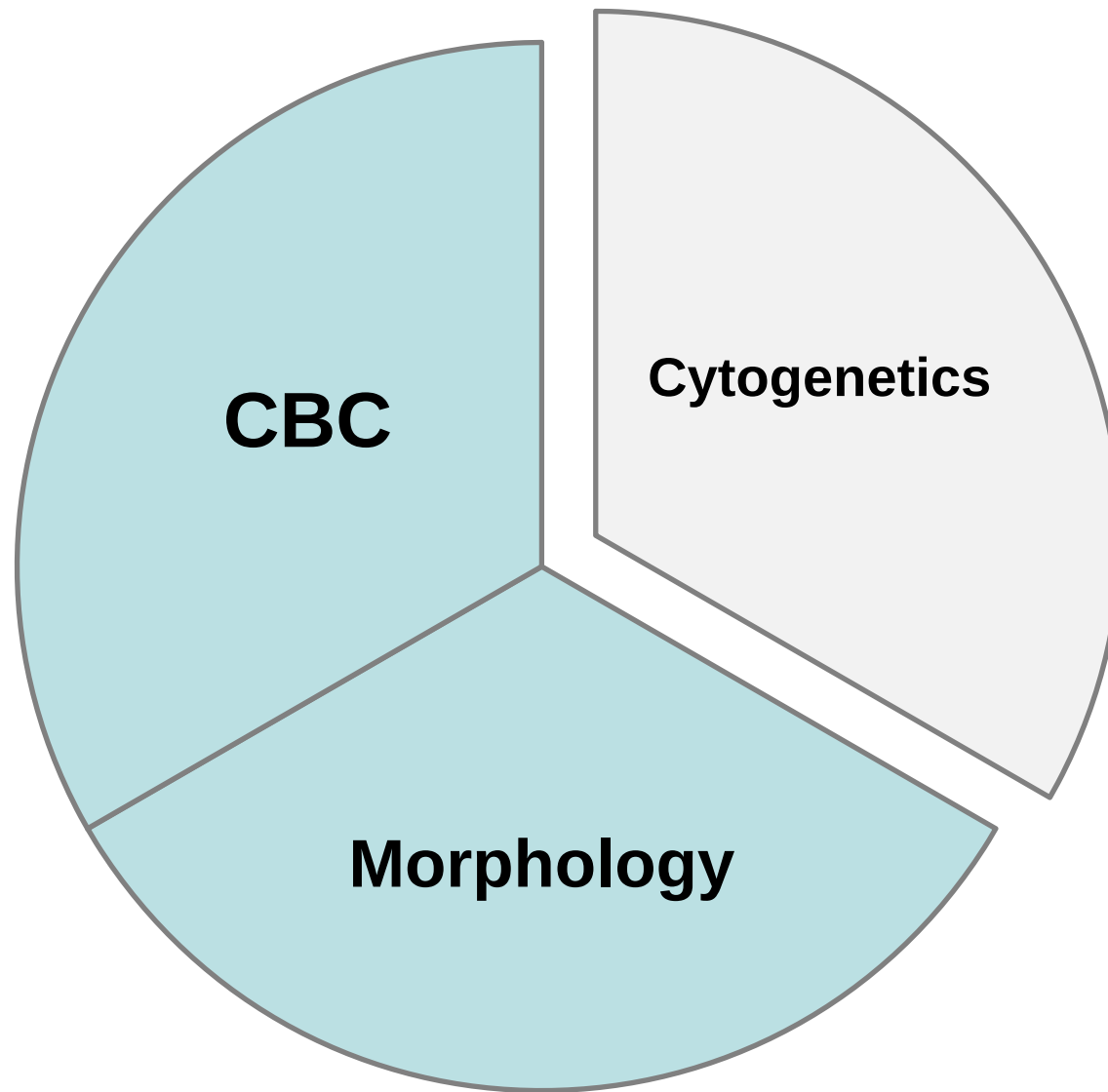


Myeloblasts



Limits of morphology

- Patients with MDS may not show definitive morphologic evidence of dysplasia
- Significant dysplasia may accompany non-neoplastic cytopenias
- Dysplasia is not entirely reproducible among pathologists
- Sample quality

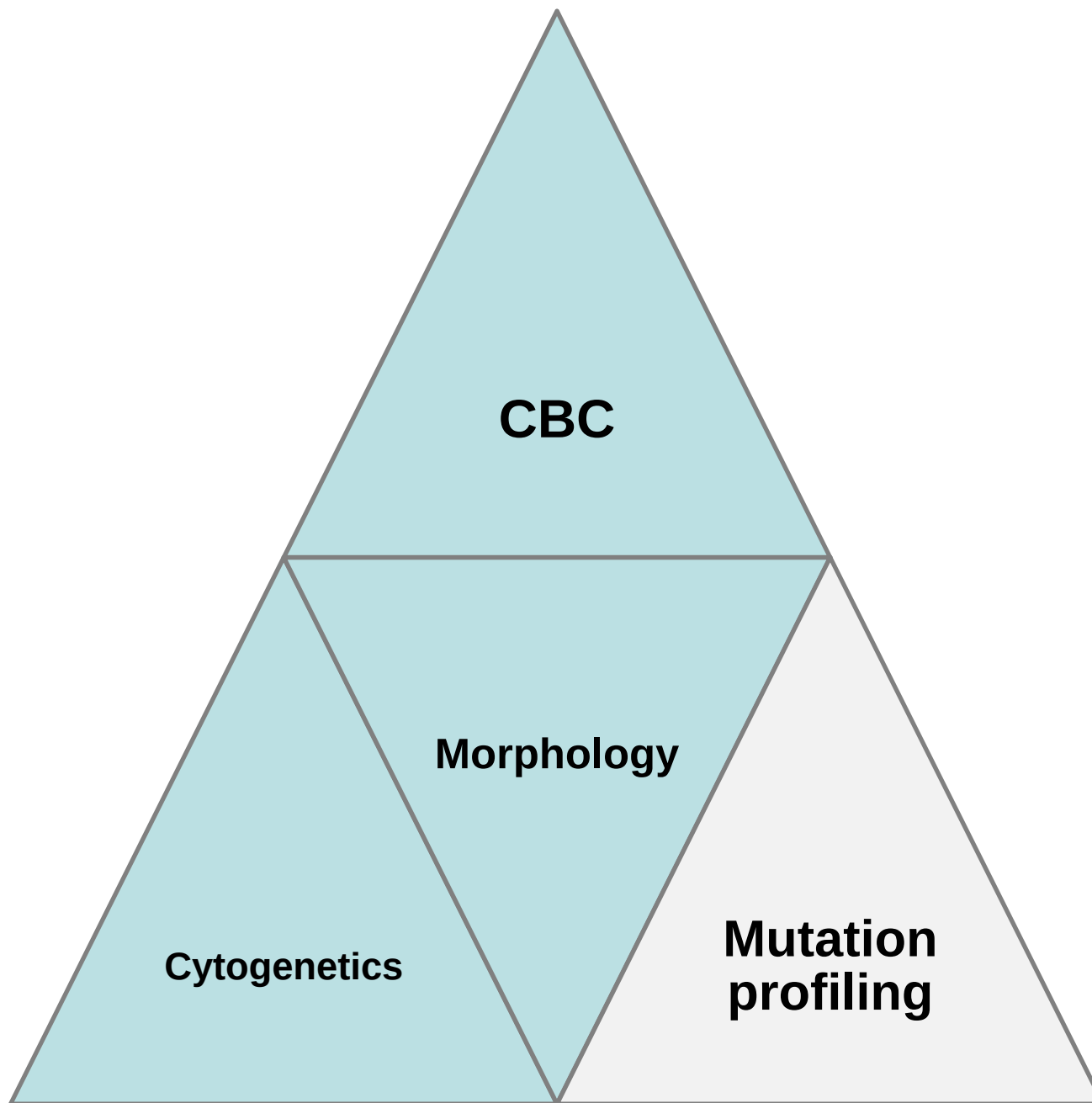


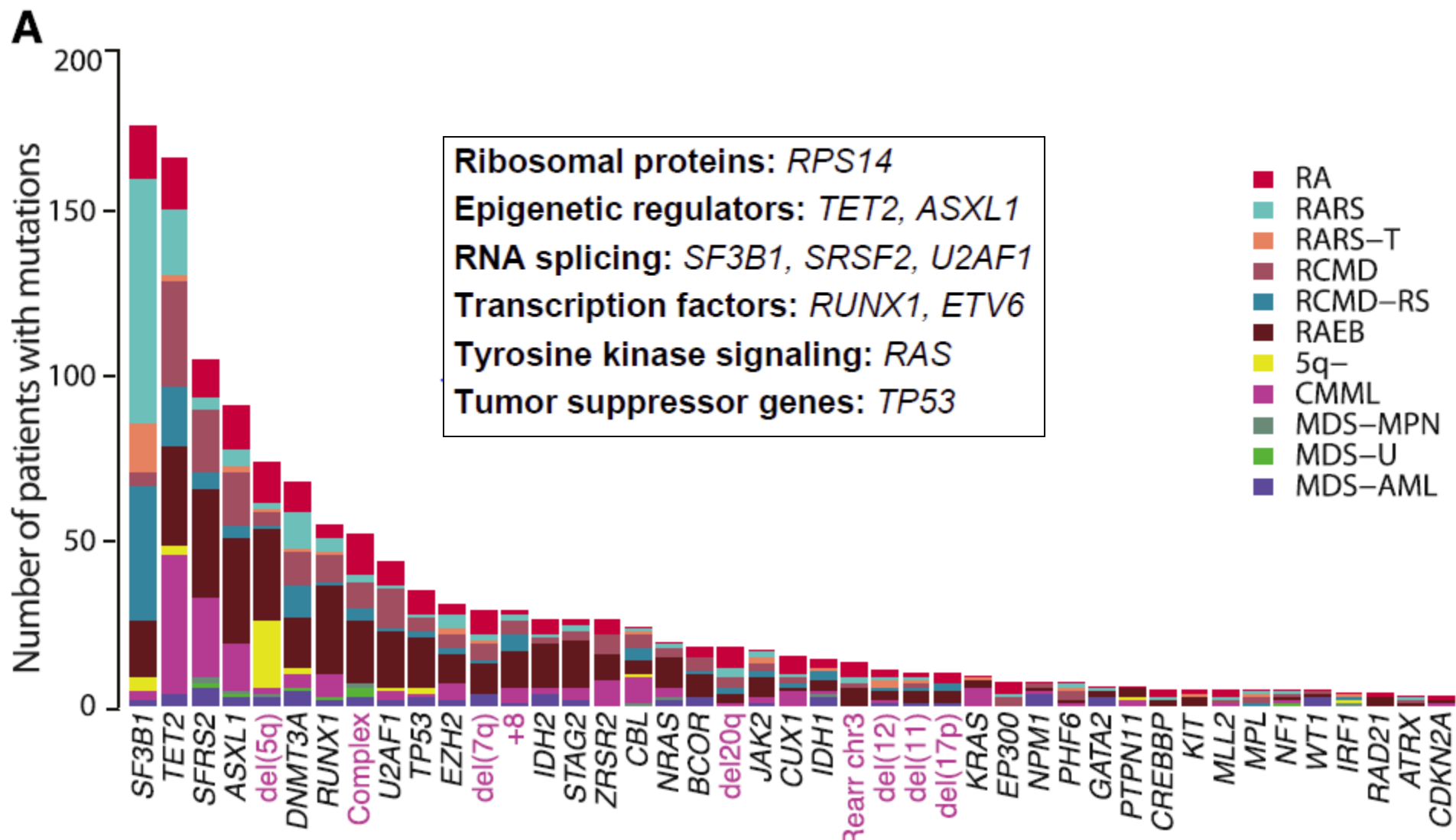
MDS-related cytogenetic abnormalities

- *Complex karyotype*
- *Unbalanced abnormalities*
 - -7/del(7q)
 - -5/del(5q)
 - i(17q)/t(17p)
 - -13/del(13q)
 - del(11q)
 - del(12p)/t(12p)
 - del(9q)
 - idic(X)(q13)
- *Balanced abnormalities*
 - t(11;16)(q23;p13.3)
 - t(3;21)(q26.2;q22.1)
 - t(1;3)(p36.3;q21.1)
 - t(2;11)(p21;q23)
 - t(5;12)(q33;p12)
 - t(5;7)(q33;q11.2)
 - t(5;17)(q33;p13)
 - t(5;10)(q33;q21)
 - t(3;5)(q25;q34)
- May allow for a diagnosis of MDS in the absence of morphologic dysplasia

Limits of Cytogenetics

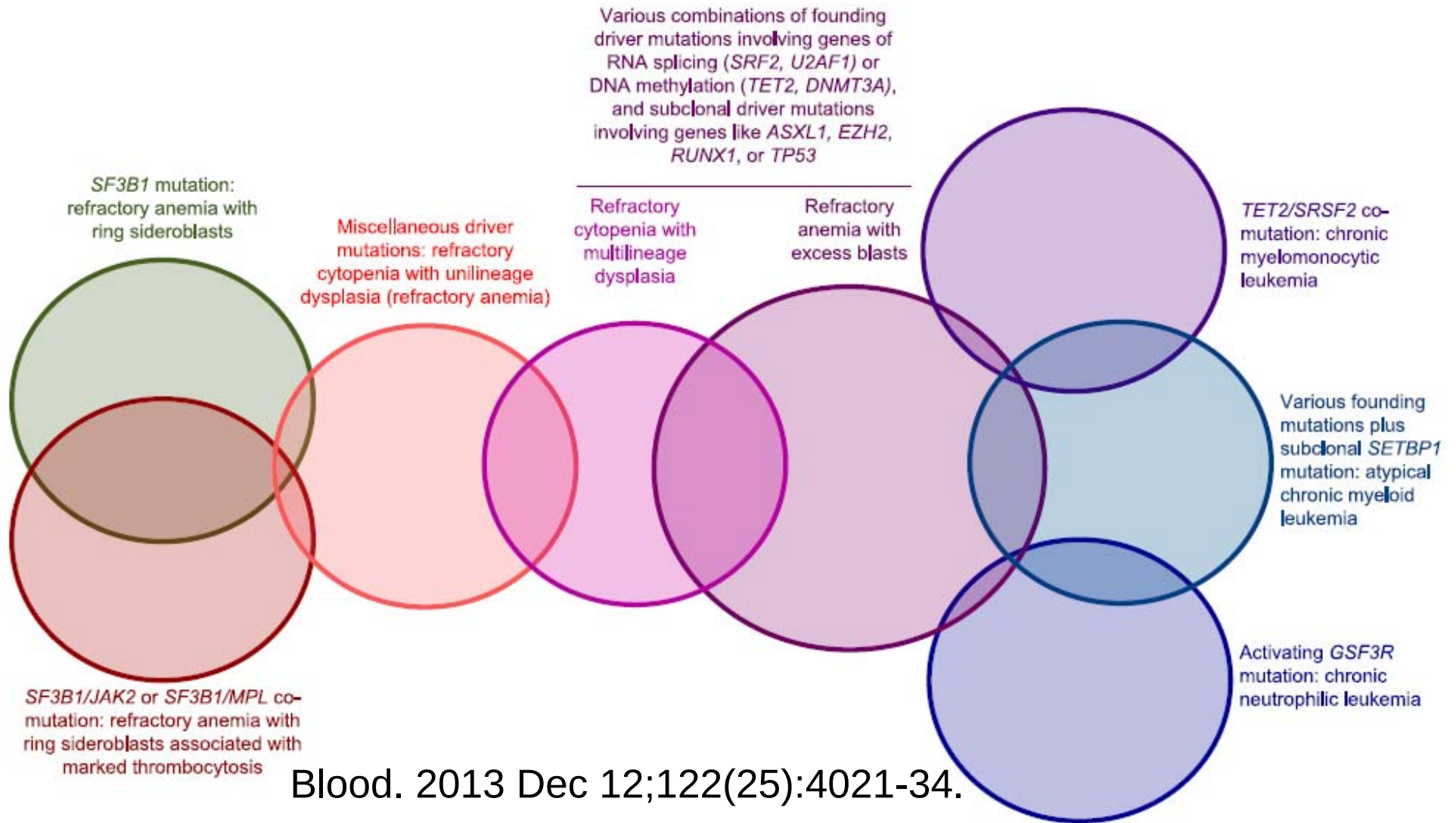
- Up to 50% of patients with MDS have a normal karyotype
- Non-specific abnormalities (e.g. del20q, trisomy 8, -Y)
- May not be available





Blood. 2013 Dec 12;122(25):4021-34.

Genotype-phenotype relationships



ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D., Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D., R. Coleman Lindsley, M.D., Ph.D., Craig H. Mermel, M.D., Ph.D., Noel Burt, B.S., Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Moltchanov, Ph.D., Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D.,

Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Gad Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin Stacey Gabriel, Ph.D., Sekar Kathiresan, M.D., Heat Mark I. McCarthy, M.D.,* Michael Boehnke, Ph.D.,* Jaal Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., James G. Wilson, M.D., Donna Neuberg, Sc.D., David and Benjamin L. Ebert, M.D., Ph.D.

N Engl J Med. 2014
Dec 25;371(26):2488-98.

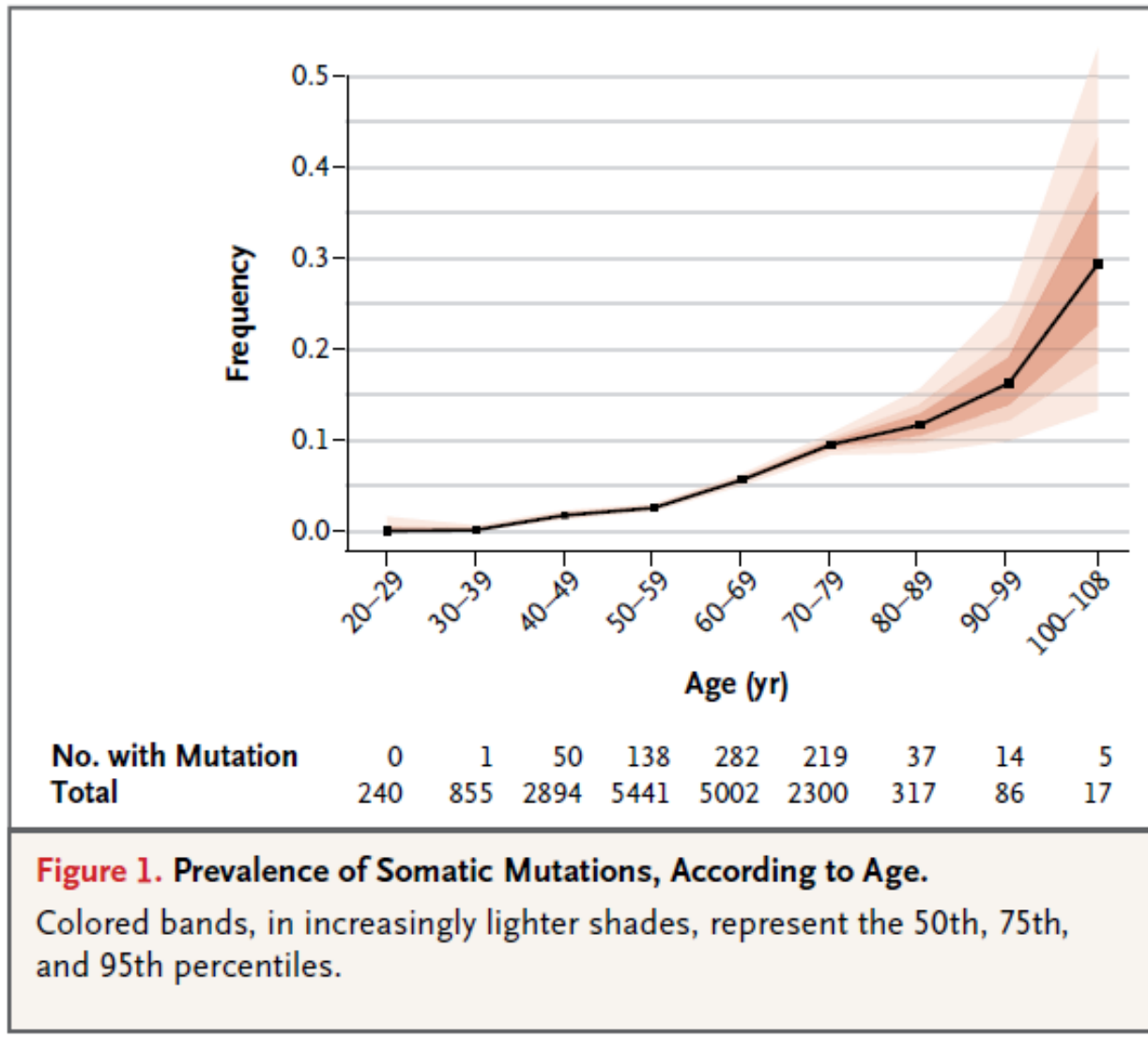
ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhoun, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svantesson, M.S., Mikael Landén, Ph.D., Martin Höglund, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.

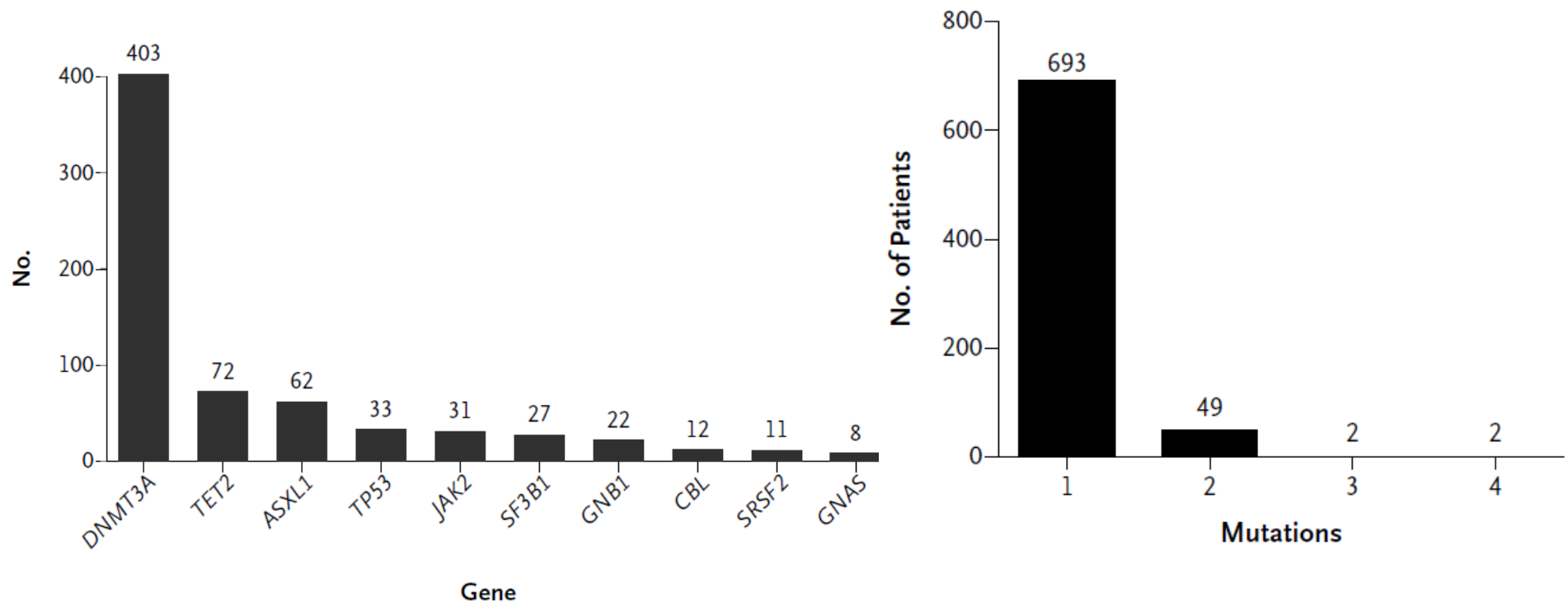
N Engl J Med. 2014 Dec 25;371(26):2477-87.

Mutation happens



Consider mutation frequency vs. disease incidence

N Engl J Med. 2014 Dec 25;371(26):2488-98.

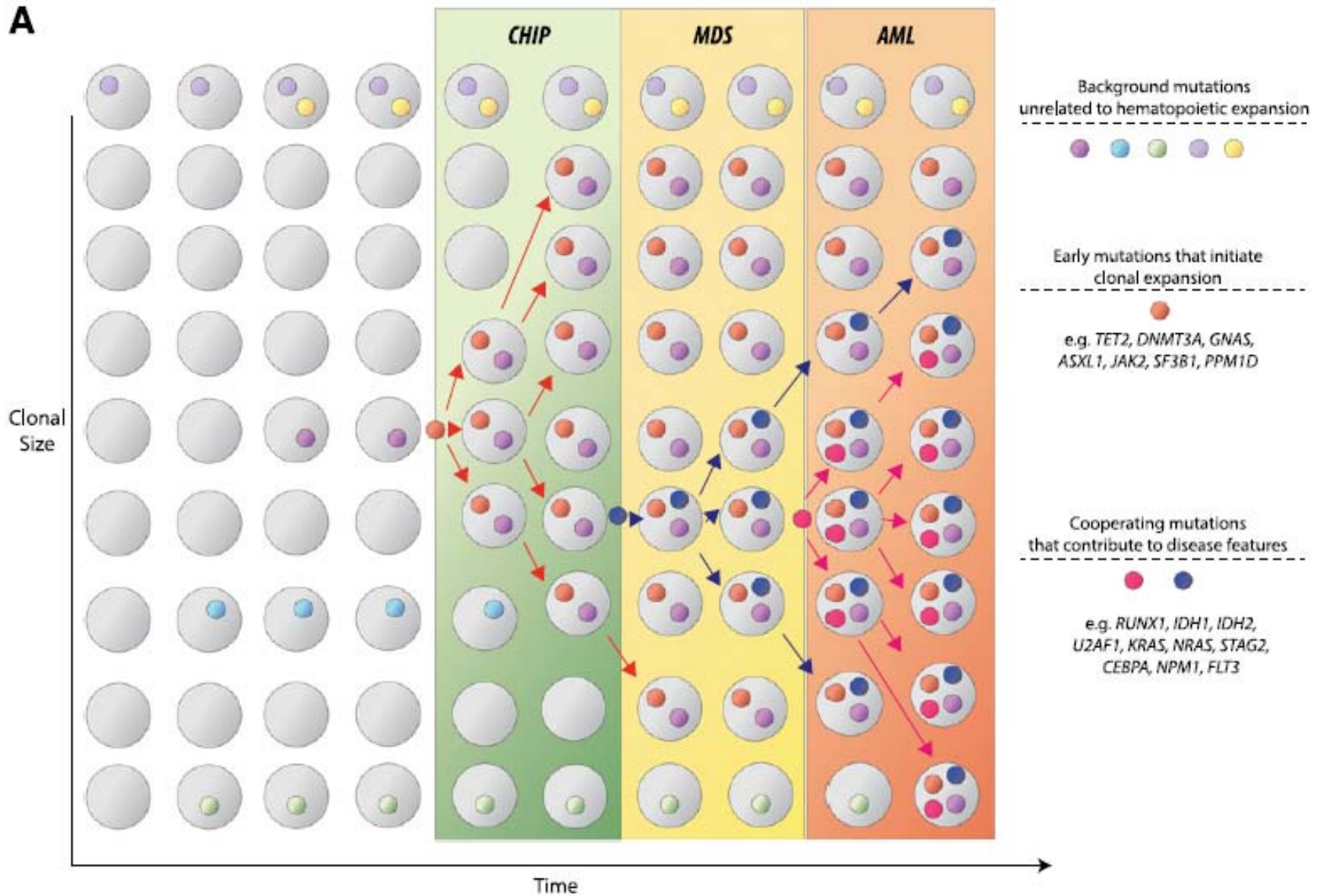


N Engl J Med. 2014 Dec 25;371(26):2488-98.

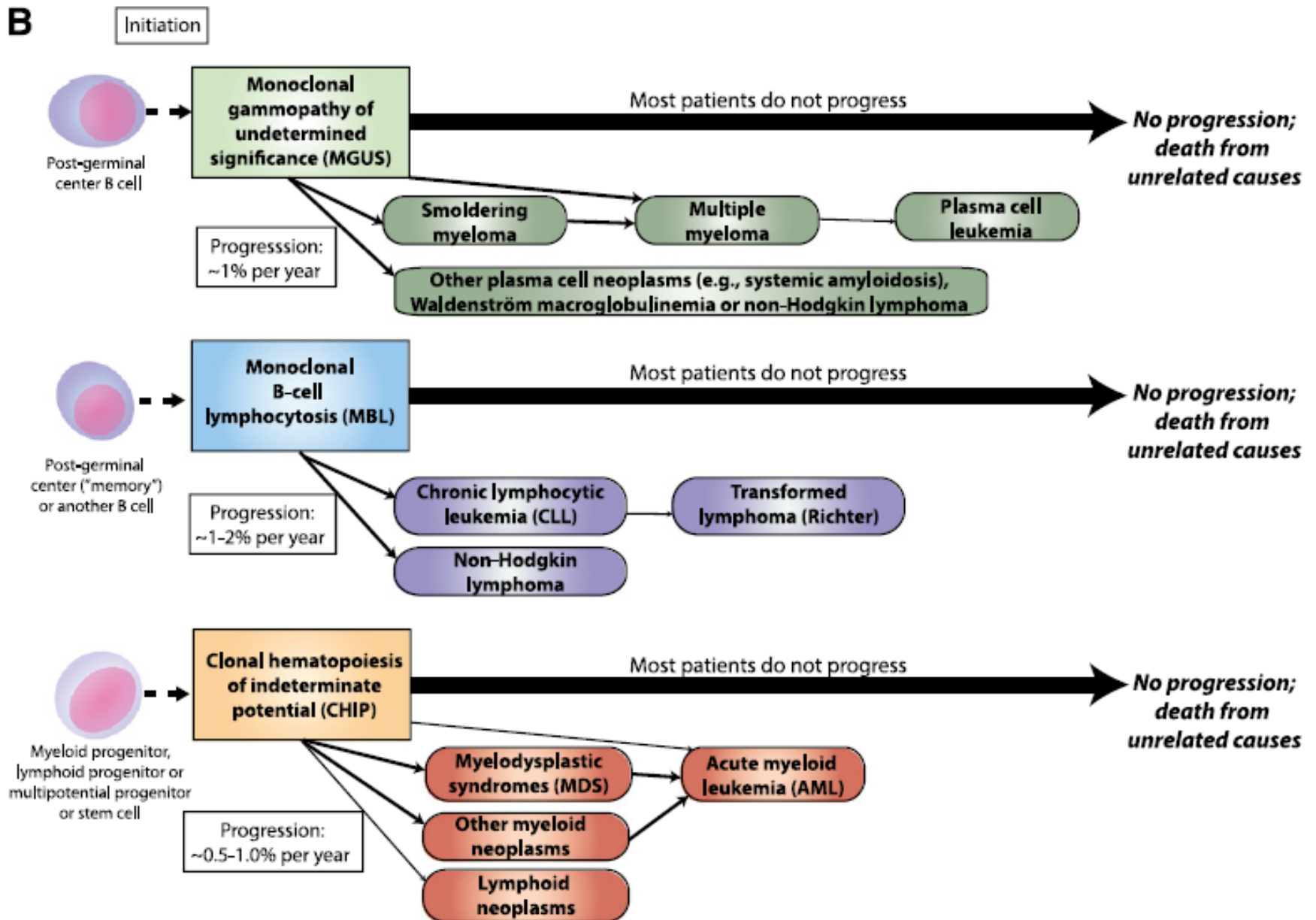
Clonal hematopoiesis of indeterminate potential (CHIP)

- No morphologic evidence of malignancy
- Exclude PNH, MGUS, MBL
- Presence of a somatic mutation associated with myeloid malignancies
 - *DNMT3A, TET2, ASXL1, SF3B1, TP53, JAK2, CBL, BCOR, BCORL1, SRSF2*
 - Variant frequency at least 2%
- Risk of progression ~0.5-1.0% per year

[Blood](#). 2015 Jul 2;126(1):9-16.

A

Blood. 2015 Jul 2;126(1):9-16.

B

Blood. 2015 Jul 2;126(1):9-16.

	Traditional ICUS			MDS by WHO	
	'Non-clonal' ICUS	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	-	+	+	+	+
Dysplasia	-	-	-	+	+
Cytopenias	+	-	+	+	+
BM Blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall Risk	Very Low	Very Low	Low (?)	Low	High
Treatments	Obs/BSC	Observation	Obs/BSC/GF	Obs/BSC/GF IMiD/IST	HMA/HCST

Clonal Cytopenias

If included as MDS,
incidence could double!

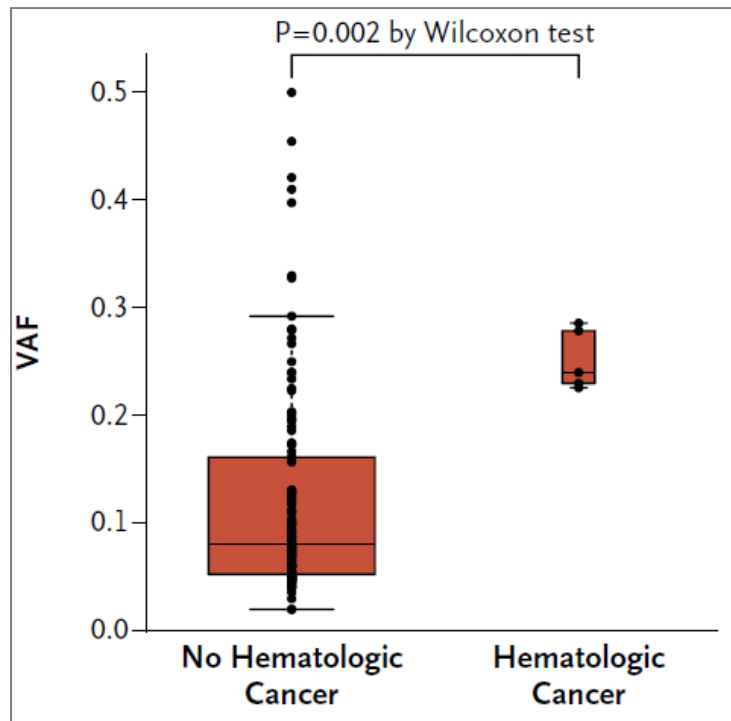
Blood. 2015 Jul 2;126(1):9-16.

Negative predictive value

- Greater than 85% of patients with MDS have one or more somatic mutations (Papaemmanuil et al, Blood 2013)
- If diagnosing MDS, a negative NGS result should prompt re-evaluation for other causes of cytopenia.

Do Variant Allele Frequencies help?

- Somatic vs. germline
- Cutoff for clinical relevancy?
- VAF > 30% appears less common in CHIP



N Engl J Med. 2014
Dec 25;371(26):2488-98.

Take home

- Sequencing capabilities have advanced much faster than our understanding of genomics
- Detection of somatic variant(s) alone is **insufficient** to diagnose MDS
- For patients with possible MDS, integration of clinical history, CBC, morphology, conventional cytogenetics, and mutation data is *essential*
- Data is accumulating...stay tuned (i.e. 'MDS-related somatic mutations'? 'IPSS-Mol'?)