Advancing the Diagnosis of Myeloid Neoplasms: The 2016 WHO Classification

Robert P Hasserjian, MD

Professor of Pathology

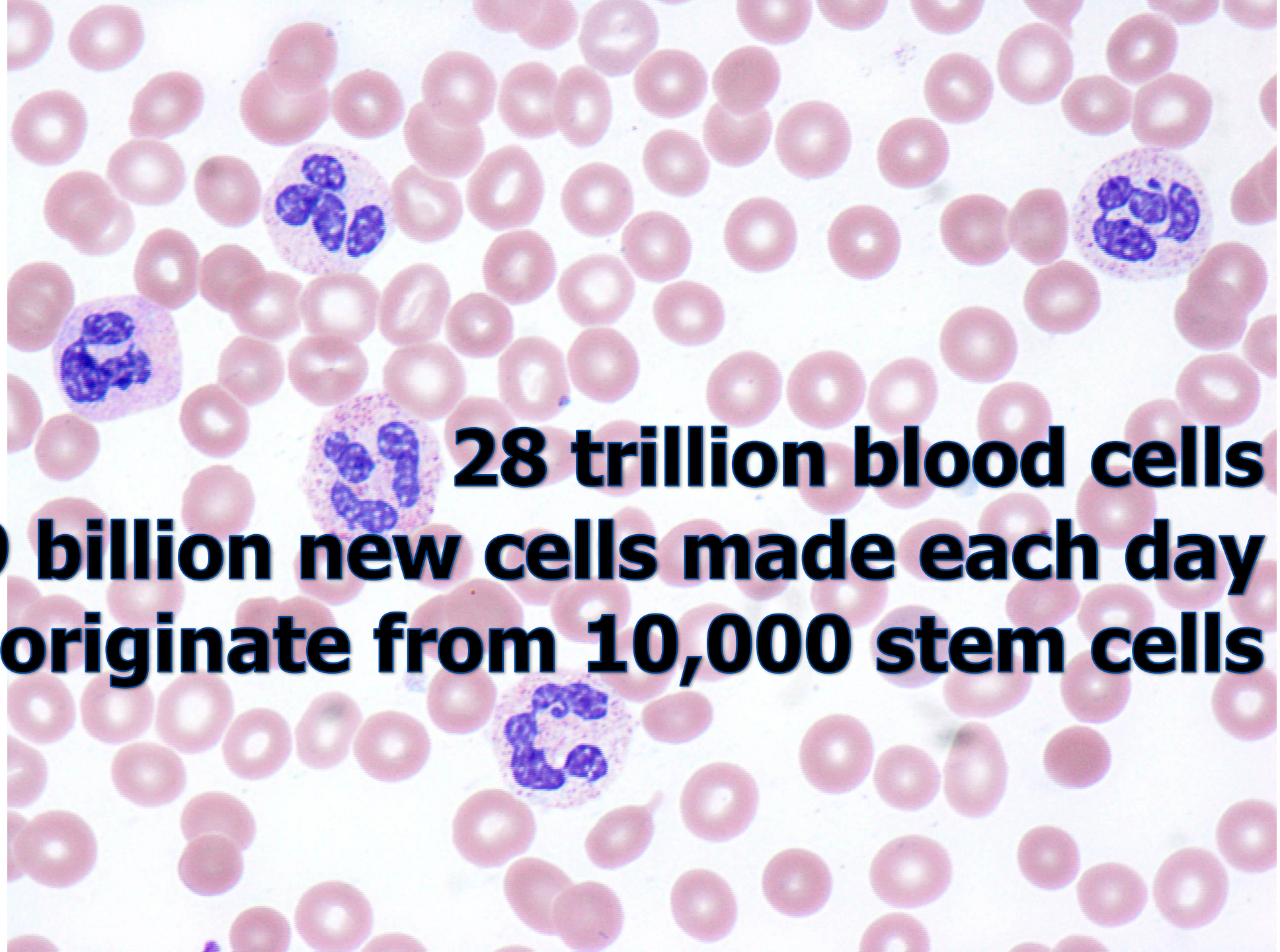
Massachusetts General Hospital and
Harvard Medical School

Outline of lecture

- Overview our current concepts regarding the molecular etiology of myeloid neoplasia
- Review the application of a clinically relevant classification system (WHO 2016) across the spectrum of myeloid neoplasms
- Provide examples of how both genetics and morphology cooperate in creating meaningful disease entities

Myeloid neoplasms

- Clonal proliferations of hematopoietic cells that replace normal hematopoiesis in the blood and bone marrow
- Disease is recognizable when peripheral blood counts are perturbed, leading to patient symptoms
- Many disease subtypes based on differentiating features
  - Clinical manifestation(s)
  - Morphologic appearance
  - Genetic features
  - Expected clinical behavior

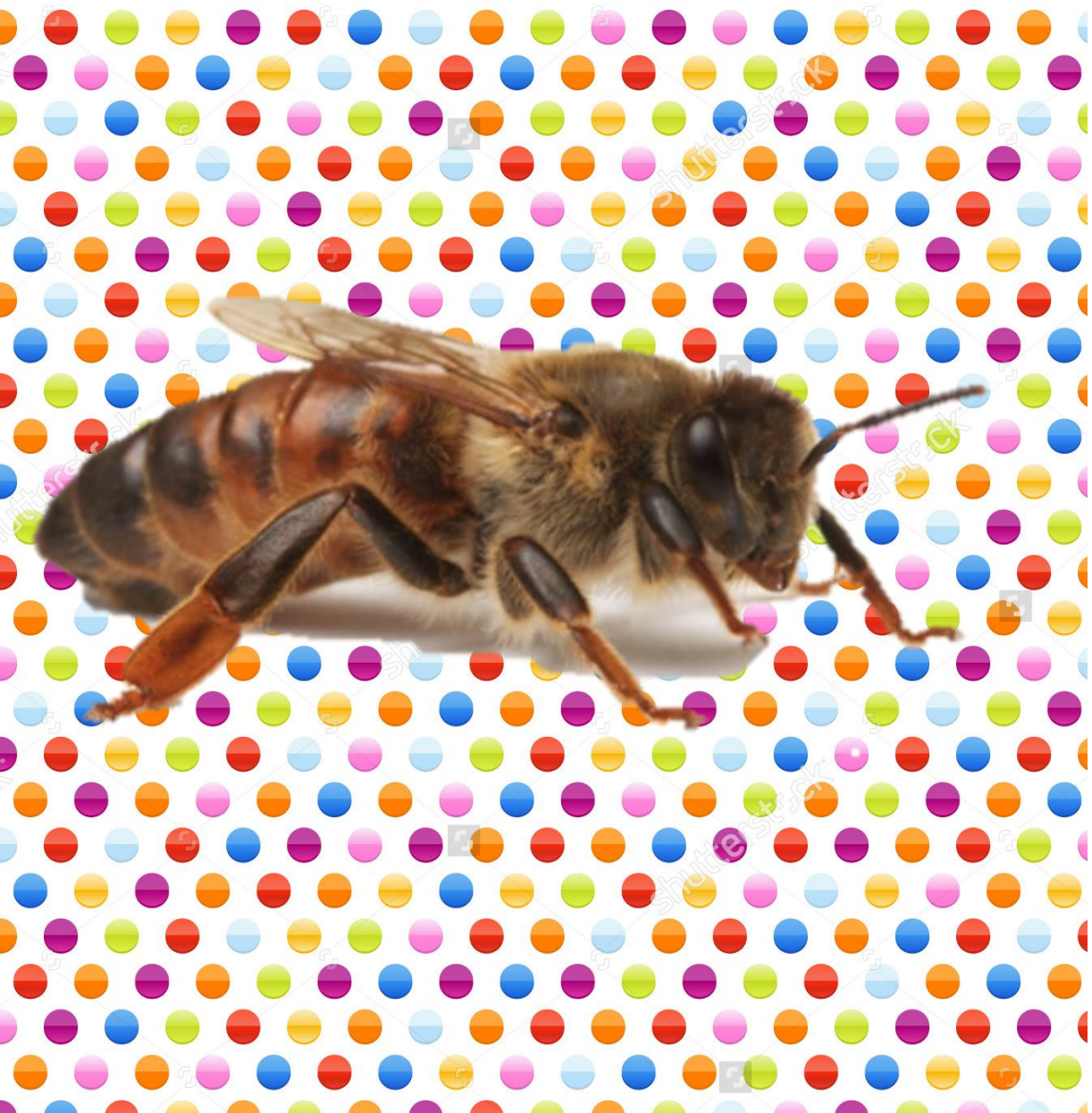


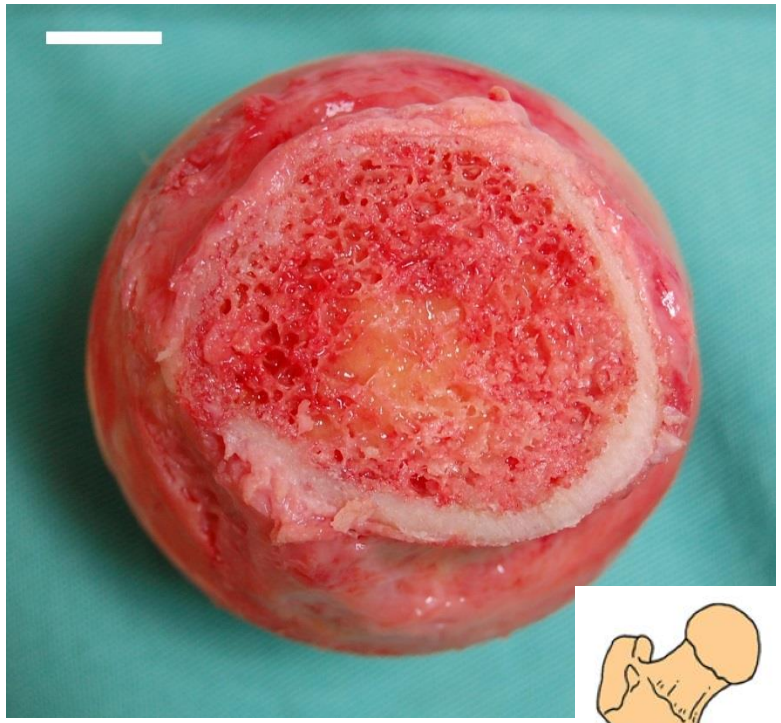
28 trillion blood cells

239 billion new cells made each day

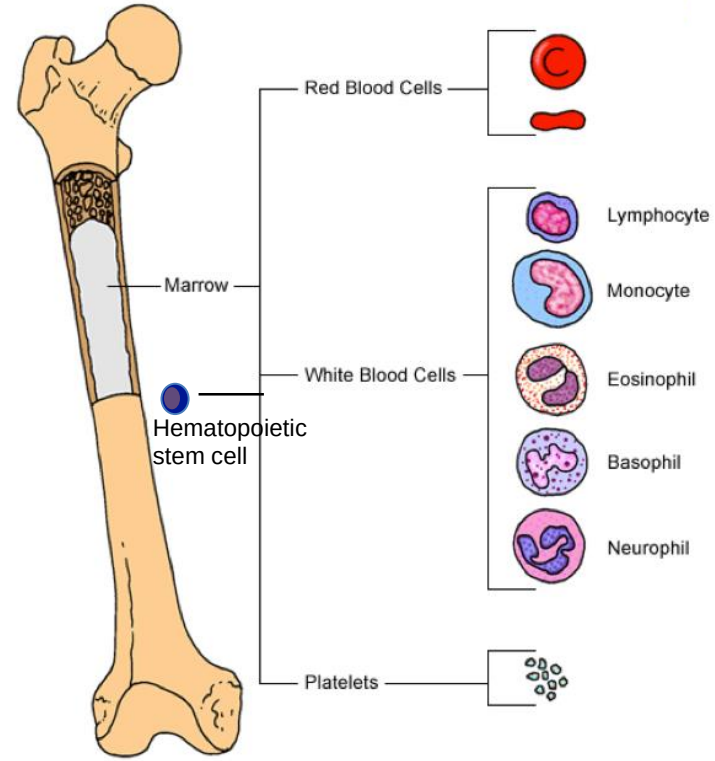
All originate from 10,000 stem cells

Our loyal stem cells



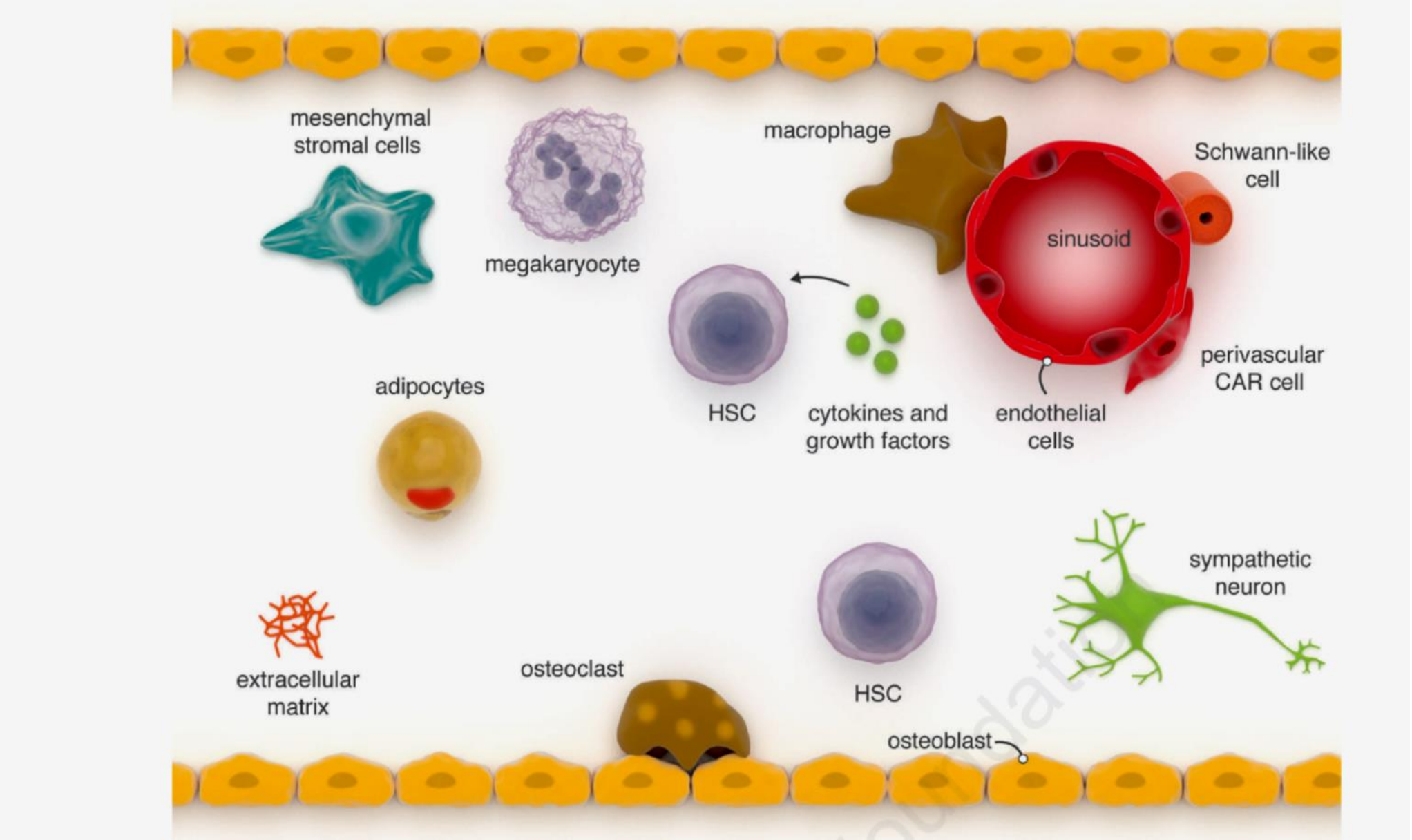


- Totipotent
- Quiescent
  - Divide 1x/month
  - Resistant to injury
- Generate daughter cells that create the entire hematopoietic system



Courtesy of Dr Daniela Krause, University of Frankfurt

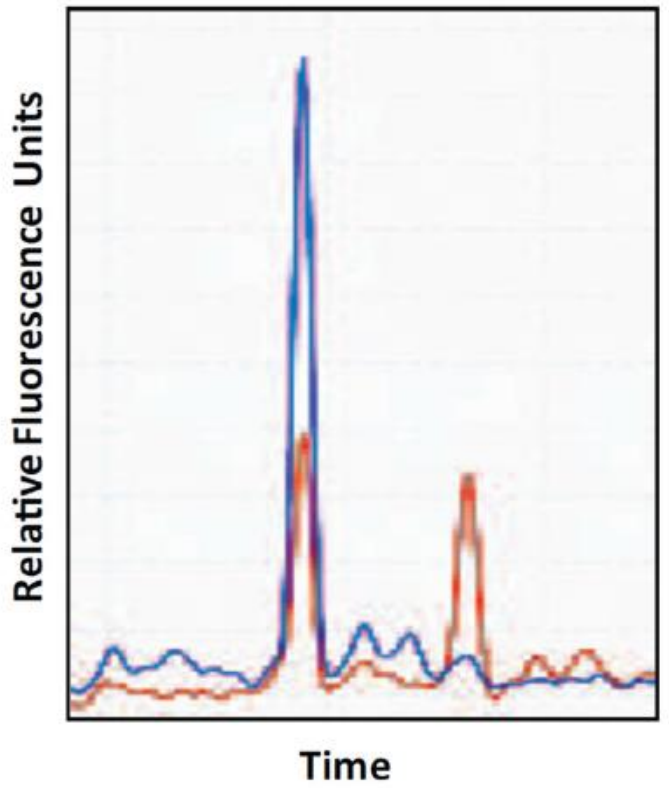
The stem cell niche



Krause DS and Scadden DT Haematologica 2015

The stem cell pool is vulnerable. . .

- As some individuals age, stem cell clones originating from a single ancestor cell assume a dominant role in making blood cells
  - 33% clonal X-inactivation by HUMARA assay
  - Engraftment experiments show that a restricted stem cell subpopulation takes over at late timepoints
- Stem cells accumulate mutations as they divide
- Some mutations confer survival advantages, allowing affected stem cells to replicate and assume a broader role in hematopoiesis

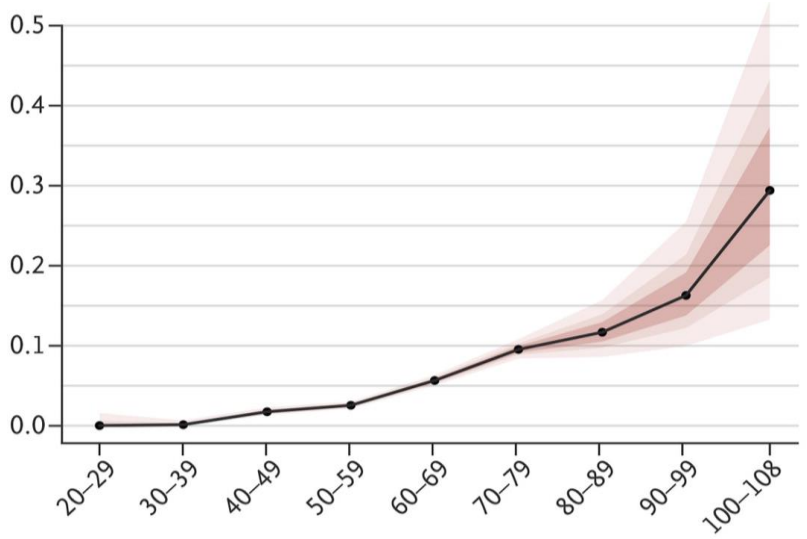


HUMARA assay
for X inactivation

Wiedmeier JE et al. Exp Hematol 2016;44:867, Buscarlet M et al. Blood 2017; 130:753

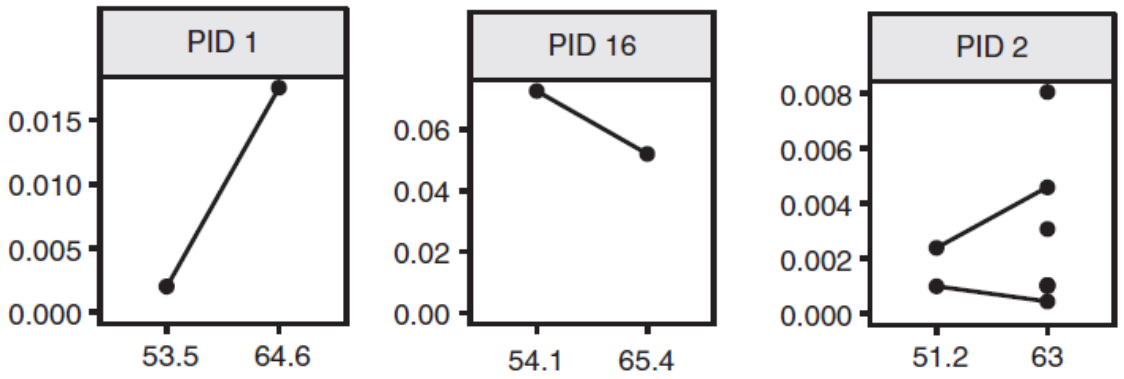
The spectrum of clonal hematopoiesis (CHIP)

- With current NGS methods, clonal mutated hematopoiesis is readily identified in many healthy people
  - Incidence increases with age
  - Mutations affect genes predicted to give survival advantage to stem cells and their progeny
    - Epigenetic regulators, spliceosome, transcription factors, tyrosine kinases, tumor suppressor genes
  - Mutated clones may be source of a large portion of blood cells



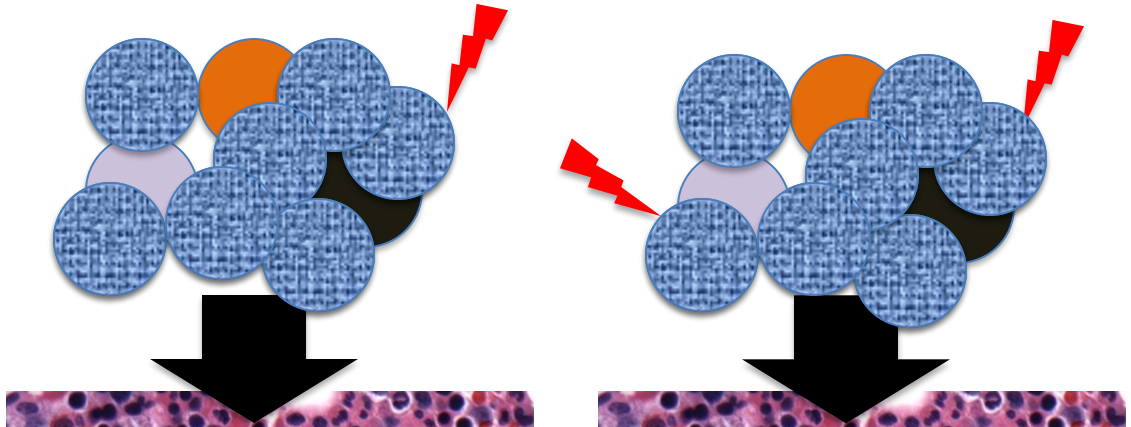
Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults

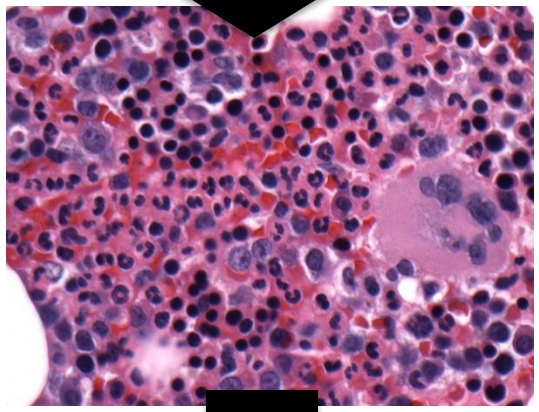
Andrew L. Young[1,2], Grant A. Challen[3], Brenda M. Birmann[4] & Todd E. Druley[1,2]

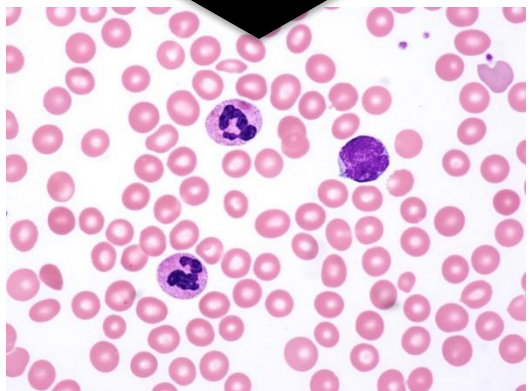


Buscarlet M et al. Blood 2017; 130:753, Young AL et al. Nat Commun 2016, Jaiswal S et al. NEJM 2014; 371:2488, Steensma D et al. Blood 2015; 126:9

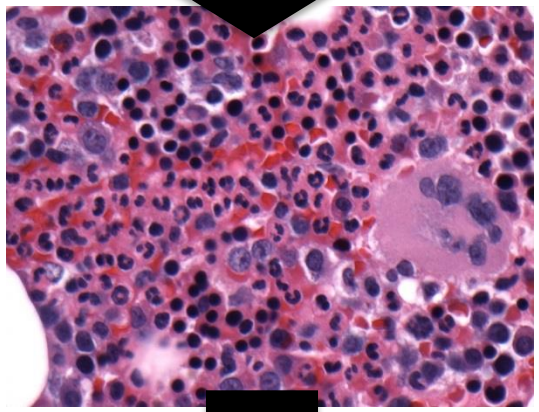
10,000 stem cells

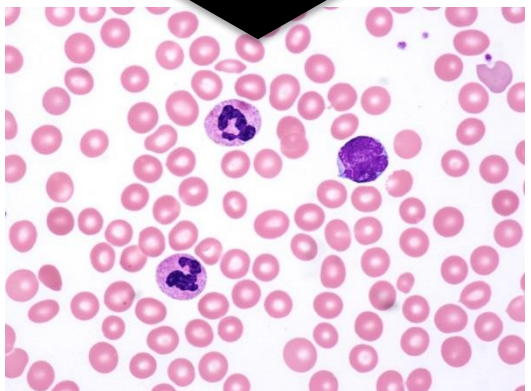




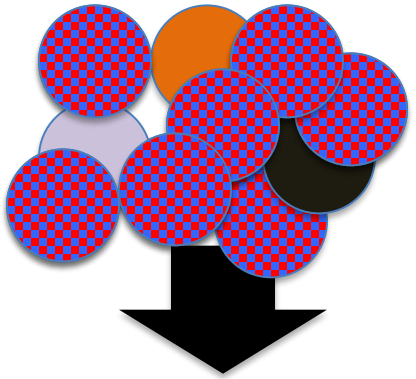


Clonal hematopoiesis





Clonal abnormal hematopoiesis



Altered appearance of marrow cells

Altered appearance and behavior of blood cells

Myeloid neoplasia

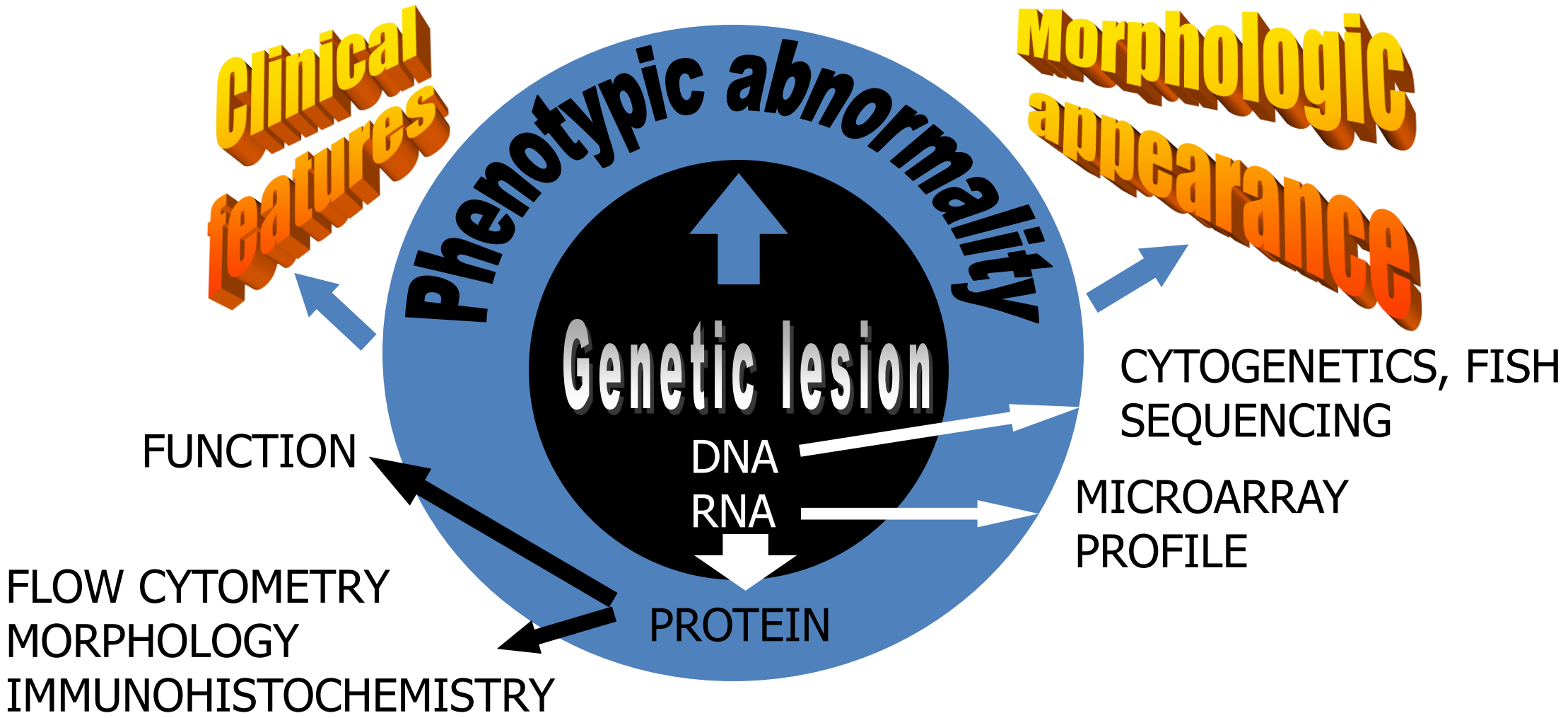
Organization of 2016 WHO Classification

MPN	Myeloproliferative neoplasms
	Mastocytosis
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MDS	Myelodysplastic syndromes
	Myeloid neoplasms with germline predisposition
MLN Eo	Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, *FGFR1* or *PCM1-JAK2*
AML	Acute myeloid leukemia
BPDCN	Blastic plasmacytoid dendritic cell neoplasm

Why are myeloid neoplasms so diverse in appearance and behavior?

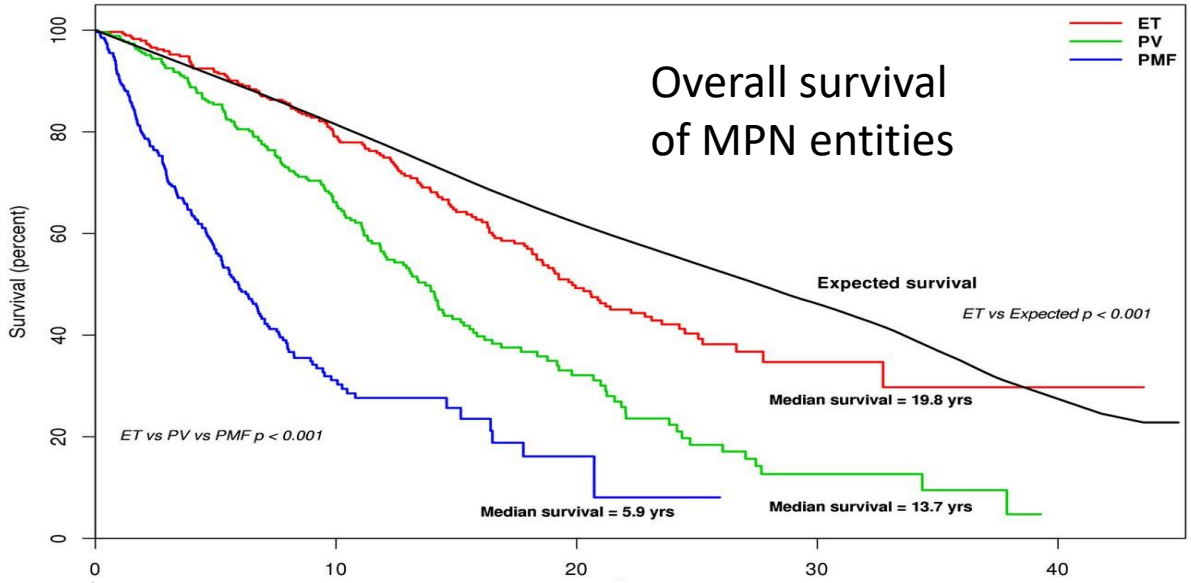
- Different portfolios of mutations
  - Multiple mutations display complex interactions
- Epigenetic changes altering gene expression
- Response of the neoplastic clone to the specific marrow microenvironment
  - Benign and malignant hematopoietic cells interact extensively with marrow stromal cells
  - Inflammatory cells
  - Influence of age and genetics of host

Evaluation of the disease at multiple levels maximizes our ability to understand it

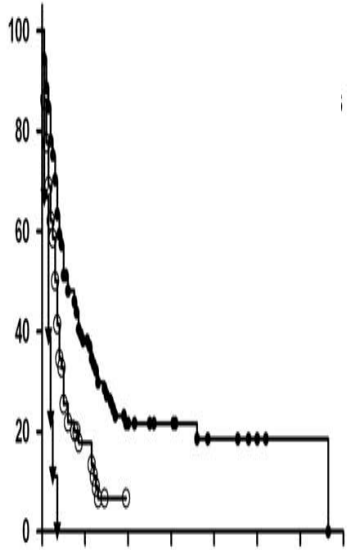


Why do we need to identify different types of myeloid neoplasms?

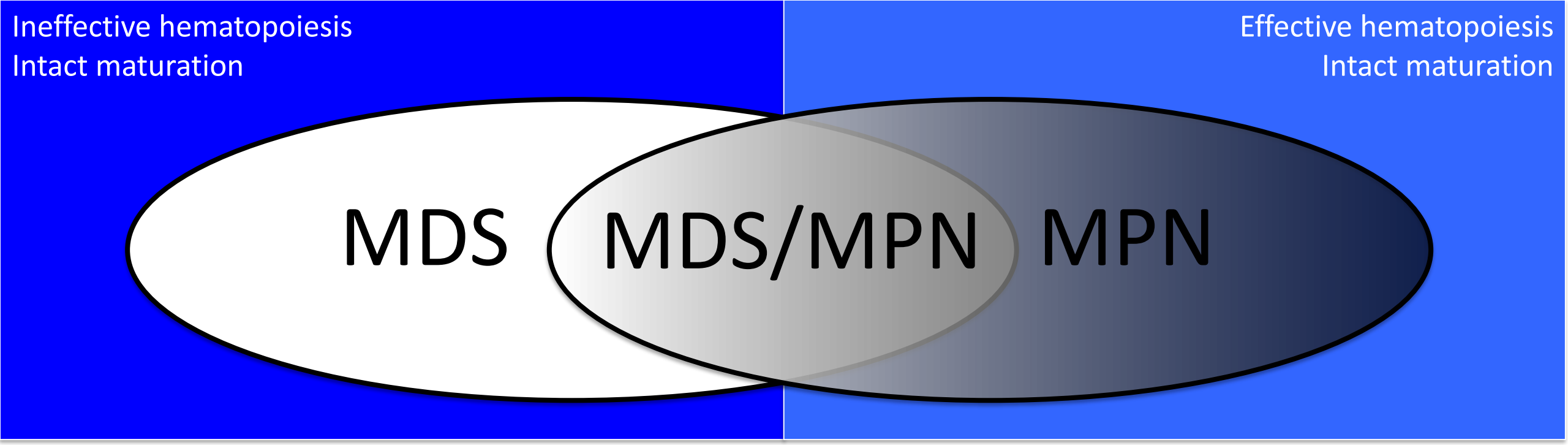
- Alert clinician to expected clinical problems that will arise during disease course
- Predict patterns of disease progression
- Identify therapeutic responsiveness
  - Responsiveness to ‘generic’ therapies
  - Sensitivity to specific targeted therapies
- Predict patient survival



Overall survival of MPN entities

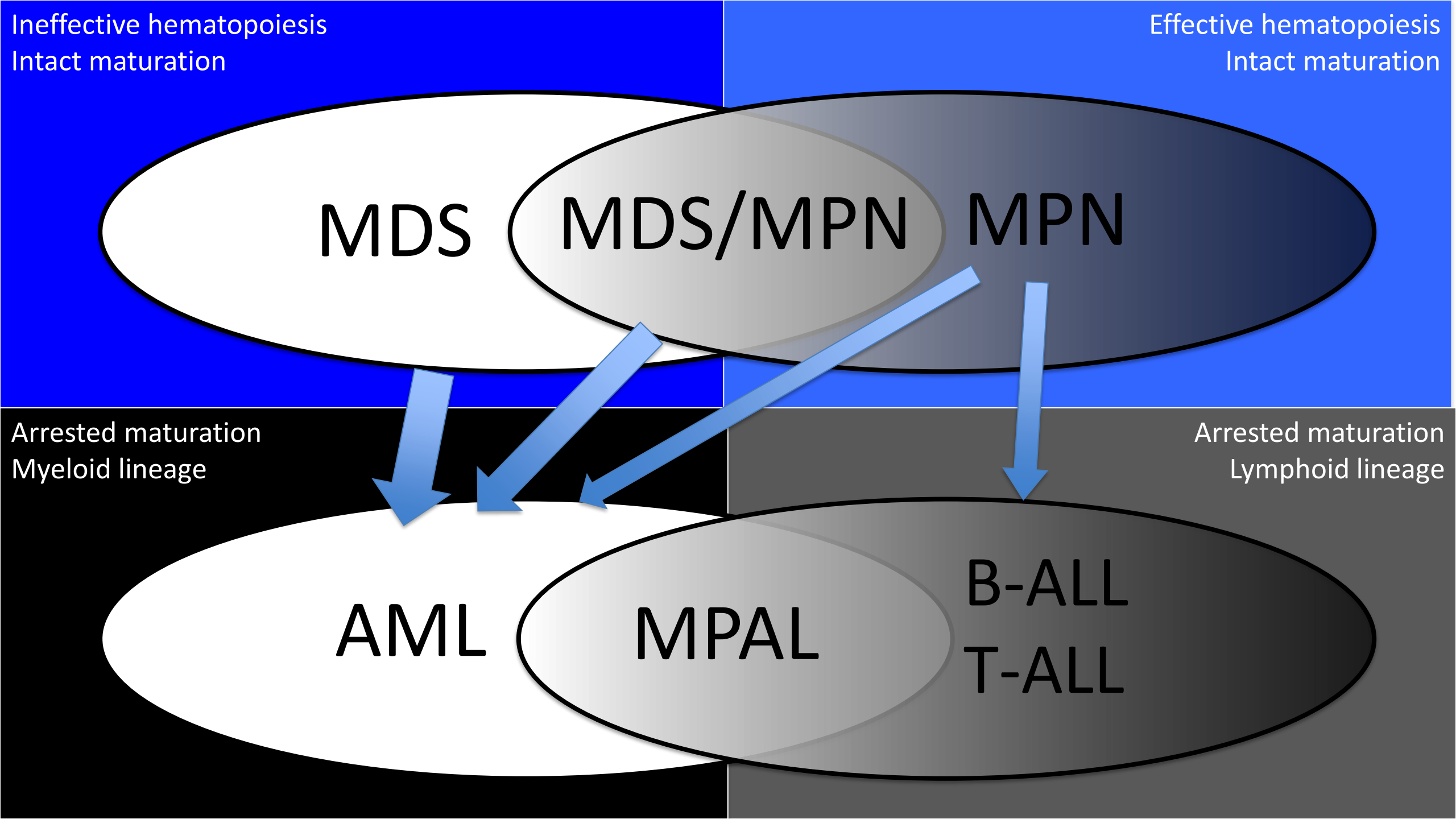


Overall survival of aggressive AML entities



- *Cytopenias*
- *Dysplastic morphology*
- *Altered cell function*
- *No organomegaly*

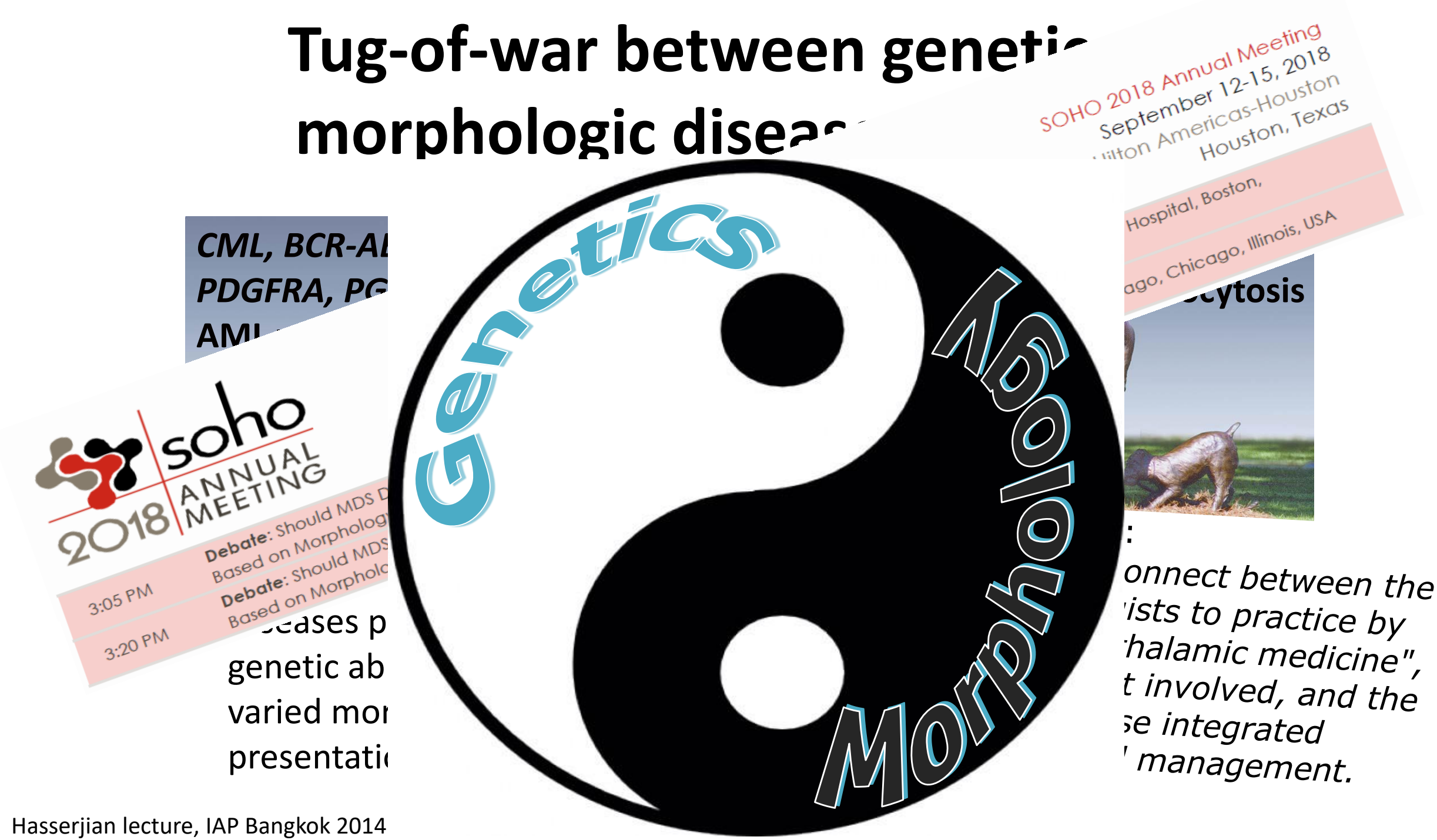
- *Elevated counts*
- *Non-dysplastic morphology*
- *Normal cell function*
- *Often splenomegaly*


Ineffective hematopoiesis
Intact maturation
Effective hematopoiesis
Intact maturation
MDS
MDS/MPN
MPN
Arrested maturation
Myeloid lineage
Arrested maturation
Lymphoid lineage
AML
MPAL
B-ALL
T-ALL

The role of the diagnostic team

- Interrogate the disease morphology/immunophenotype and biologic behavior, at the current time point and in the context of prior history and/or treatment
- Interrogate for an underlying genetic lesion
  - Characterize the portfolio of driver mutations
  - Attempt to create a model mutation hierarchy (based on VAF, patient history, and experience with disease)
- Synthesize the underlying genetic lesion(s) with the ‘face’ of the disease to arrive at a clinically actionable diagnosis
  - Primary diagnosis is important to set a starting point
  - Understanding changes in followup samples is critical in guiding clinical care

Tug-of-war between genetic
morphologic disease



genetic ab
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presentati

Hasserjian lecture, IAP Bangkok 2014

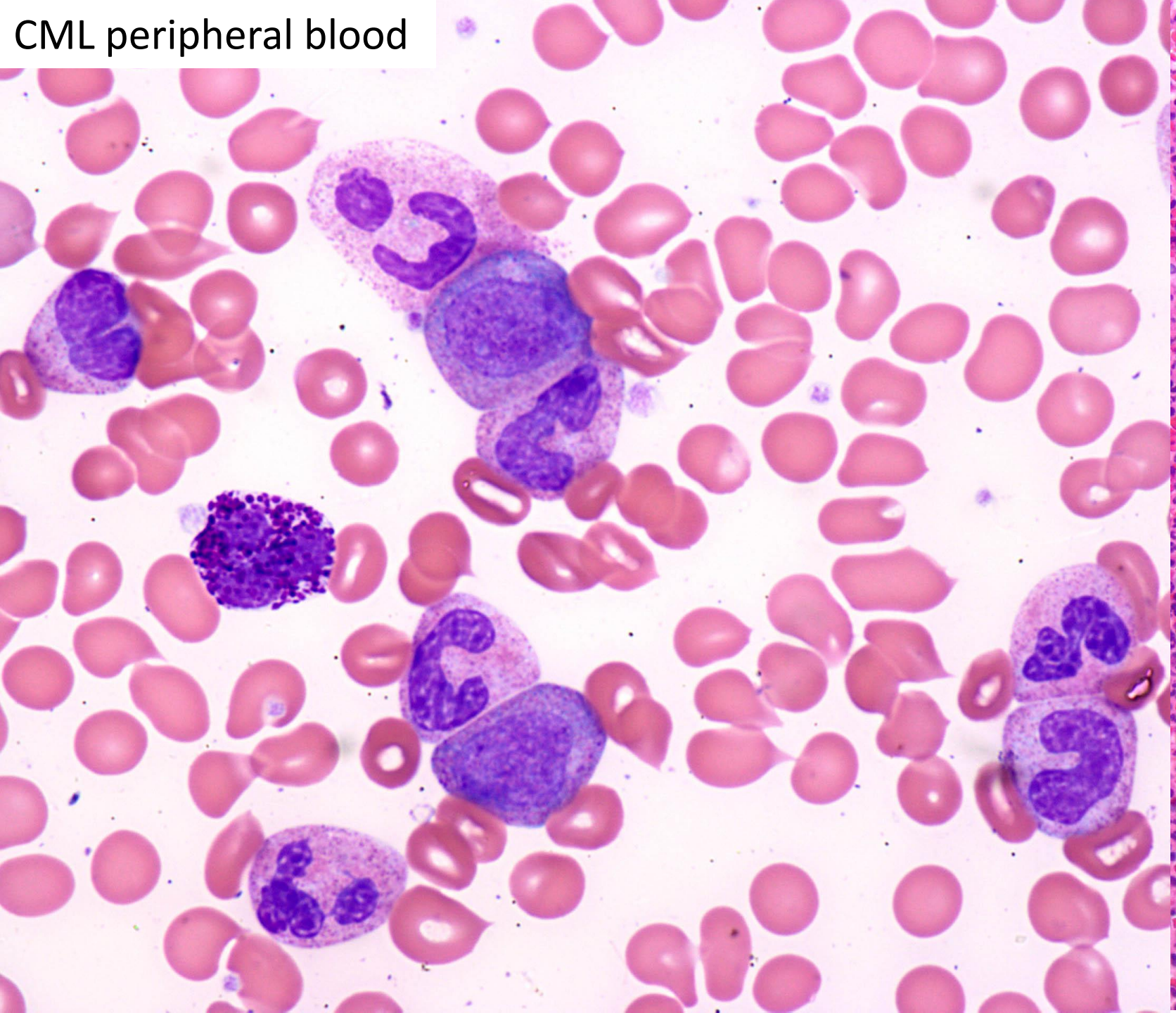
Myeloproliferative neoplasms

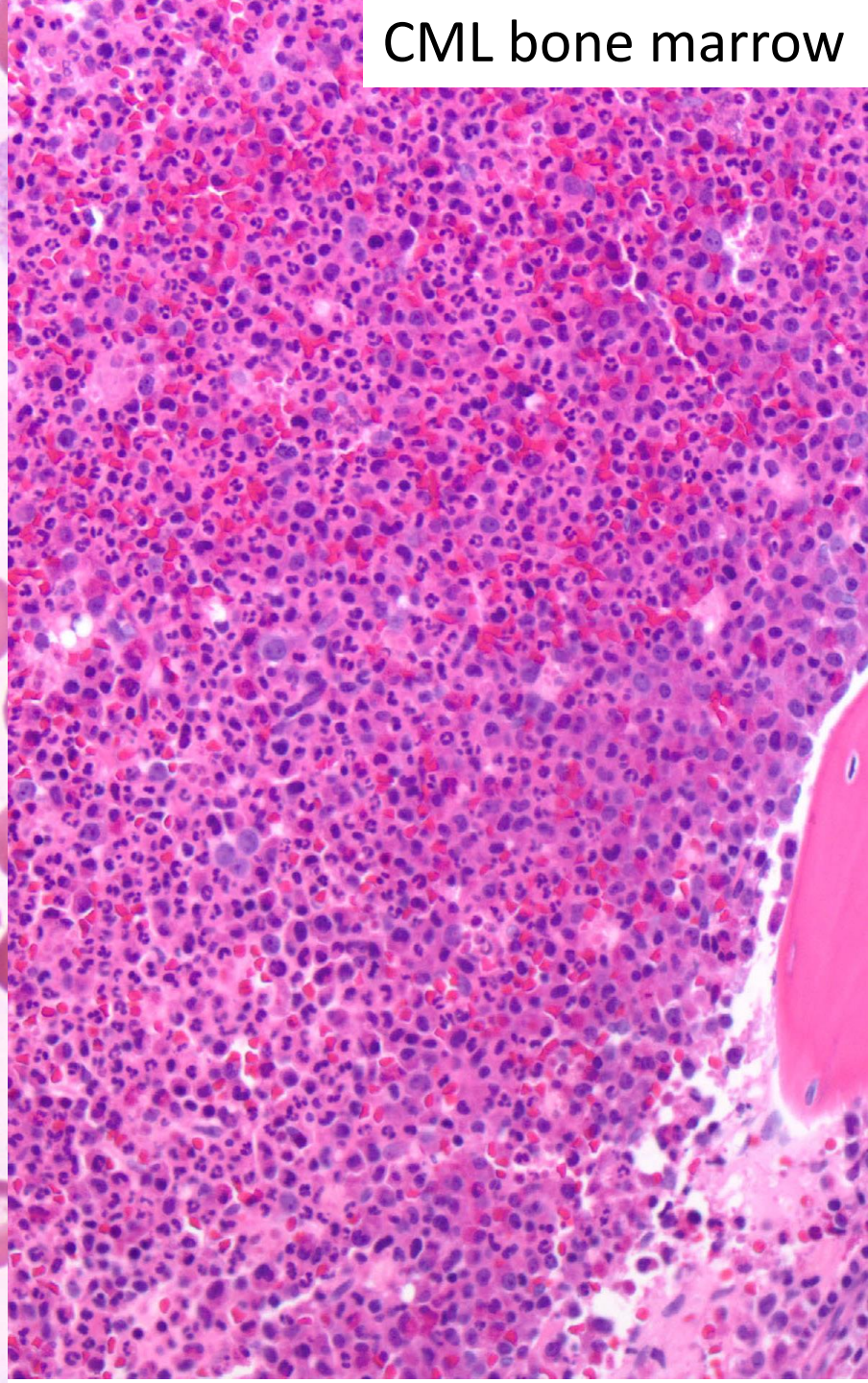
- Hematopoietic stem cell neoplasms characterized by effective/overexuberant hematopoiesis
  - Manifest as overproduction of one or more of the hematopoietic cell lineages with increased blood counts and often organomegaly
- Genetic lesion typically causes a constitutive tyrosine kinase activation

Chronic myeloid leukemia (CML): the early 20th century

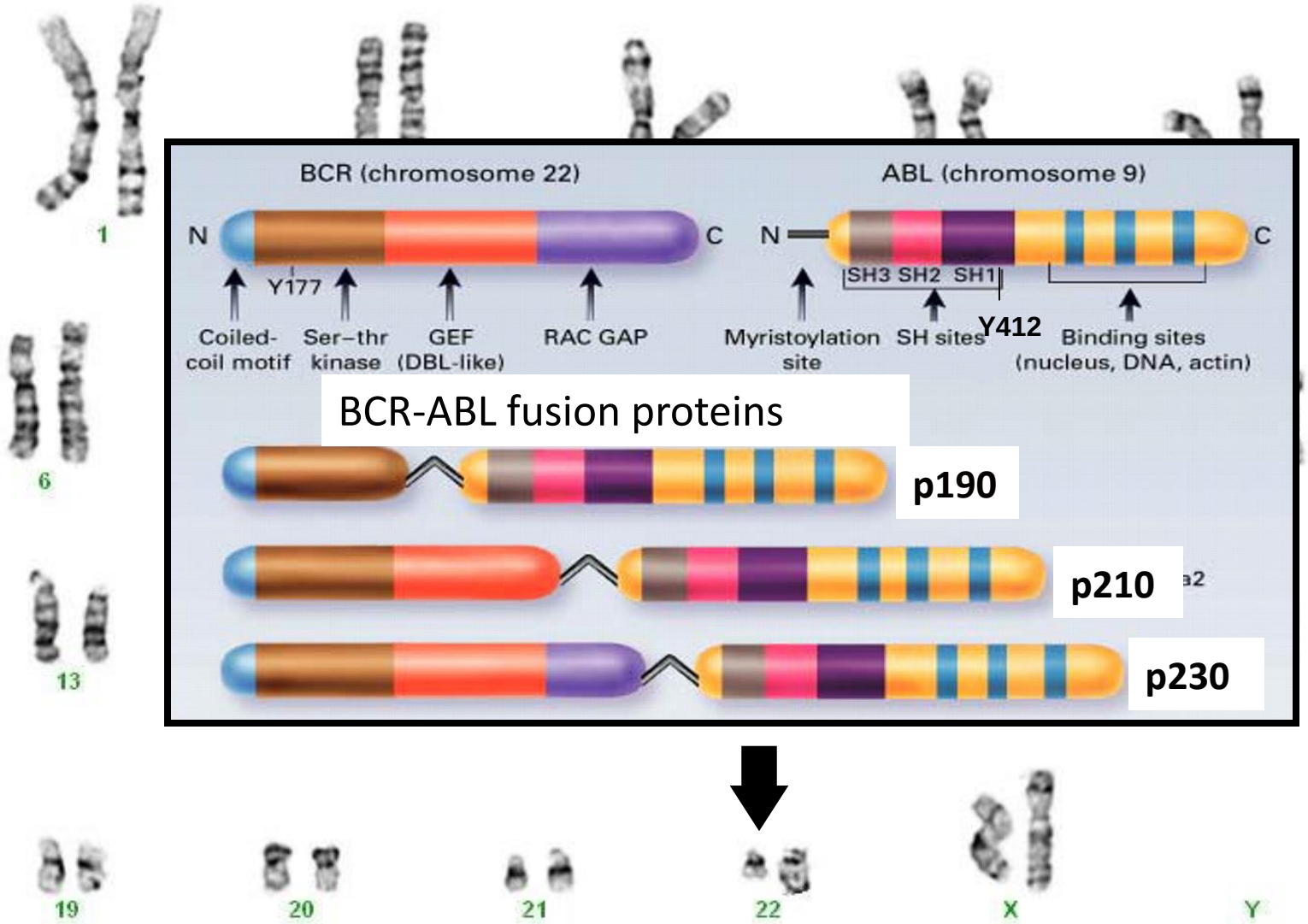
- Defined by morphology
  - Marked leukocytosis with neutrophils, immature myeloid forms, basophils in marrow and blood
  - 'Philadelphia-positive' and 'Philadelphia-negative' subtypes recognized
- Inexorable progression to blast phase and eventual patient death
  - Bone marrow transplant offered only cure

Bela Bartok (1881-1945)

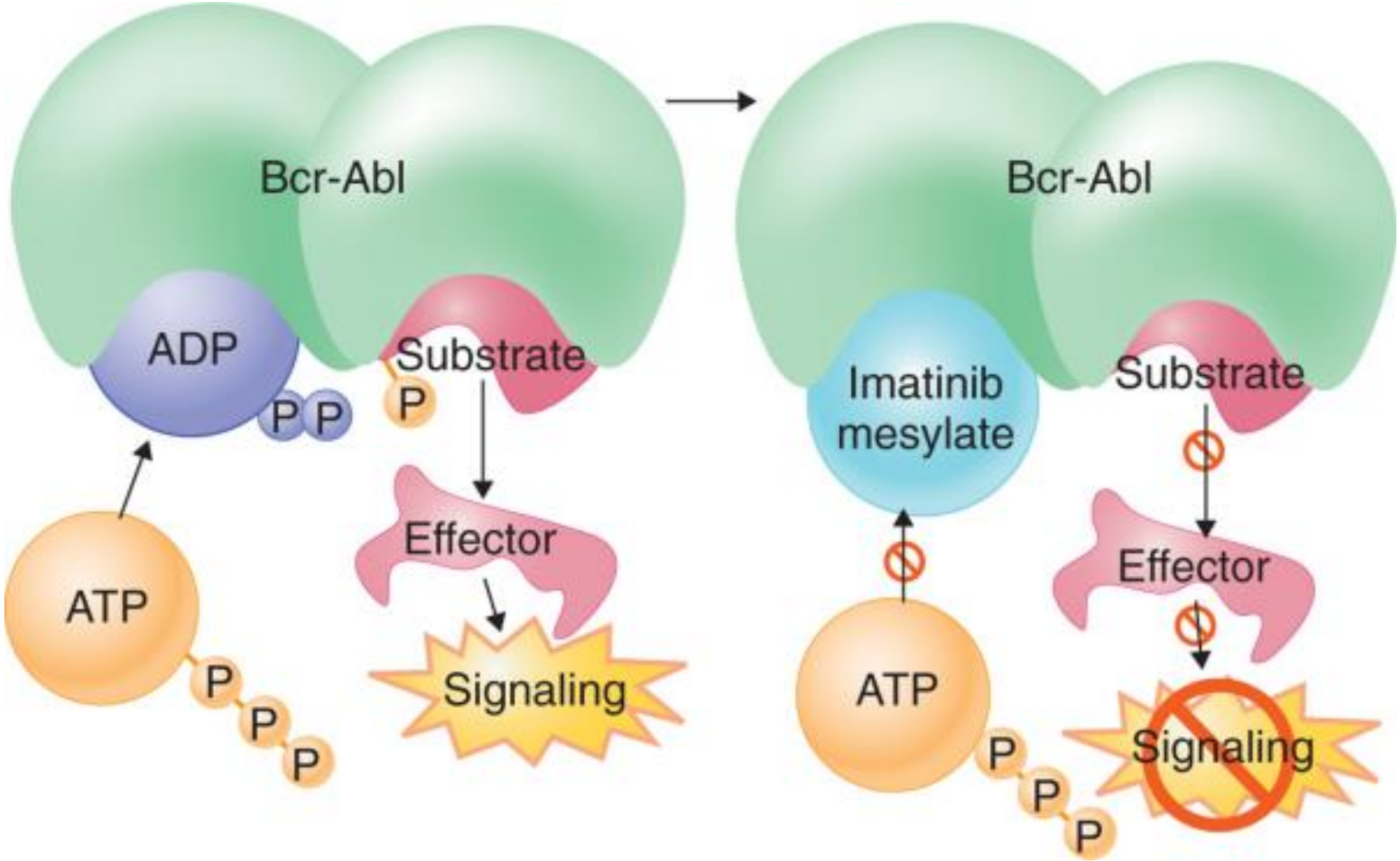

CML peripheral blood


CML bone marrow

Philadelphia chromosome: the genetic basis of CML



Tyrosine kinase inhibitors



Faderl S et al. N Engl J Med 1999;341:164-172, Goldman J and Melo J. N Engl J Med 2003;349:1451-1464

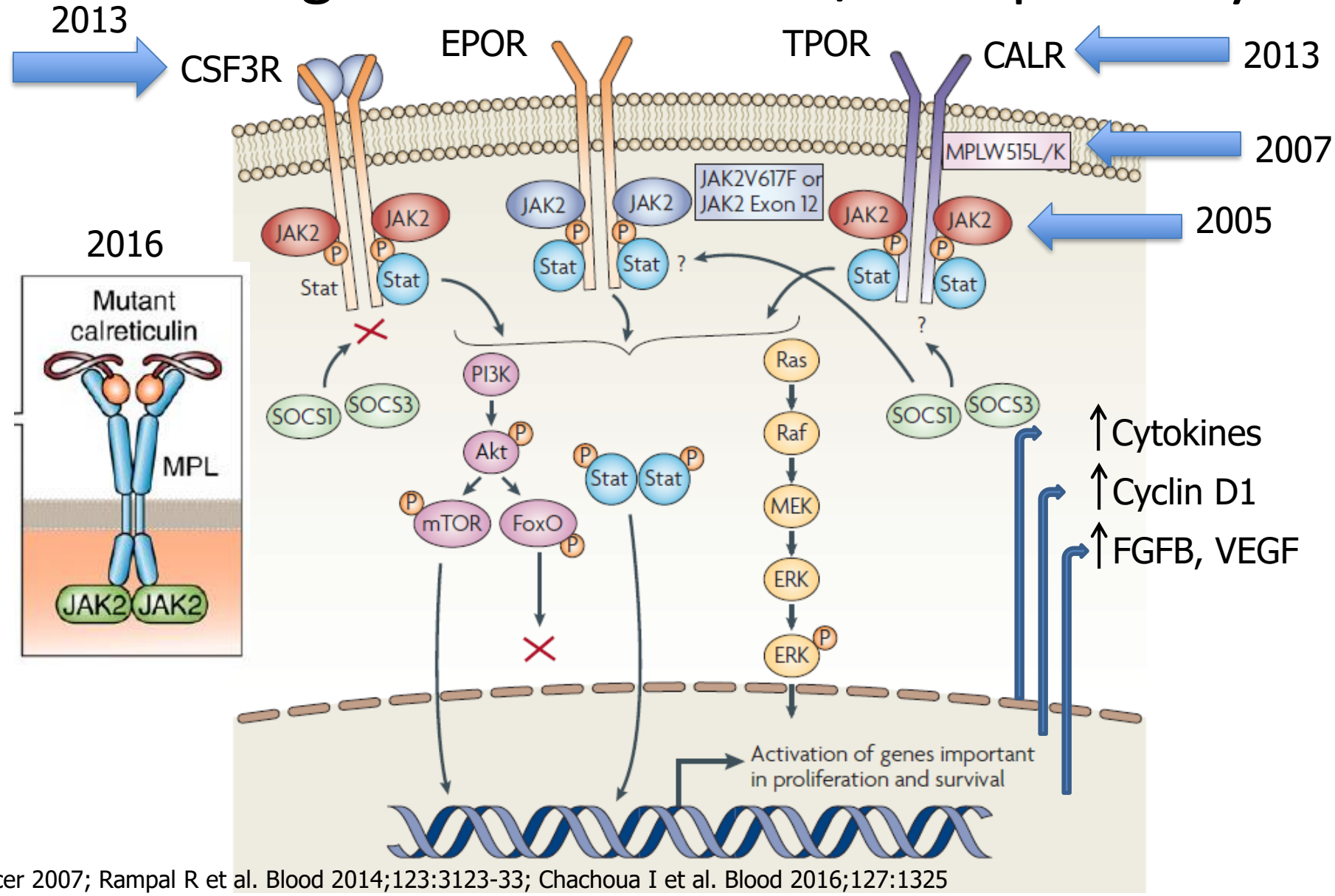
CML in the 21st century

- Defined by *BCR-ABL1* fusion
- Treated very effectively with tyrosine kinase inhibitors (TKI) that target BCR-ABL1 fusion protein
  - Disease progression no longer inevitable
  - Patterns of disease evolution are closely linked to responsiveness versus resistance to TKI therapy

CML is a posterchild for a genetically-defined disease

- Genetic abnormality, not morphology, defines disease behavior
  - 'Philadelphia-chromosome-negative' CML resembles CML morphologically, but has much poorer outcome: no longer considered as part of CML
  - Morphologic variants of CML mimicking other diseases behave like classic CML
- Genetic landscape is relatively simple, with no or few cooperating genetic events
  - *BCR-ABL1* is both necessary and sufficient to create CML
- Targeted therapy that neutralizes the oncoprotein effectively cures the disease
- Diagnosis and monitoring of disease rely mainly on genetics

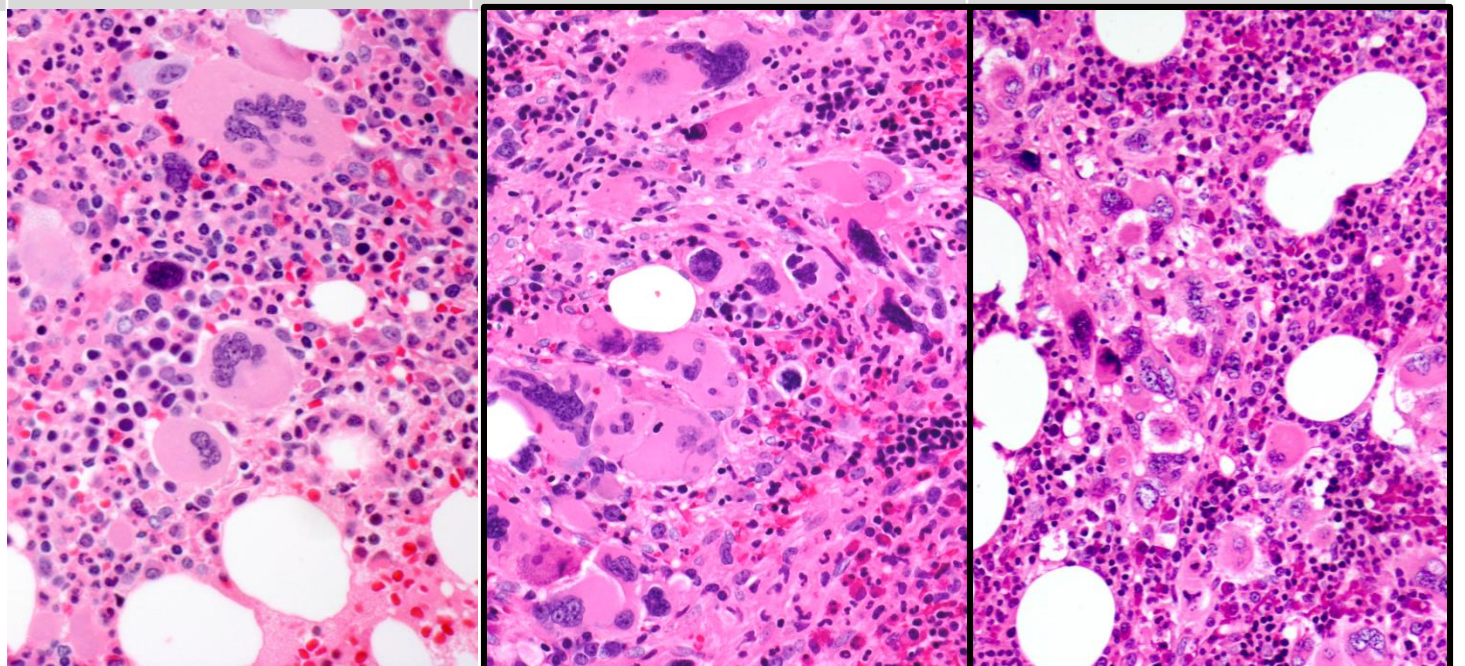
JAK2-associated MPN: Deregulation of the JAK/STAT pathway



Nature Reviews Cancer 2007; Rampal R et al. Blood 2014;123:3123-33; Chachoua I et al. Blood 2016;127:1325

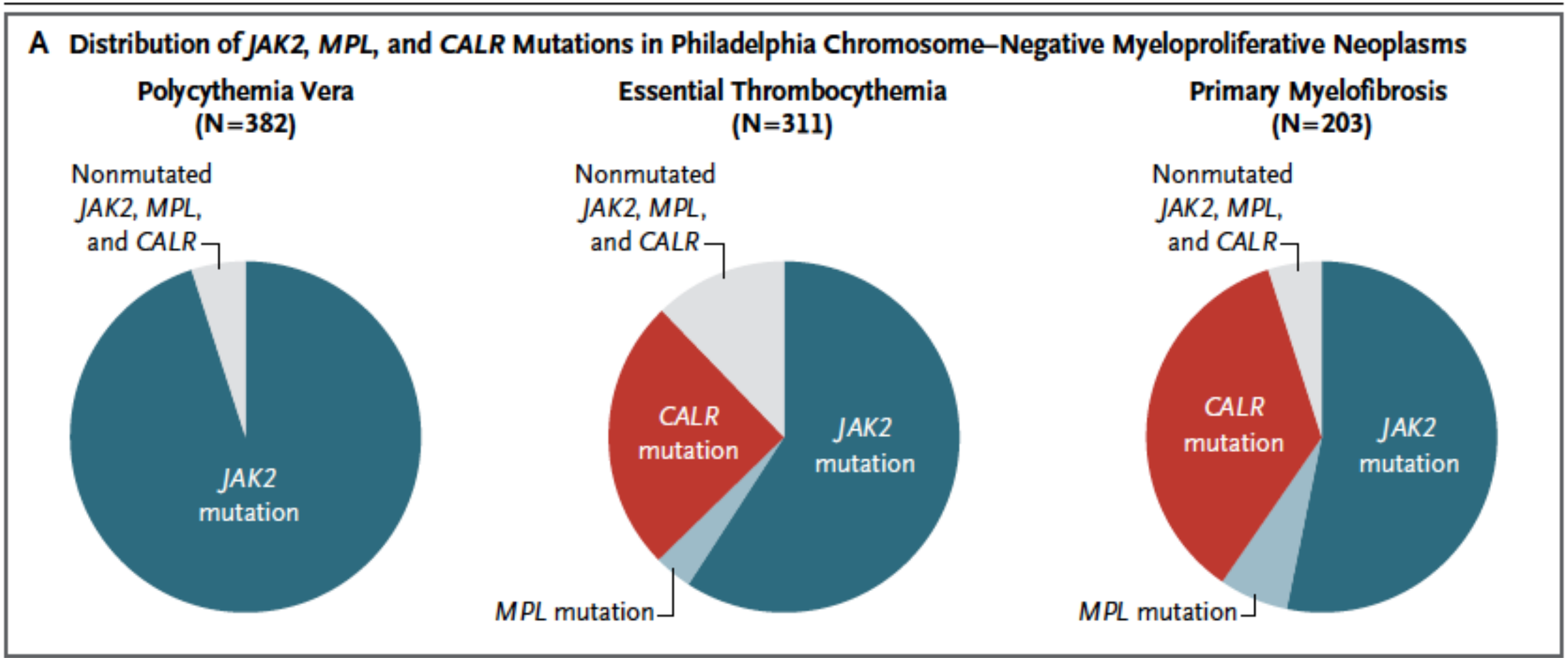
	Essential thromocythemia	Primary myelofibrosis	Polycythemia vera
Counts	Platelets ≥450 x 10^9/L	Variable	Hemoglobin >16.5/16.0 g/dL
Mutations	*JAK2, CALR*, or *MPL*	*JAK2, CALR*, or *MPL*	*JAK2*
Morphology	Normal cellularity Normal M:E ratio	↑ Cellularity Normal or ↓ M:E ratio	↑ Cellularity ↑ M:E ratio
Reticulin	Not increased	Progressive increase	May be increased
Clinical features	Mild thrombosis or hemorrhage risk	Splenomegaly, fatigue, systemic symptoms	Significant thrombosis risk

Bone marrow morphology

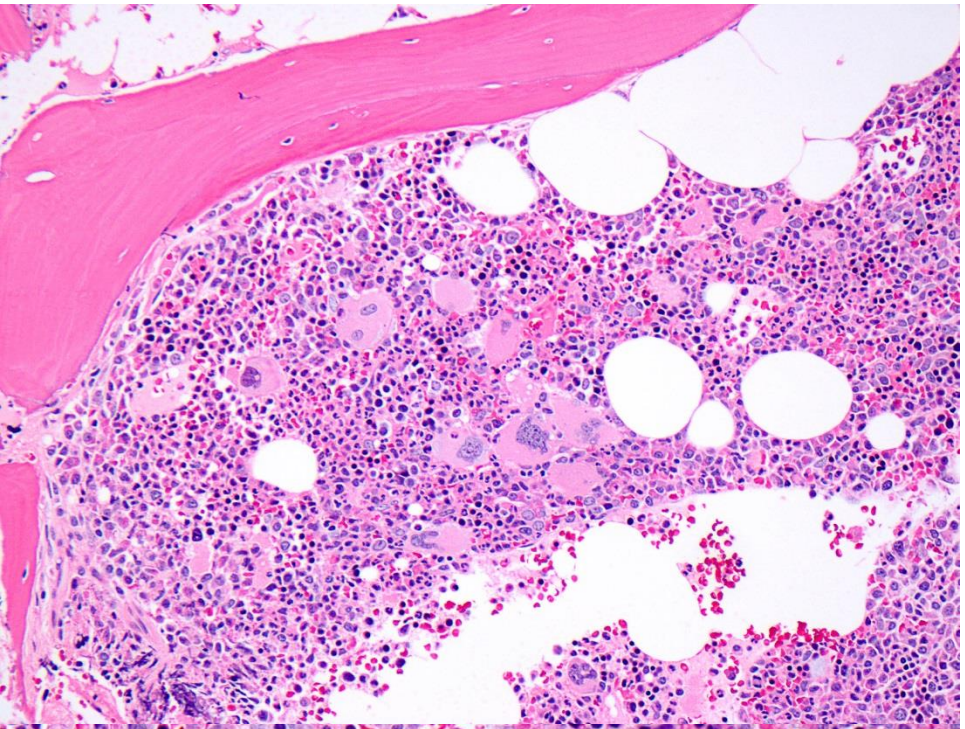


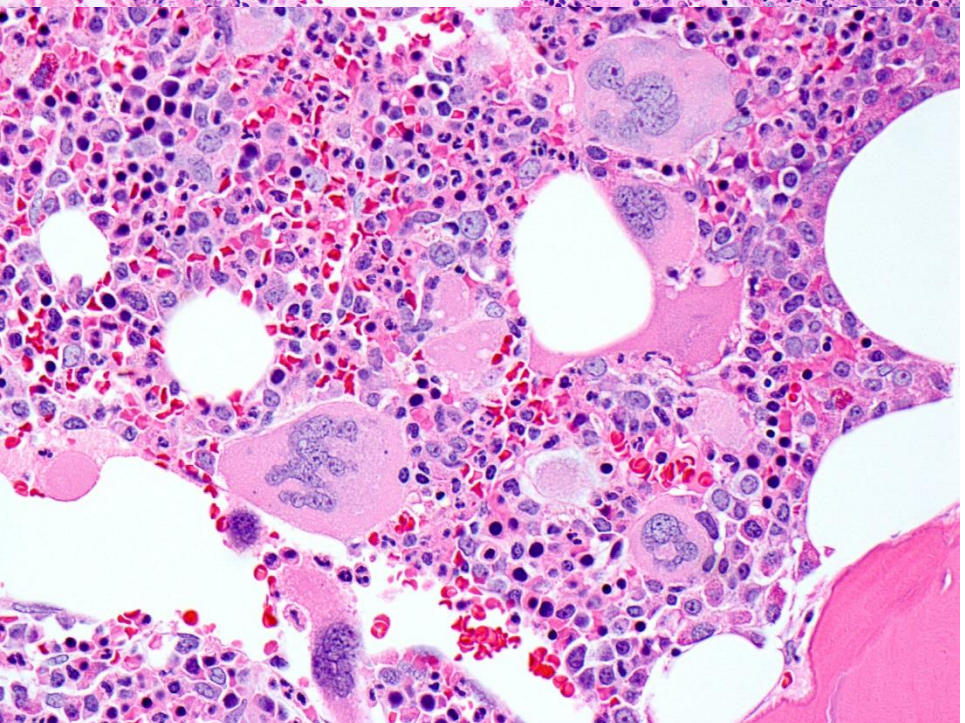
Courtesy of Dr. Olga Pozdnyakova, BWH

Distribution of mutation types in the non-CML MPN



Klampfl et al. NEJM 2013;379:2379



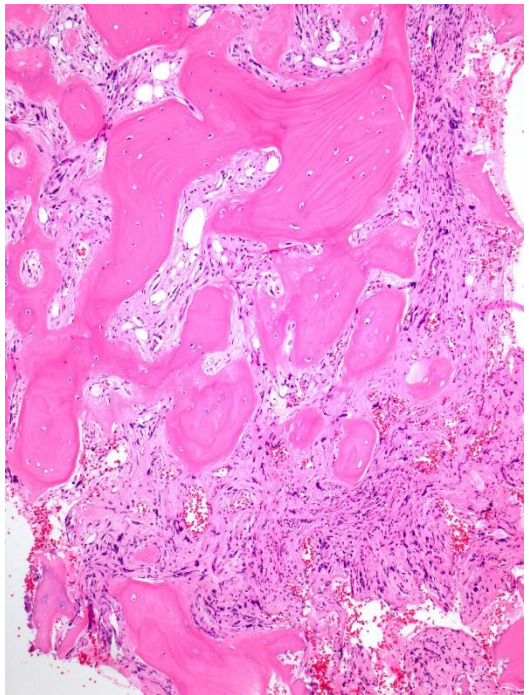


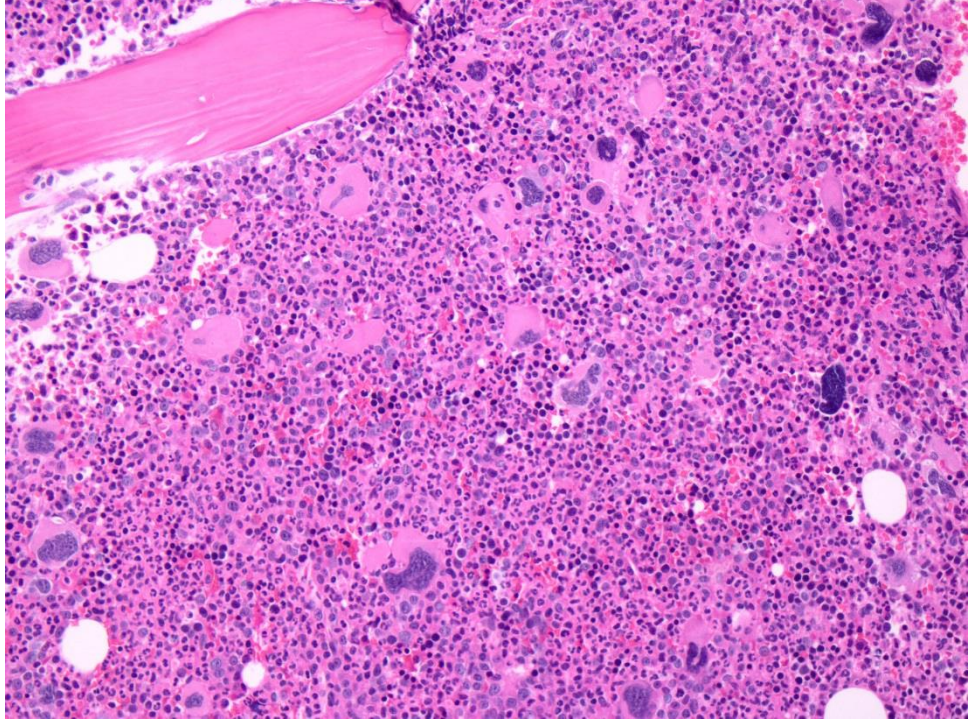
60-ish year old patients

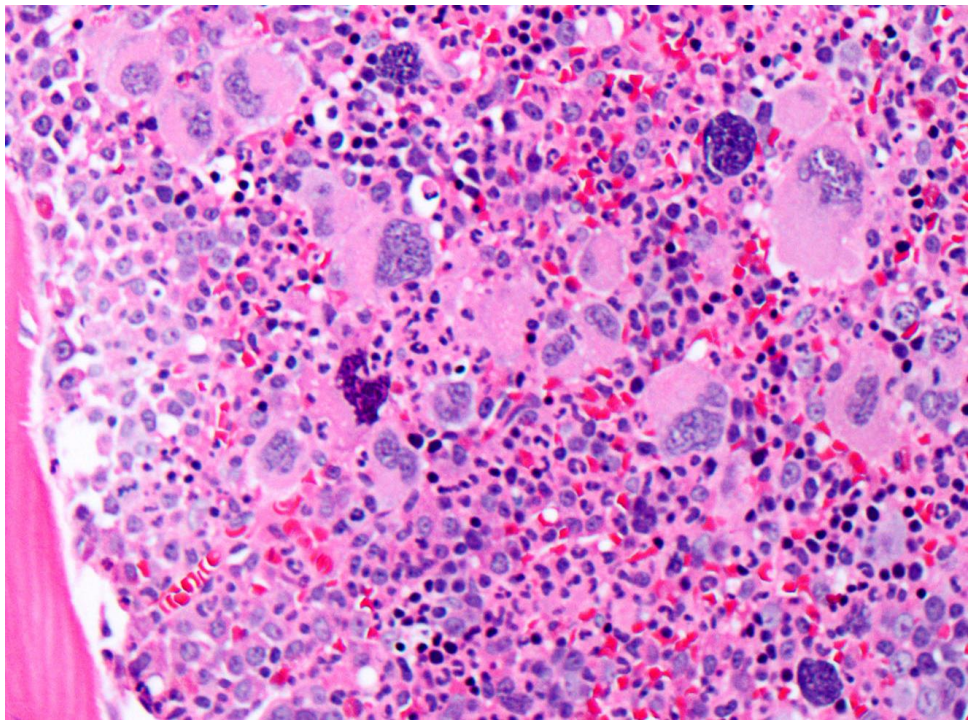
Isolated thrombocytosis

Solitary JAK2 mutation at similar VAF

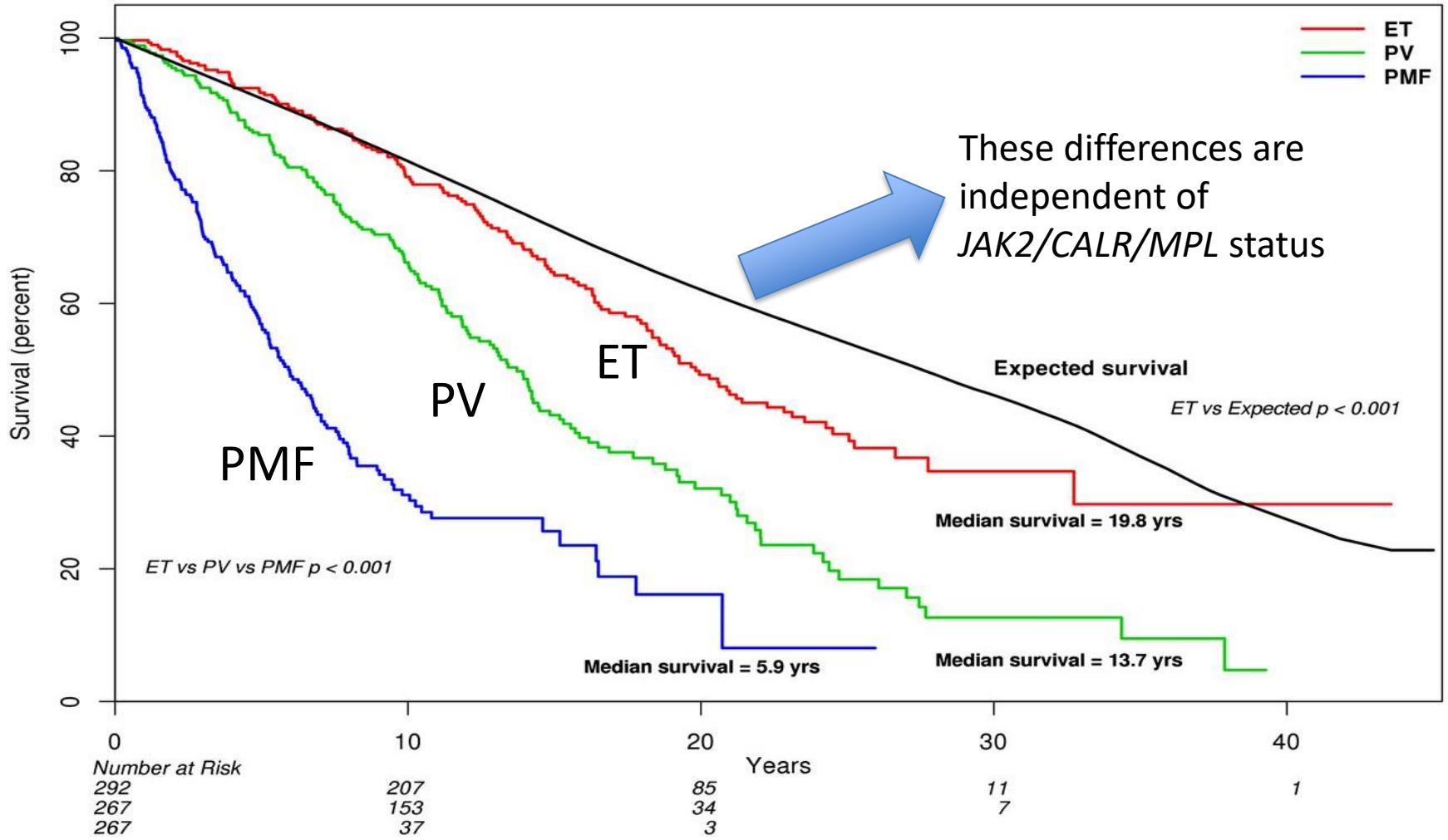
?







Importance of accurate diagnosis of MPN to inform prognosis (and guide therapy)



Tefferi et al. Blood 2014;124:2507

Courtesy of Hans-Michael Kvasnicka, University Hospital, Frankfurt

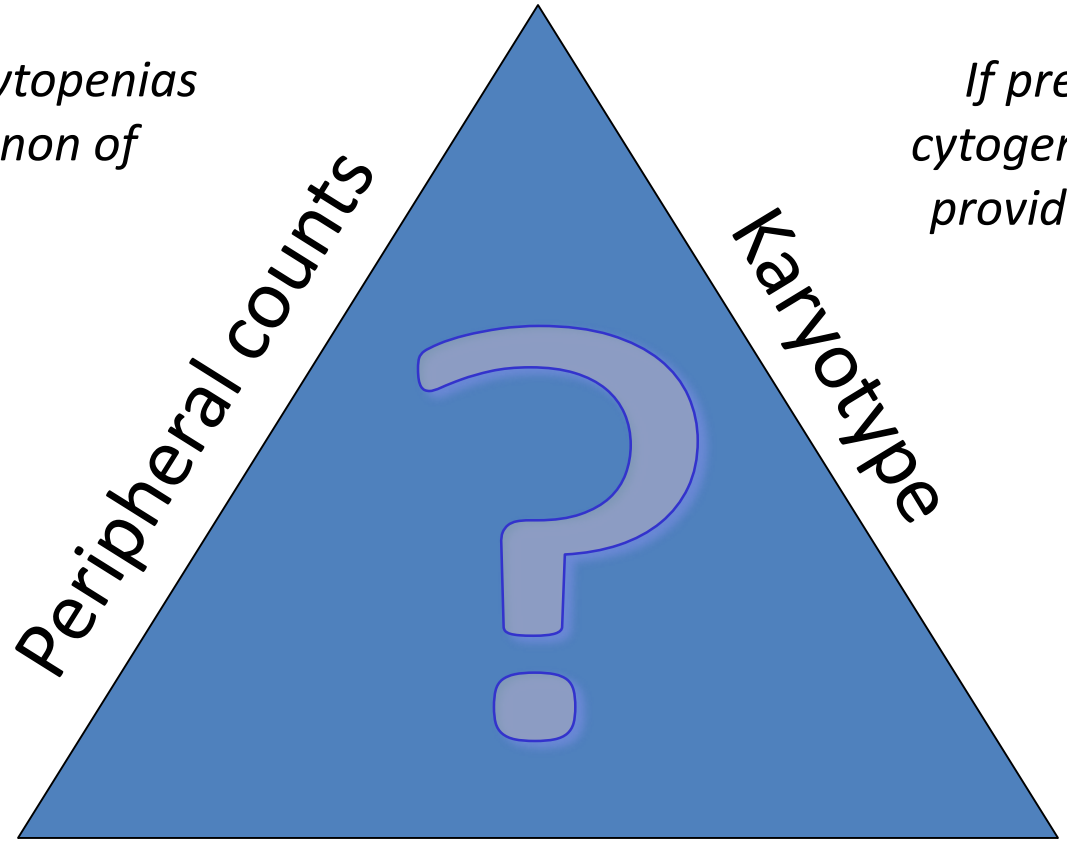
Myelodysplastic syndromes

- Clonal hematopoietic stem cell neoplasms with *ineffective* hematopoiesis and intact maturation
  - Peripheral blood cytopenias
  - Cytologic dysplasia of hematopoietic elements
- Varying propensity to develop maturation arrest in hematopoietic cells, with accumulation of blasts and progression to AML

Components of MDS diagnosis and classification according to 2016

Unexplained cytopenias are a sine qua non of MDS

Prognostic



If present, MDS-specific cytogenetic abnormalities provide proof of clonality

Prognostic

Dysplasia (≥10% of cells) and/or ↑blasts

Dysplasia is a sine qua non of MDS

Both degree of dysplasia and % of blasts are prognostic

Not all dysplasias are created equal. . .

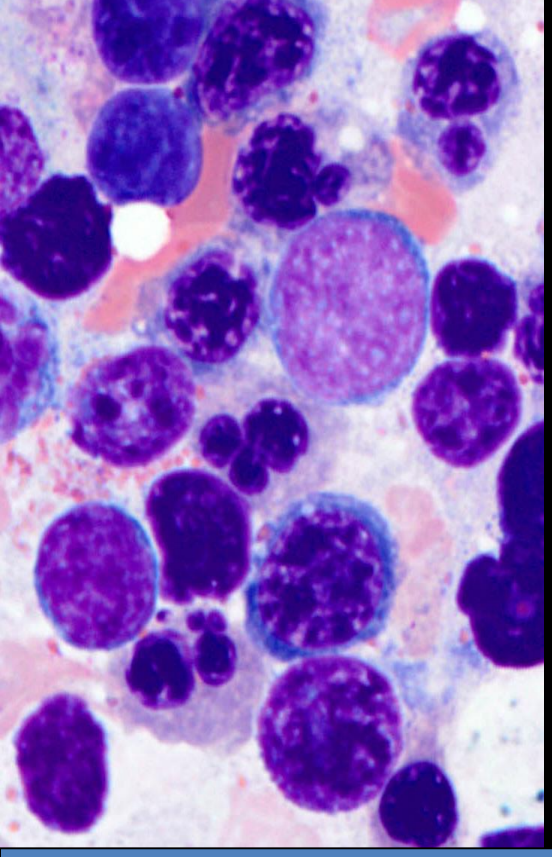
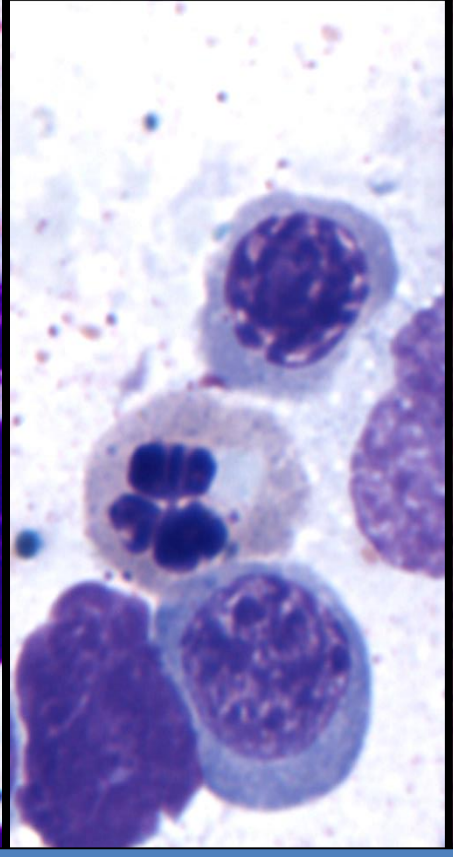
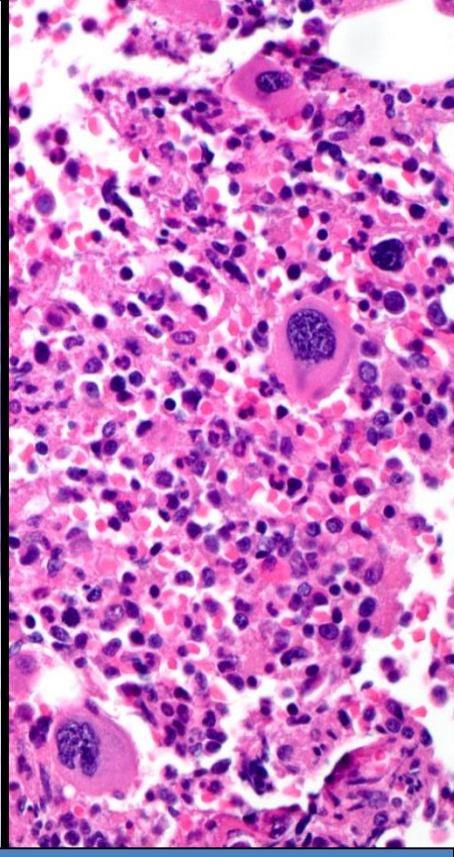
Morphological abnormalities[a]	*Cutoff values*[b]	*AUC*	*Cohen's K-coefficient (inter-observer agreement)*[c]
Erythroid lineage			
Megaloblastoid changes	>5%	0.814, $P<0.001$	0.83
Bi- or multinuclearity	>3%	0.679, $P<0.001$	0.87
	>5%	0.698, $P<0.001$	
Nuclear lobulation or irregular contours	>3%	0.674, $P<0.001$	0.84
Pyknosis	>5%	0.677, $P<0.001$	0.81
Cytoplasmic fraying	⩾7%	0.602, $P<0.001$	0.82
Ring sideroblasts	>5%	0.650, $P<0.001$	0.95
	⩾15%	0.719, $P<0.001$	
Ferritin sideroblasts	⩾30%	0.670, $P<0.001$	0.92
Granulocytic lineage			
Myeloblasts	>3%	0.777, $P<0.001$	0.92
	>5%	0.723, $P<0.001$	
Auer rods	⩾1%	0.524, $P=0.001$	0.90
Pseudo Pelger–Hüet anomaly	>3%	0.714, $P<0.001$	0.87
	>5%	0.814, $P<0.001$	
Abnormal nuclear shape	⩾7%	0.700, $P<0.001$	0.86
Neutrophil hypogranulation	>3%	0.791, $P<0.001$	0.81
	>5%	0.821, $P<0.001$	
Megakaryocytic lineage			
Micromegakaryocytes	>5%	0.916, $P<0.001$	0.88
Small binucleated megakaryocytes	>5%	0.845, $P=0.001$	0.81
Megakaryocytes with multiple separated nuclei	>5%	0.750, $P<0.001$	0.84
Hypolobated or monolobar megakaryocytes	>5%	0.646, $P<0.001$	0.86

9% false positive

5% false positive

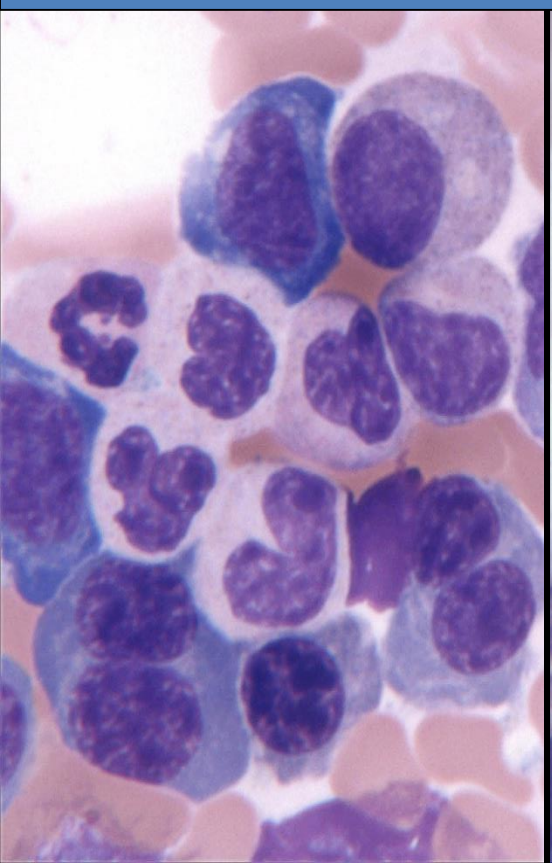
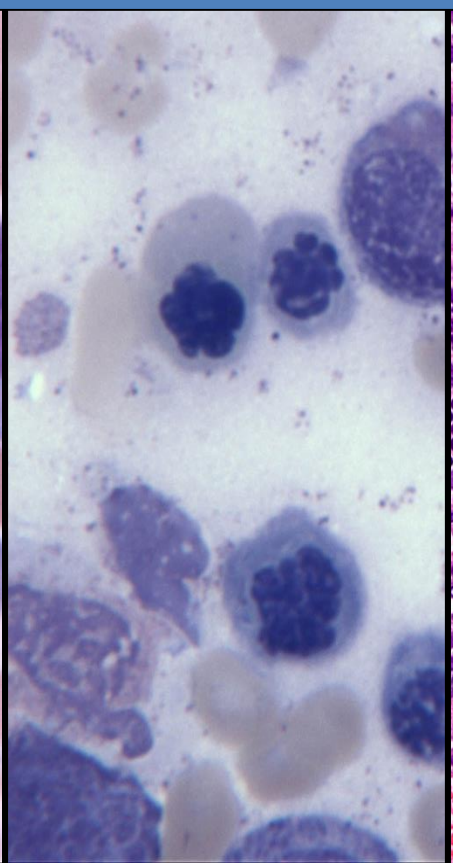
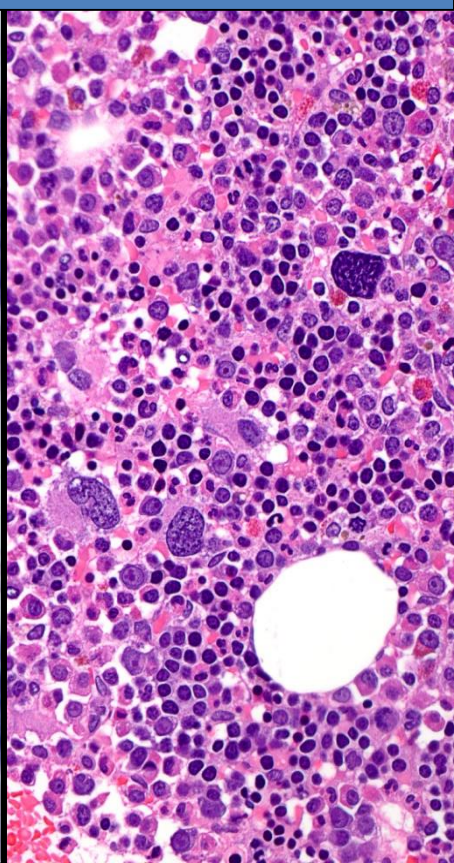
11% false positive

Della Porta MG et al. Leukemia 2015;29:66

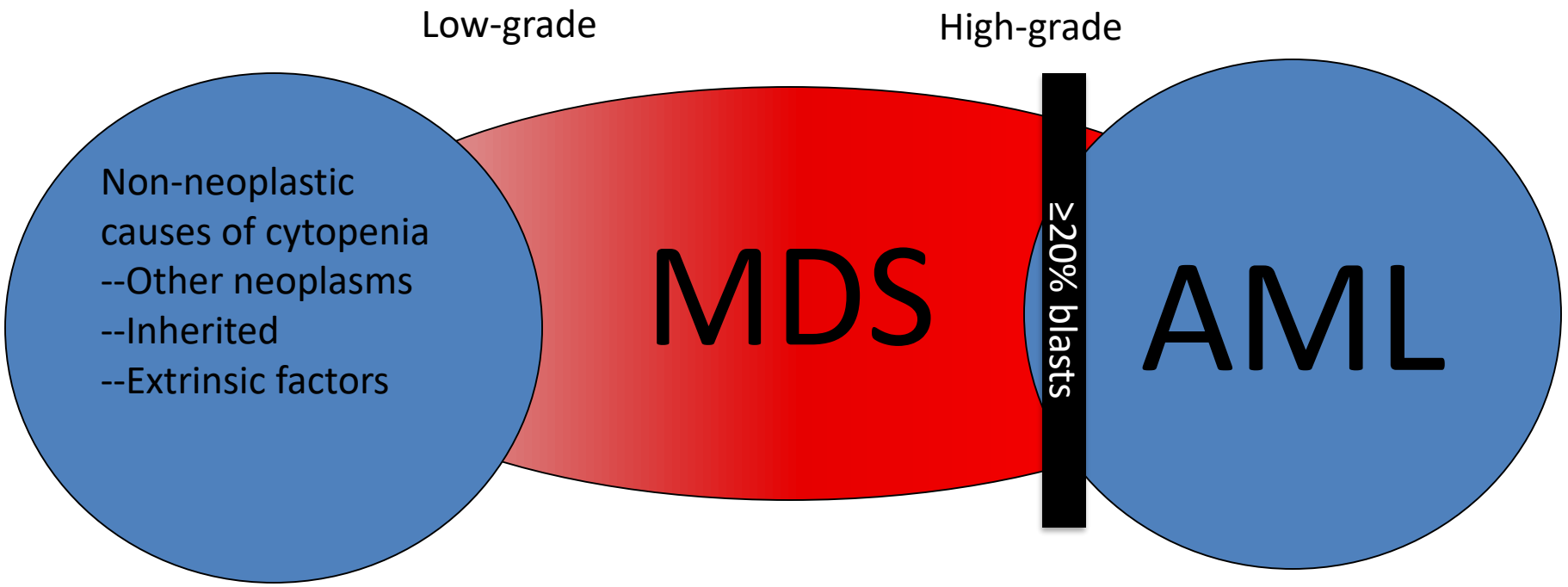




Not MDS

MDS

Challenges in MDS diagnosis



- ***Does the patient have a neoplasm?***
- ***Should the patient be treated for MDS or should another diagnosis be sought?***

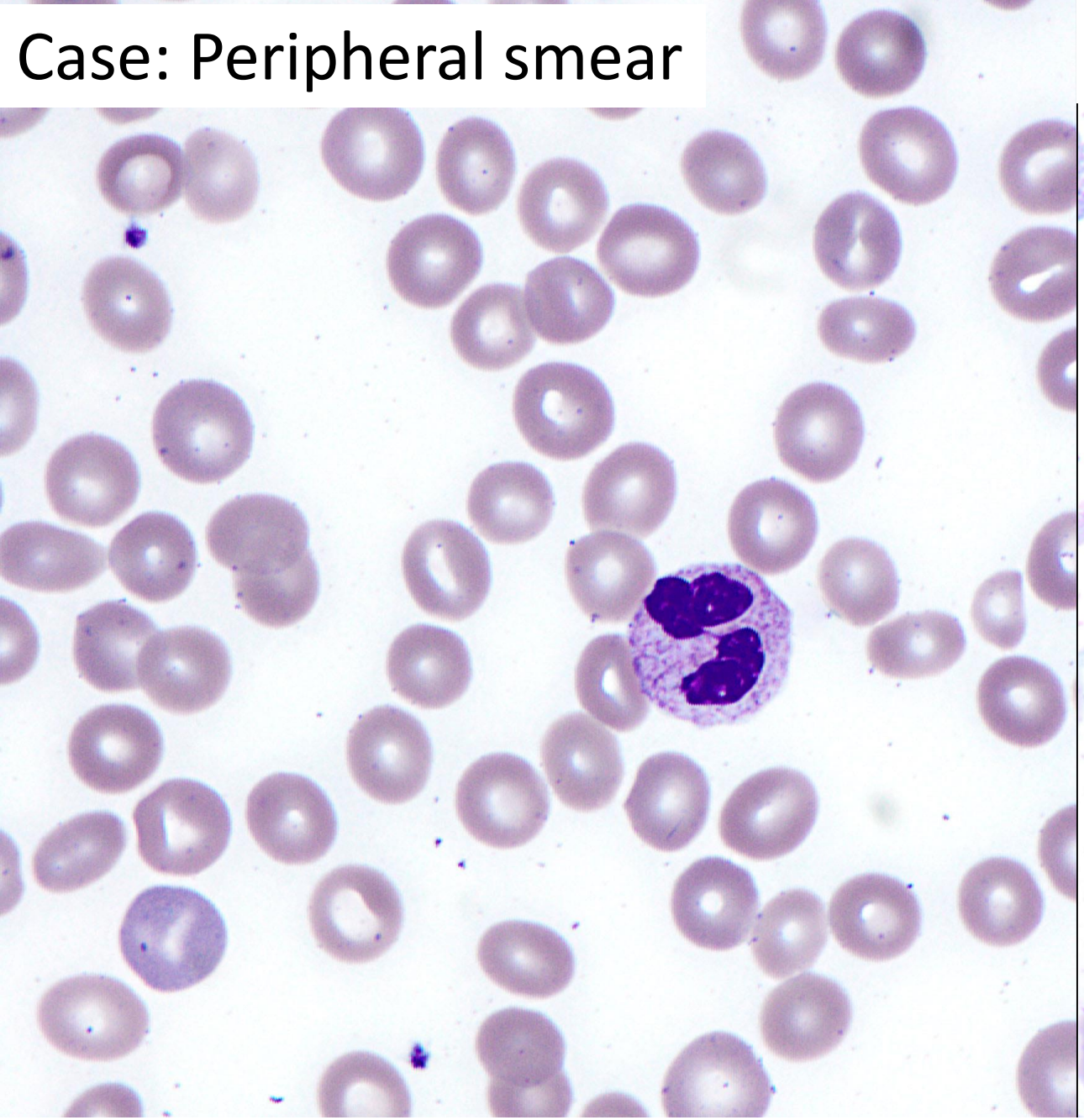
Case

- 74 year-old man presented with anemia and thrombocytopenia discovered on routine blood work
- WBC 4.34 x 10^9/L
  - 52% polys (ANC 2.2 x 10^9/L, 36% lymphs, 11% monos, 1% eos, 0.2 nRBC/100 WBC
- HGB 8.8 g/dL (MCV 112.1 fL)
- PLT 100 x 10^9/L
- Patient is asymptomatic and past medical history is only significant for hypertension

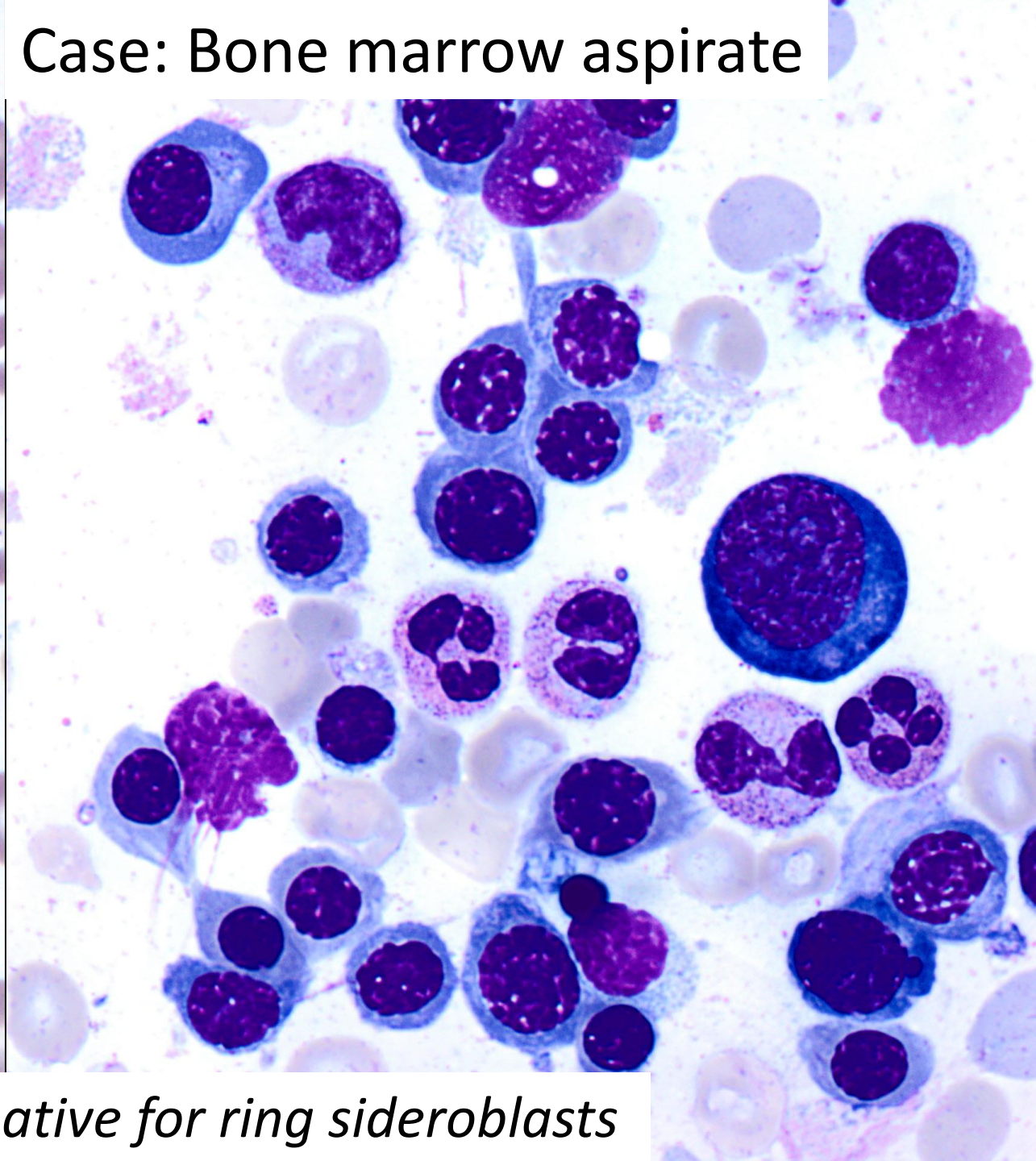
Case

- Bone marrow biopsy and aspirate were performed to evaluate etiology of cytopenias
  - Core biopsy, aspirate and peripheral smear morphology
  - Flow cytometry to evaluate for abnormal lymphoid population
  - Cytogenetics by conventional karyotyping
  - Next-generation sequencing panel

Case: Peripheral smear

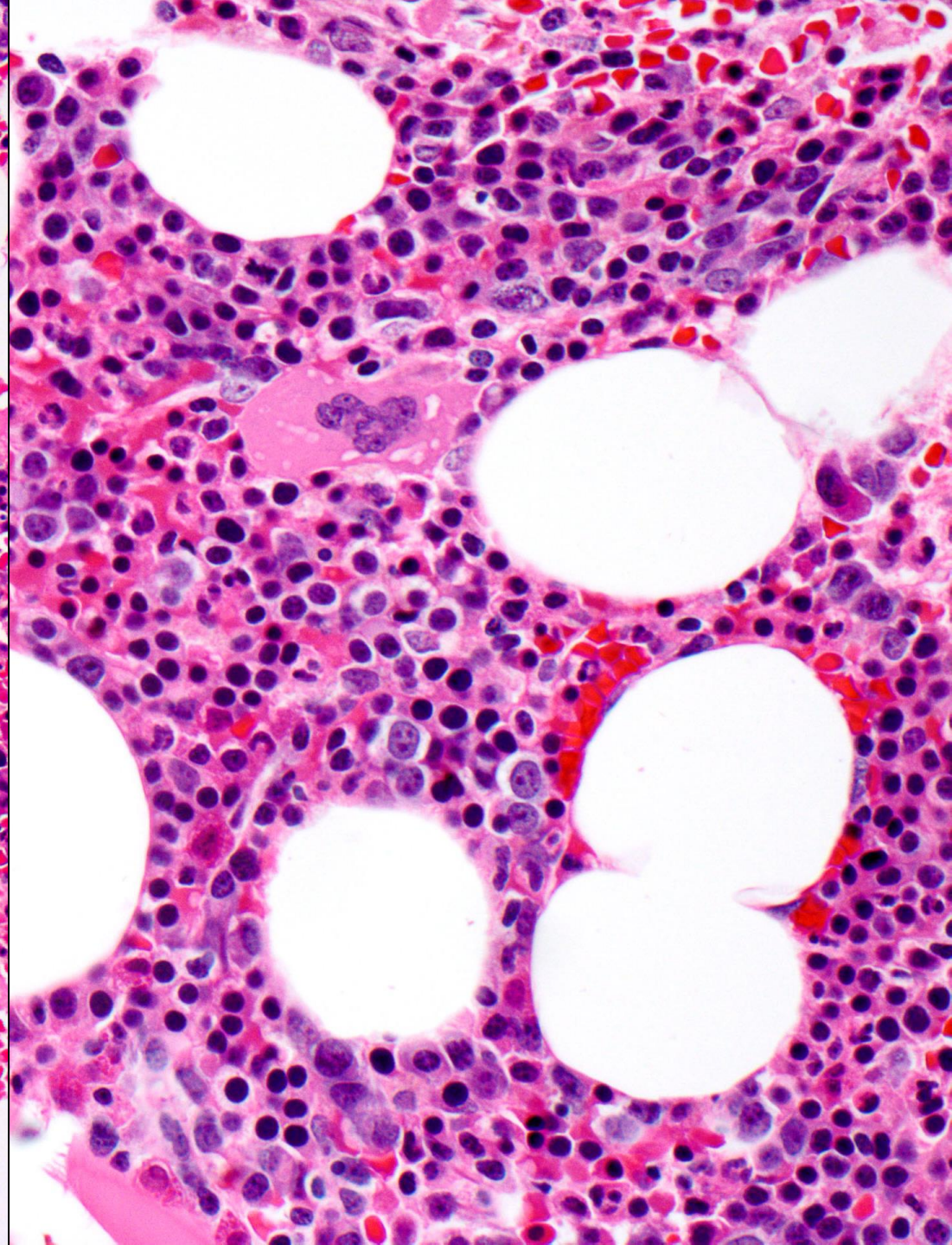


Case: Bone marrow aspirate



Iron stain on bone marrow aspirate is negative for ring sideroblasts

Case: Bone marrow biopsy



Case Diagnosis

Moderately hypercellular marrow with maturing trilineage hematopoiesis and erythroid hyperplasia

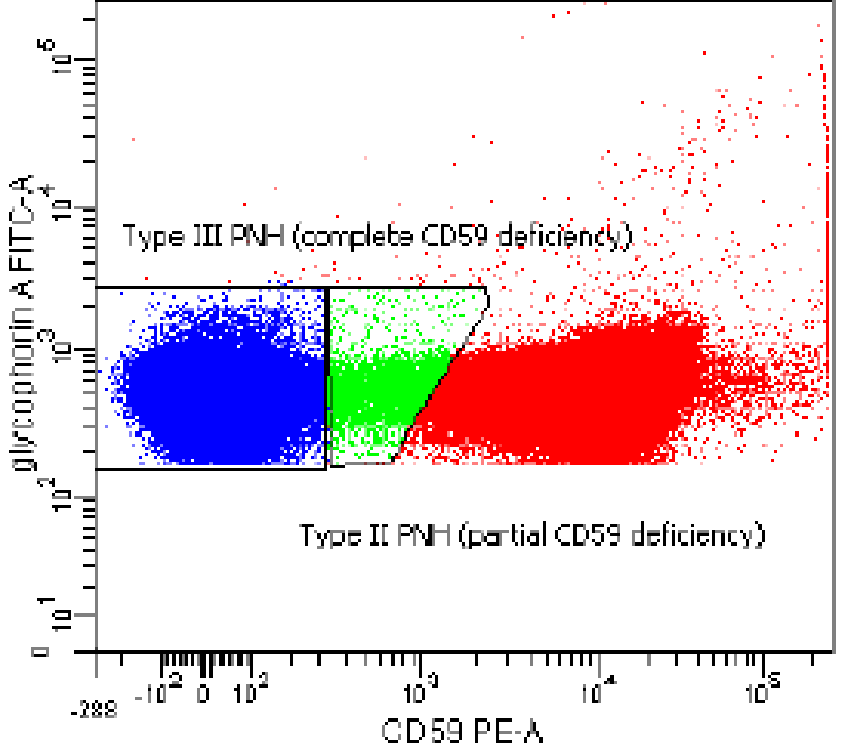
Diagnostic features of a myelodysplastic syndrome are not recognized

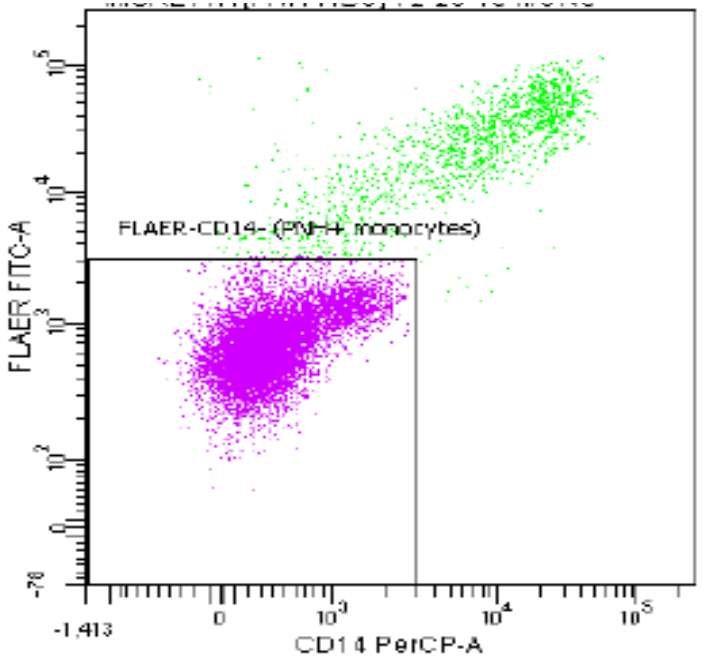
Correlate with pending cytogenetics and molecular genetic studies (54-gene NGS panel)

Case Further information

- Coombs negative
- No iron, B12 or folate deficiency
- LDH 1312 U/L (110-210 U/L)
- Reticulocyte count: 8%
- Peripheral blood PNH study:
  58% of granulocytes showing
  GPI-deficiency

Features are consistent with paroxysmal nocturnal hemoglobinuria (PNH)





Case: 2 weeks later. . .

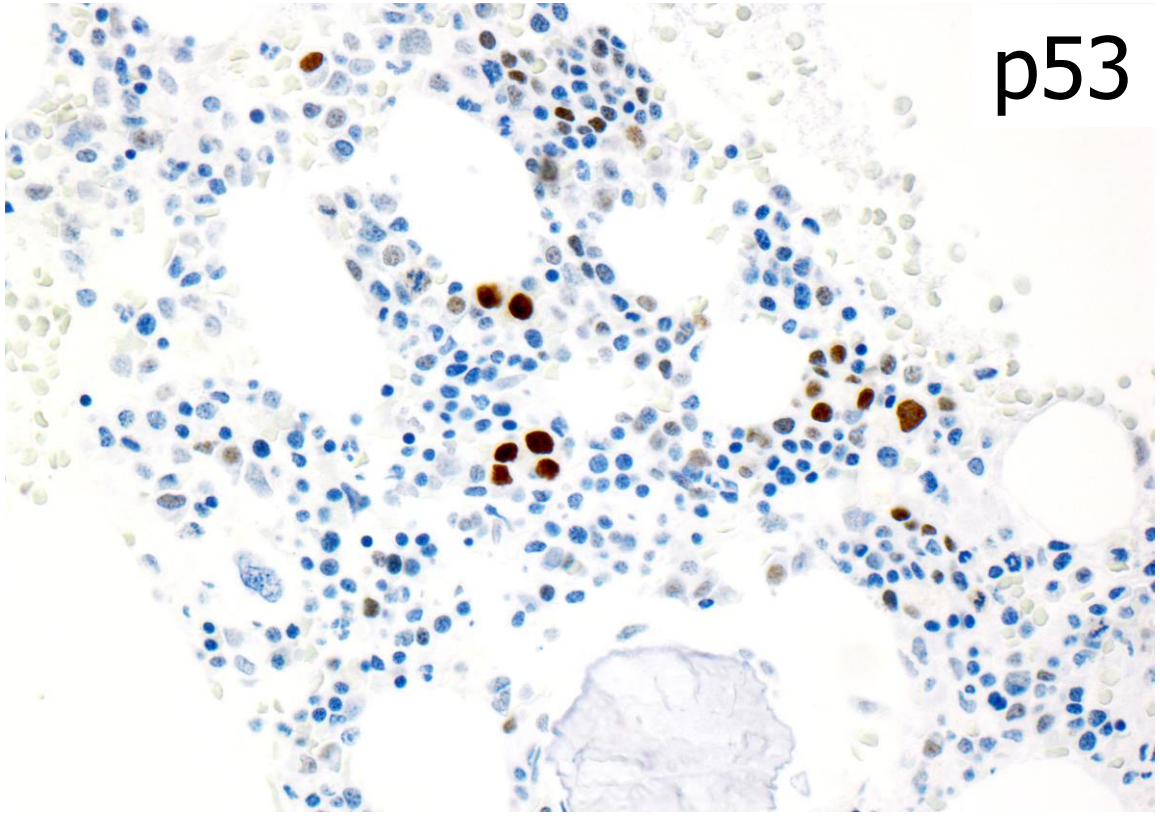
Bone marrow karyotype:

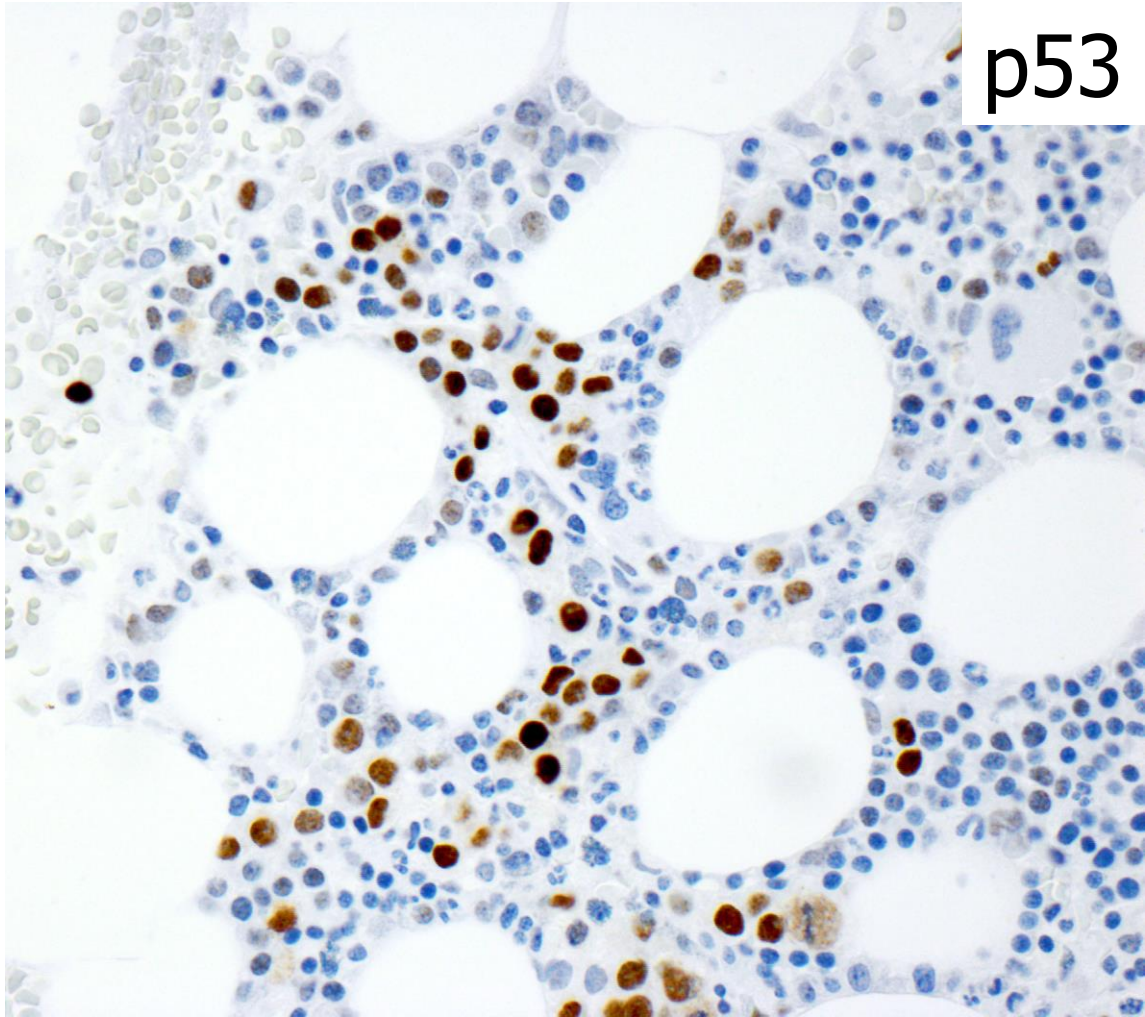
45, X,-Y [15]/46,XY [5]

Not a problem: loss of Y chromosome is common in older males and is not considered as evidence of a hematologic maligancy

Case: 54-gene NGS panel for myeloid neoplasm-associated mutations

- Single nucleotide variant: *TP53* p.Tyr163Cys, c.488A>G
- Variant allele frequency: 73%





Case Diagnosis

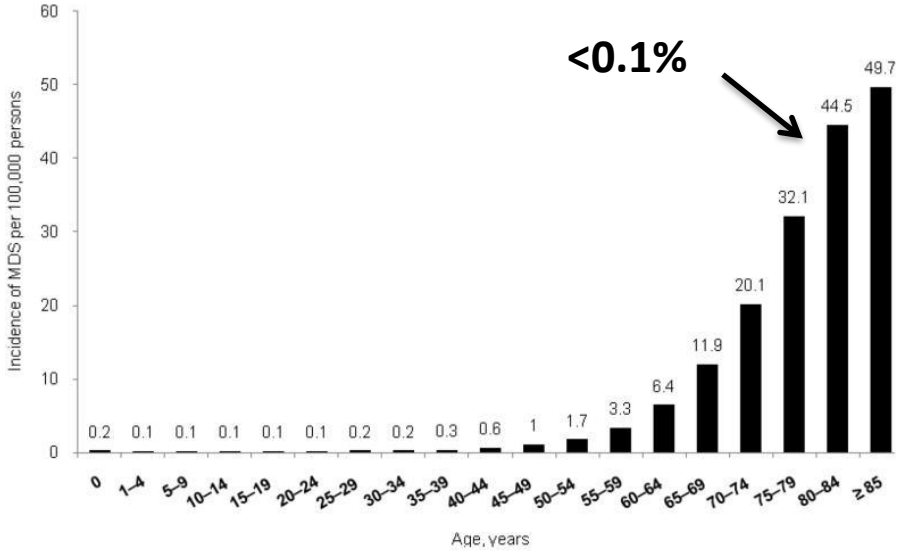
Moderately hypercellular marrow with maturing trilineage hematopoiesis and erythroid hyperplasia

Diagnostic features of a myelodysplastic syndrome are not recognized

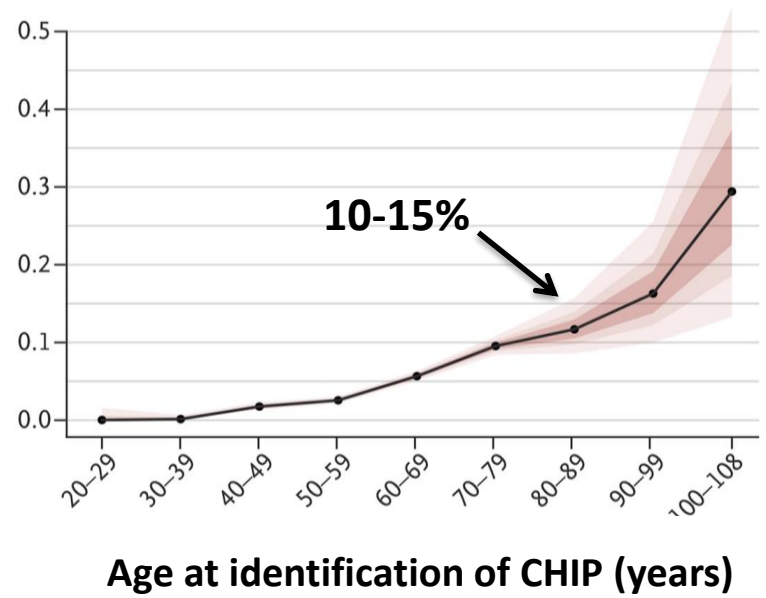
In light of the NGS results, do we need to amend the diagnosis to MDS?

CHIP and anemia are frequent in elderly individuals, while MDS is rare

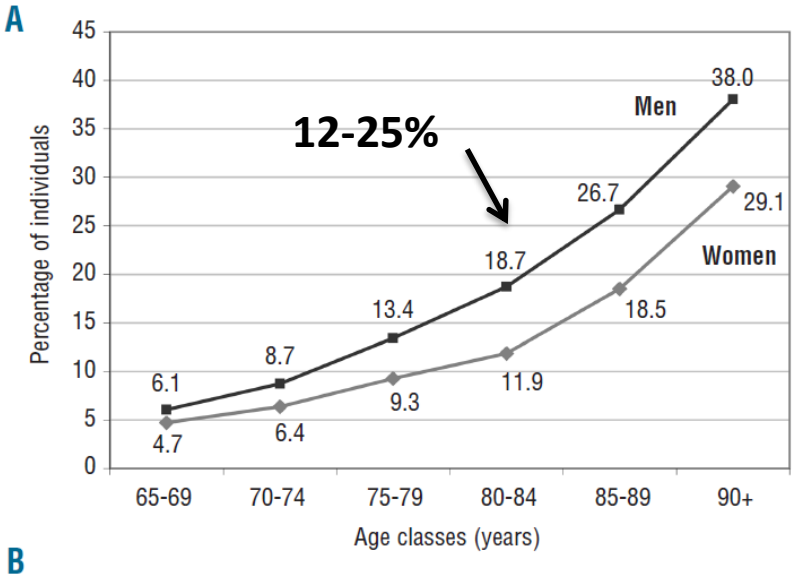
Incidence of MDS per 100,000



Frequency of CHIP



Frequency of anemia



CHIP: “Clonal Hematopoiesis of Indeterminate Potential” at VAF level of >2%

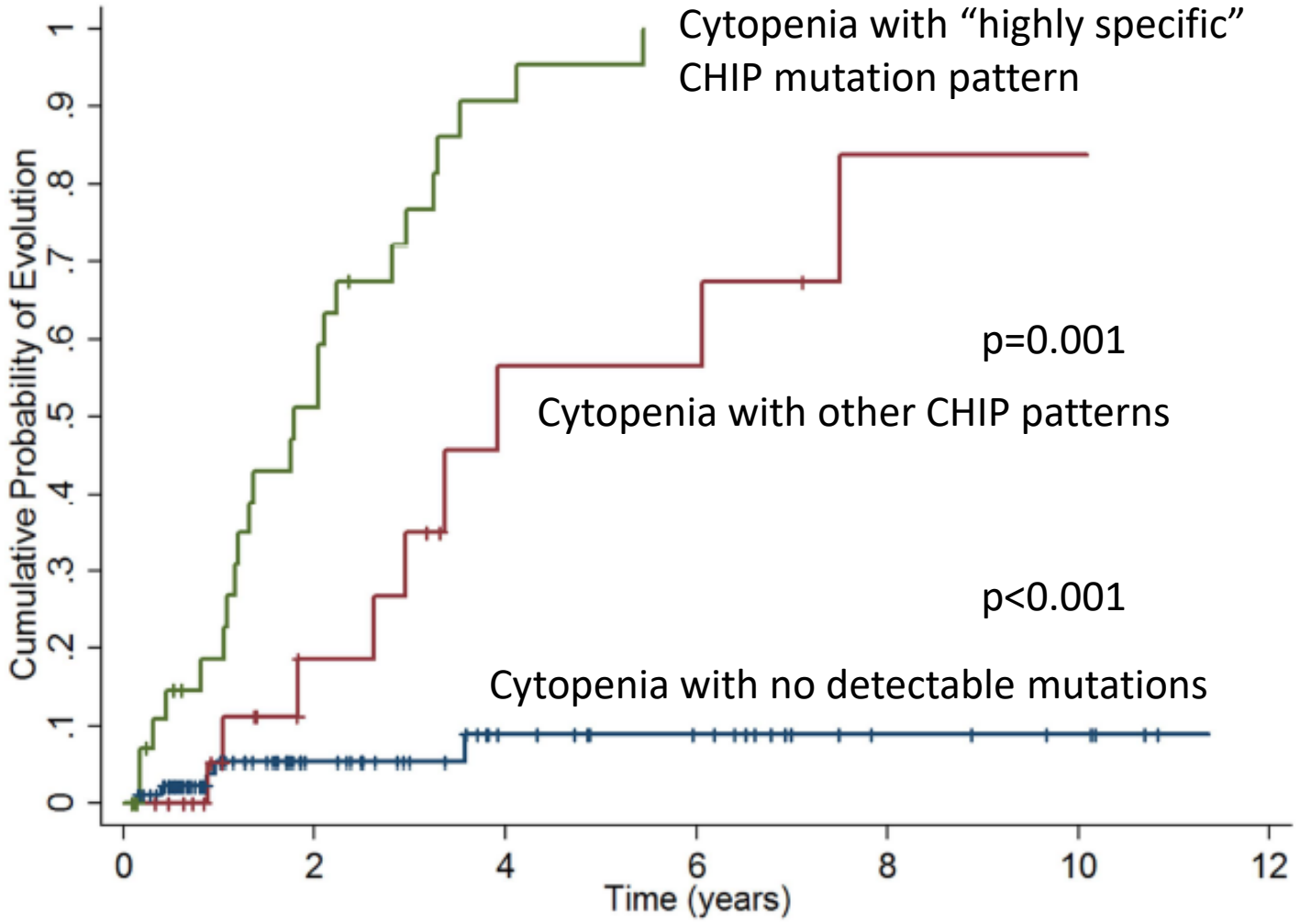
Ma X Am J Medicine 2012; 125: S2, Rollison DE Blood 2008;112:45-52, Jaiswal S NEJM 2014; 371:2488, Steensma D Blood 2015; 126:9, Tettamanti M et al. Haematologica 2010;95:1849

Relationship of CHIP to MDS

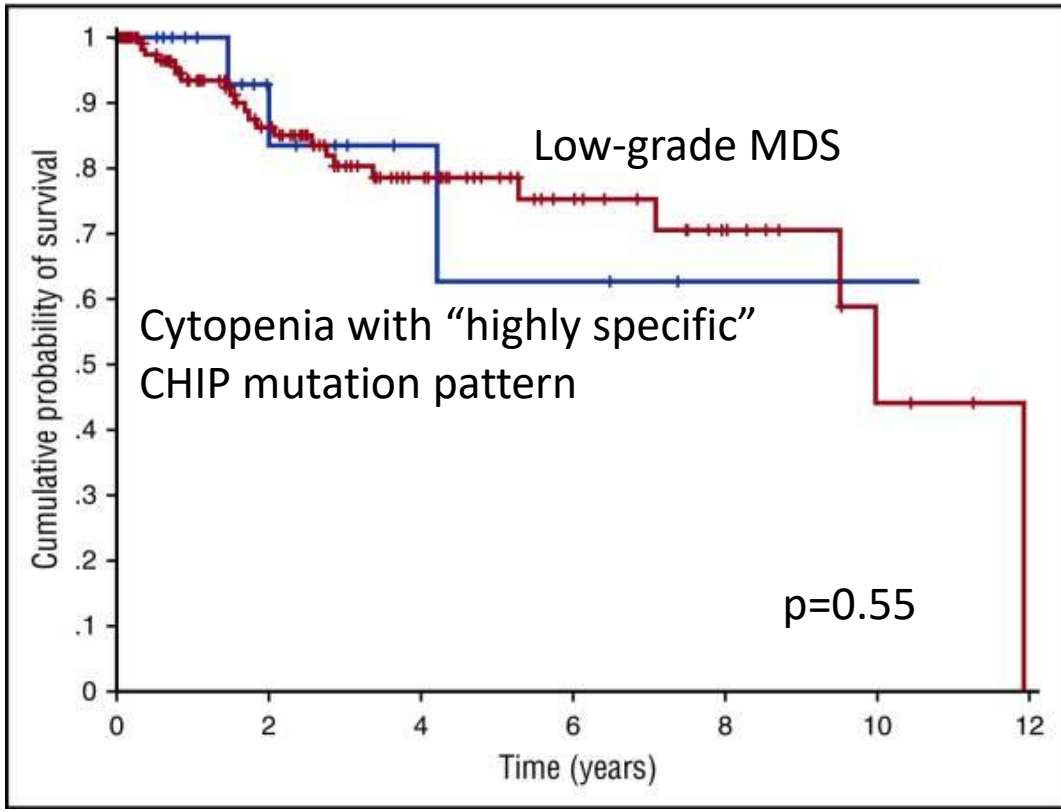
- Clonal hematopoiesis is a precursor state to MDS
- Most patients with CHIP do not develop MDS
  - At higher risk of death from cardiovascular causes
- Not all CHIPs are created equal: specific mutation patterns and high mutant allele frequency in cytopenic patients may confer higher risk of MDS
  - Mutant allele fraction ≥10%
  - Spliceosome mutation or *TET2, DNMT3A* or *ASXL1* mutation with at least one other mutation

Malcovati L et al. Blood 2017;129:3371

Cytopenic CHIP patients' progression to MDS



Is "high-risk" CHIP equivalent to low-grade MDS?



Malcovati L et al. Blood 2017;129:3371

Case Final diagnosis

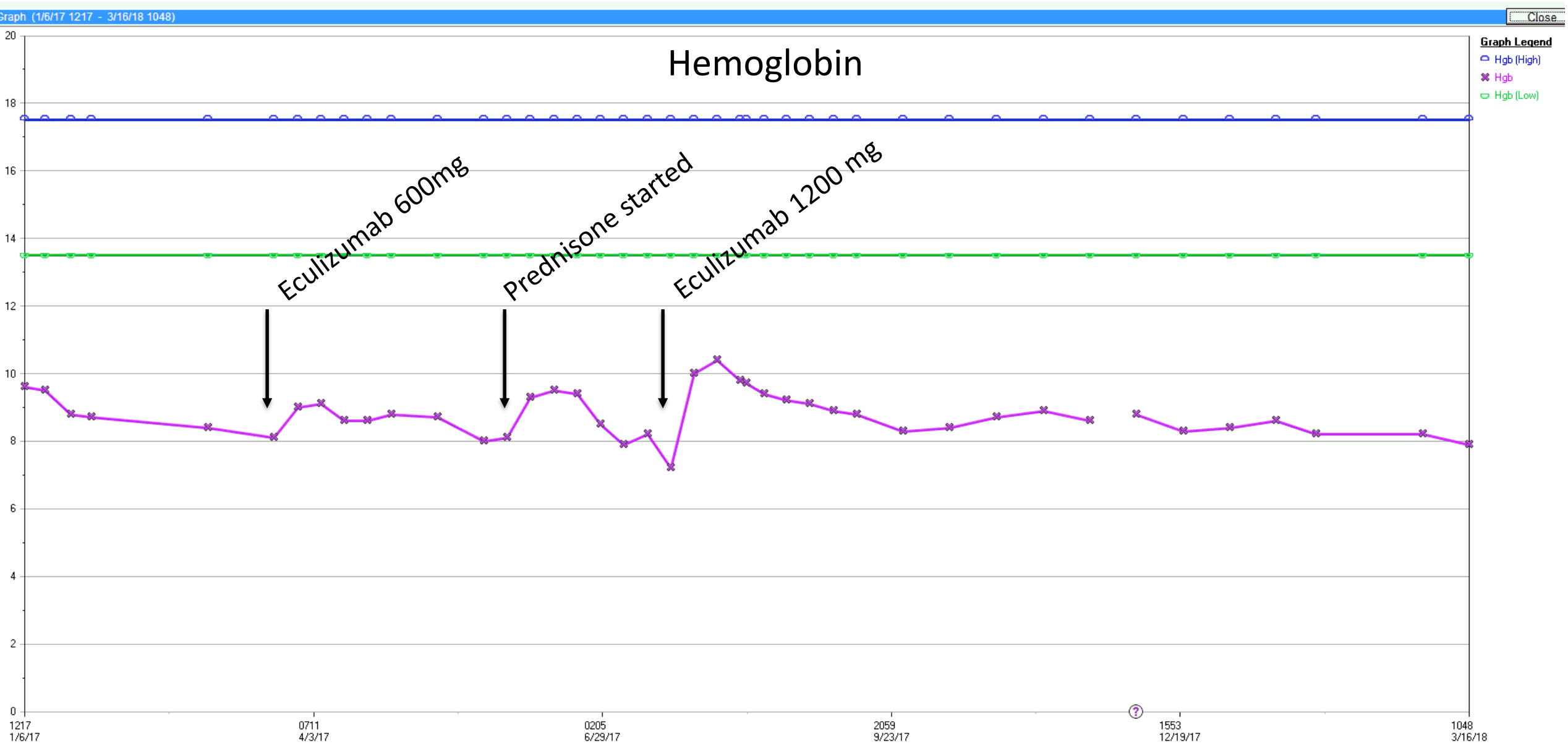
Moderately hypercellular marrow with maturing trilineage hematopoiesis and erythroid hyperplasia

Diagnostic features of a myelodysplastic syndrome are not recognized

Paroxysmal nocturnal hemoglobinuria

Loss of Y chromosome and pathogenic *TP53* mutation, consistent with clonal hematopoiesis; recommend close clinical followup

Patient followup



Prognostic schemes in MDS

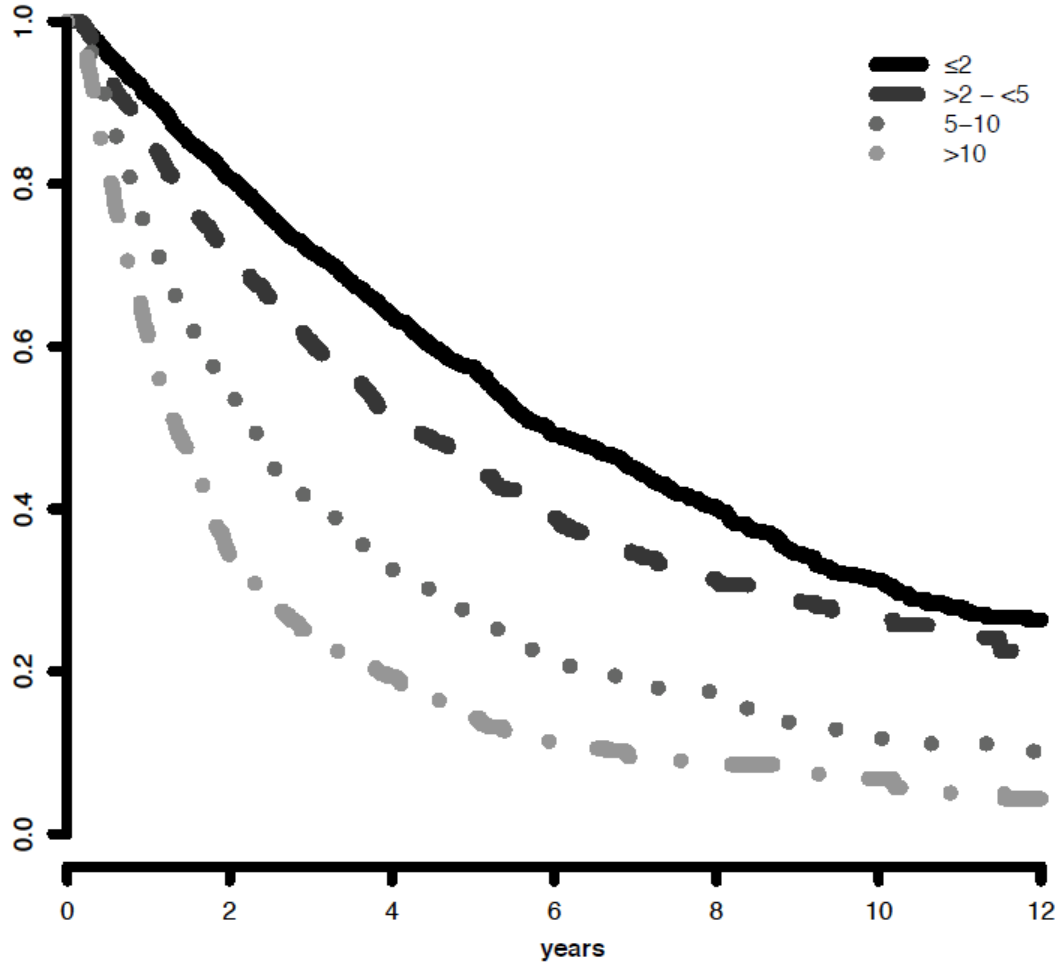
	WHO (2016)	IPSS-R* (202)	Other
Dysplasia	**Single versus multilineage and ring sideroblasts**	**Not included**	
Cytopenias	**Pancytopenia**	**Number and depth of cytopenias**	**Transfusion dependency (WPSS**)**
Blast % in blood	**<1%, 1%, 2-4%, ≥5%**	**Not included**	
Blast % in bone marrow	**<5%, 5-9%, 10-19%**	**≤2%, 3-4%, 5-10%, 11-19%**	
Karyotype	**Isolated del(5q)**	**5 prognostic groups**	
Molecular genetic abnormalities	***SF3B1* mutation**	**Not included**	**Number and specific types of mutations**
Flow cytometry abnormalities	**Not included**	**Not included**	**Prognostic impact**
Gene expression profile	**Not included**	**Not included**	**Prognostic impact**

*Revised International Prognostic Scoring System of MDS
**WHO-based Prognostic Scoring System of MDS

Greenberg PL et al. Blood 2012;120:2454

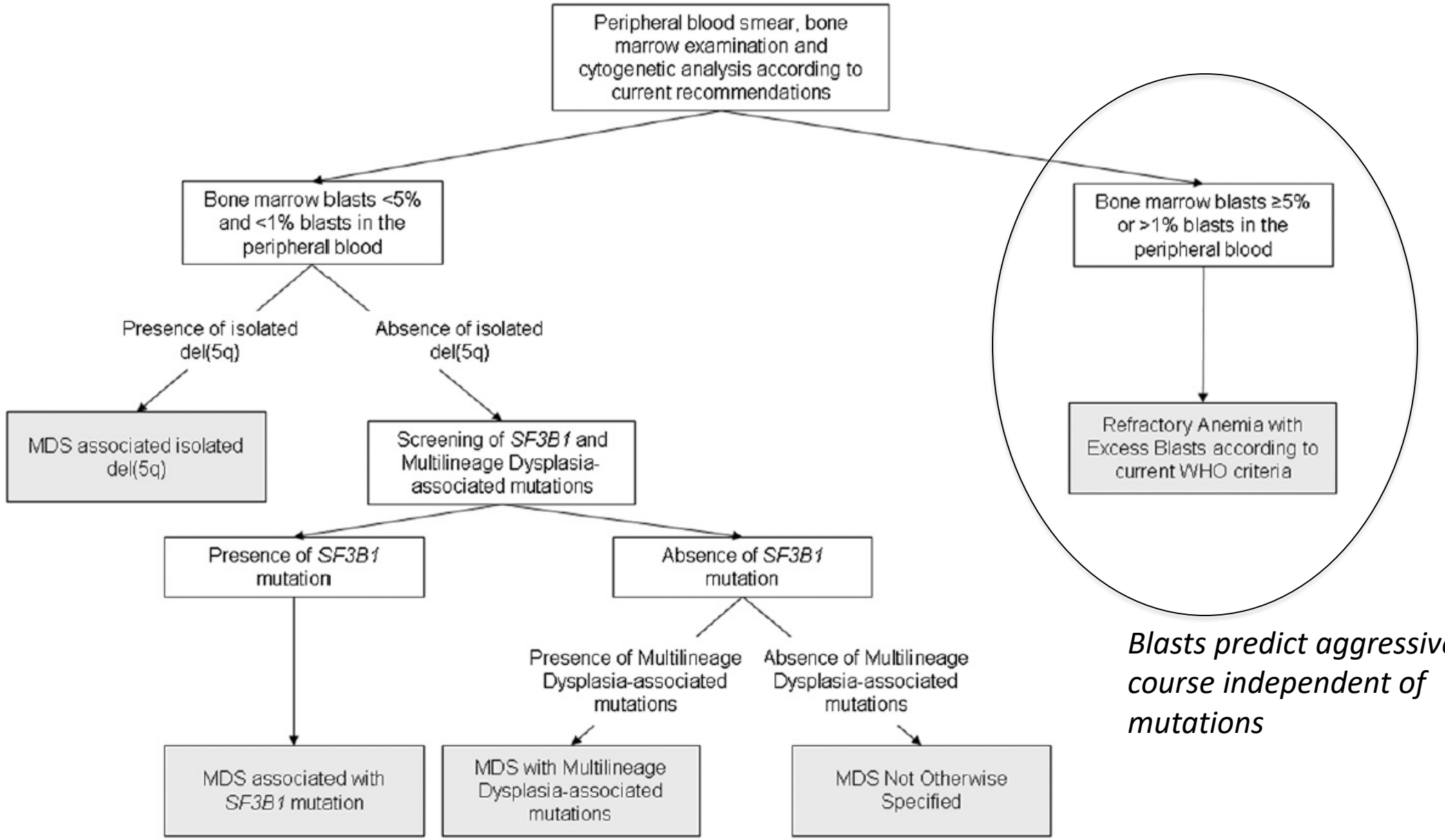
Blast percentage in MDS: a cornerstone of disease prognosis

- Increased blasts in blood or bone marrow are a very strong and independent indicator of aggressive behavior in MDS
- There is no mutation profile surrogate for increased blast count



7,000 MDS patients

Malcovati L et al. Blood 2014;124:1513, Greenberg PL et al. Blood 2012;120:2454



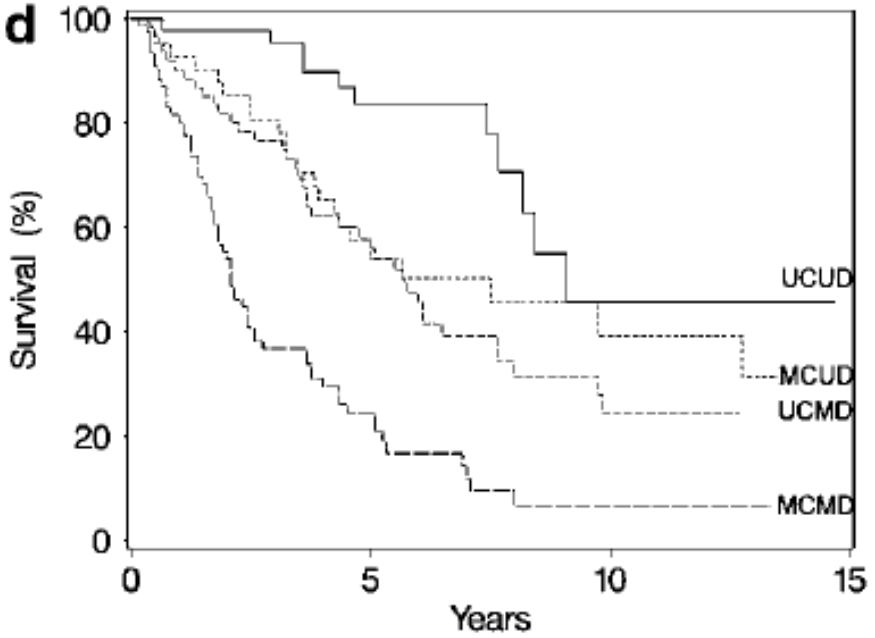
Blasts predict aggressive course independent of mutations

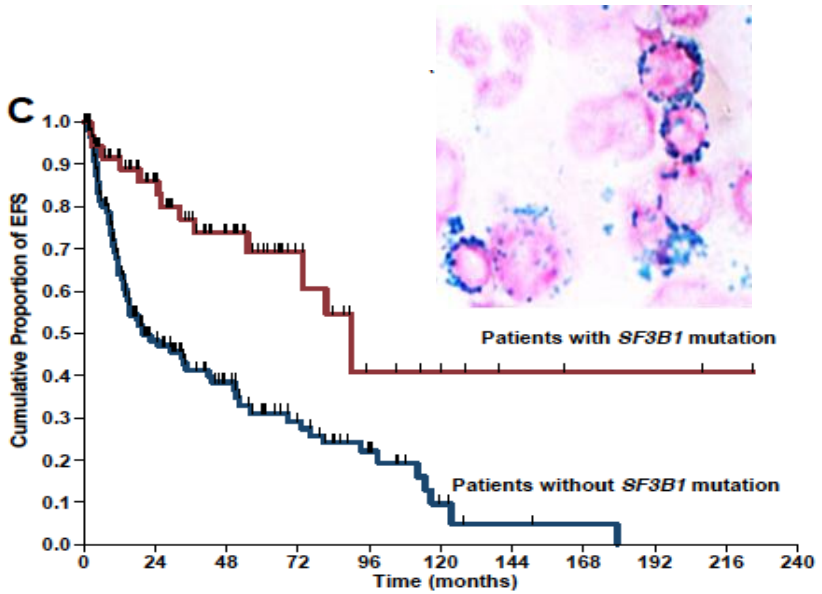
Figure 5. Algorithm illustrating the classification process based on morphologic and genetic criteria identified by the unsupervised clustering analyses. According to these analyses, the threshold of 5% BM blasts retains a significant discriminant value, irrespective of the underlying driver mutation pattern. In MDS with no excess blasts, the presence of isolated del(5q), SF3B1 mutation or multilineage dysplasia-associated mutations recognize genetically-defined disease subtypes.

Malcovati L et al. Blood 2014;124:1513

What are the interactions of dysplastic morphology and mutations?

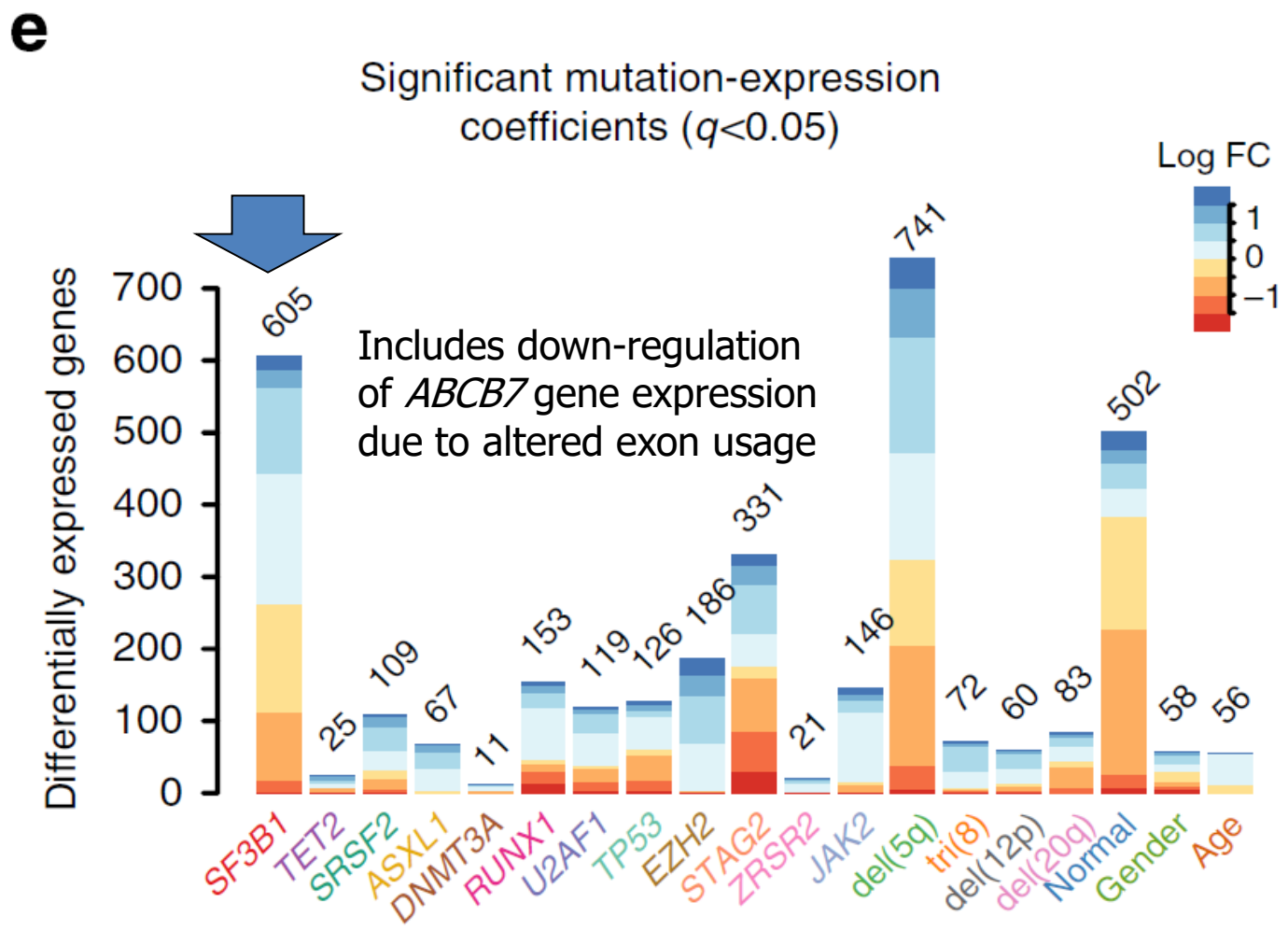
- Multilineage (versus unilineage) dysplasia has significant negative prognostic impact in MDS
- *SF3B1* mutation has significant positive prognostic impact in MDS
  - Correlates strongly with ring sideroblast morphology





Verburgh E et al. Leukemia 2007; 21:668, Papaemmanuil E et al. NEJM 2011;365:1384, Patniak et al. MM Blood 2012;119:5674

SF3B1 mutation is associated with highly differential gene expression in MDS

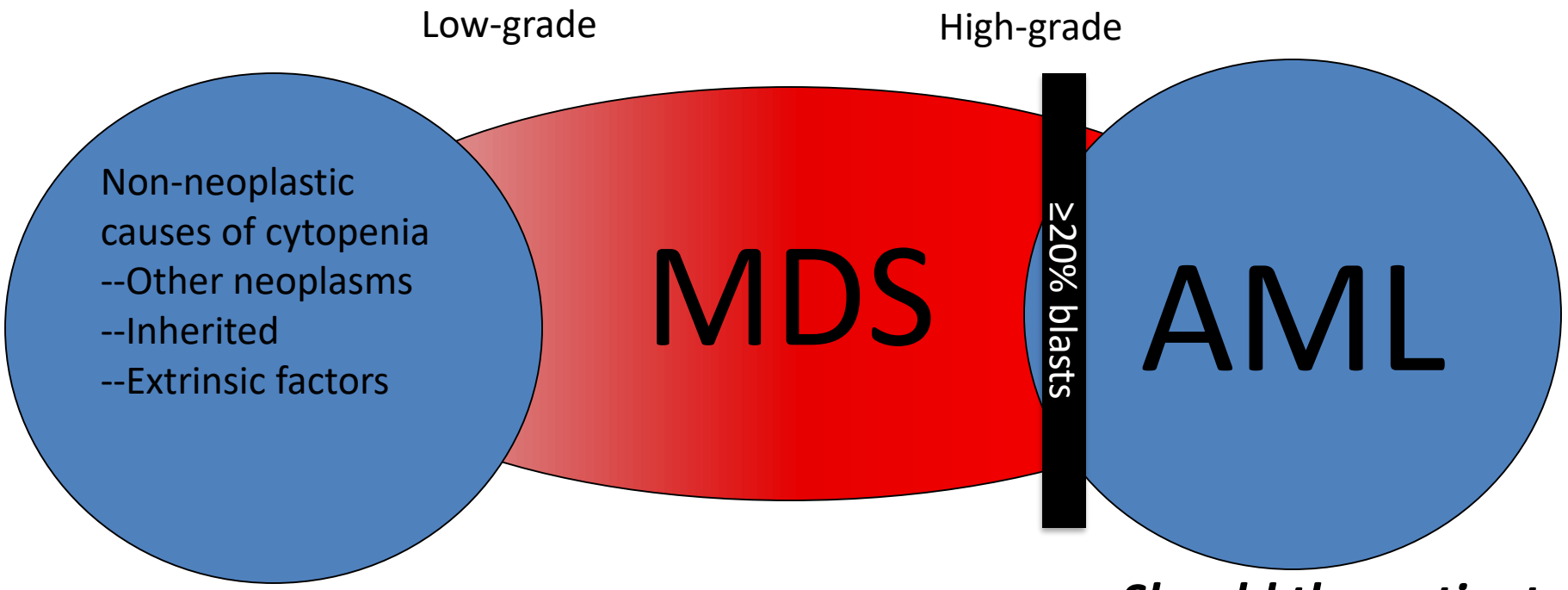


Gerstung M et al. Nature Comm 2015;6:5901, Papaemmanuil E et al. NEJM 2011;365:138, Nikpour M et al. Leukemia 2013; 27:889

New handling of MDS with ring sideroblasts in WHO 2016

- MDS with ring sideroblasts (MDS-RS) is broadened to include:
  - "Traditional" RARS (single erythroid lineage dysplasia)
  - Cases with multilineage dysplasia
  - Cases with *SF3B1* mutation and ≥5% RS
- MDS-RS is subdivided into cases with single or multilineage dysplasia
  - Multilineage dysplasia appears to confer adverse prognosis to MDS cases with ring sideroblasts and/or *SF3B1* mutation

Challenges in MDS diagnosis

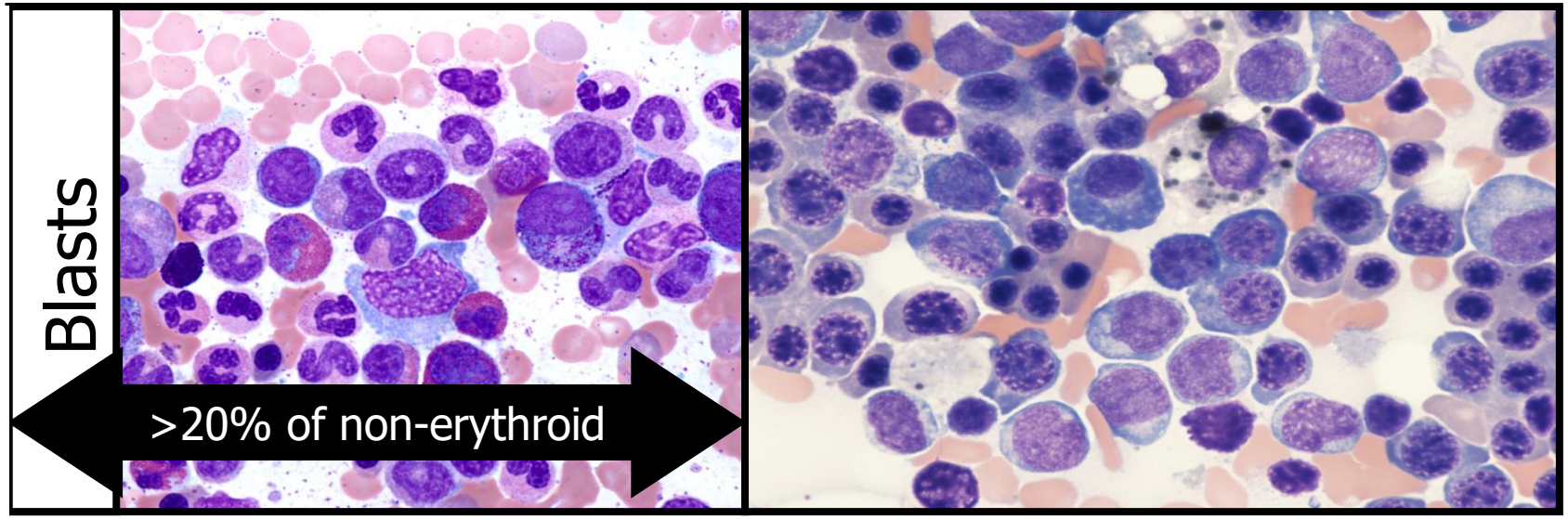


- ***Should the patient receive induction or other intensive chemotherapy with a goal of remission?***

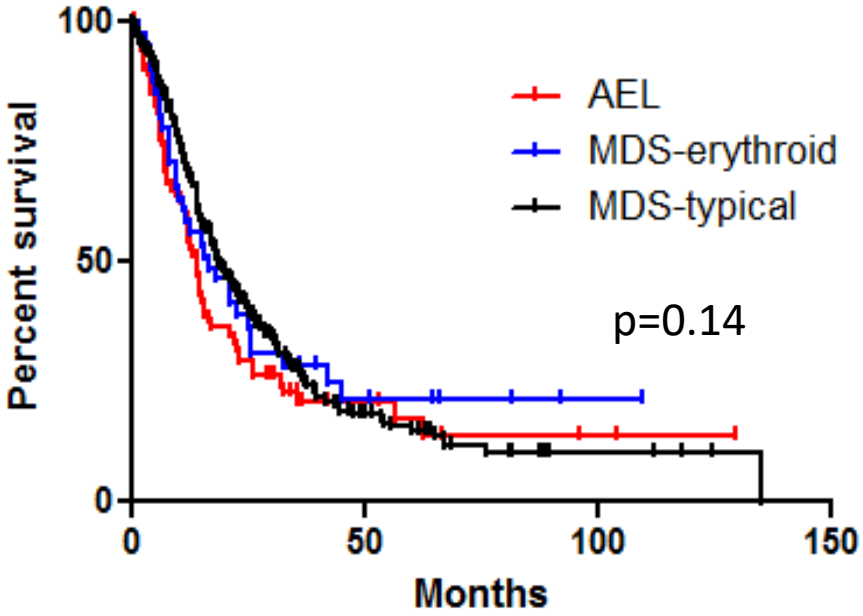
Controversies in blast counting: myeloid neoplasms with erythroid predominance (≥50% erythroids)

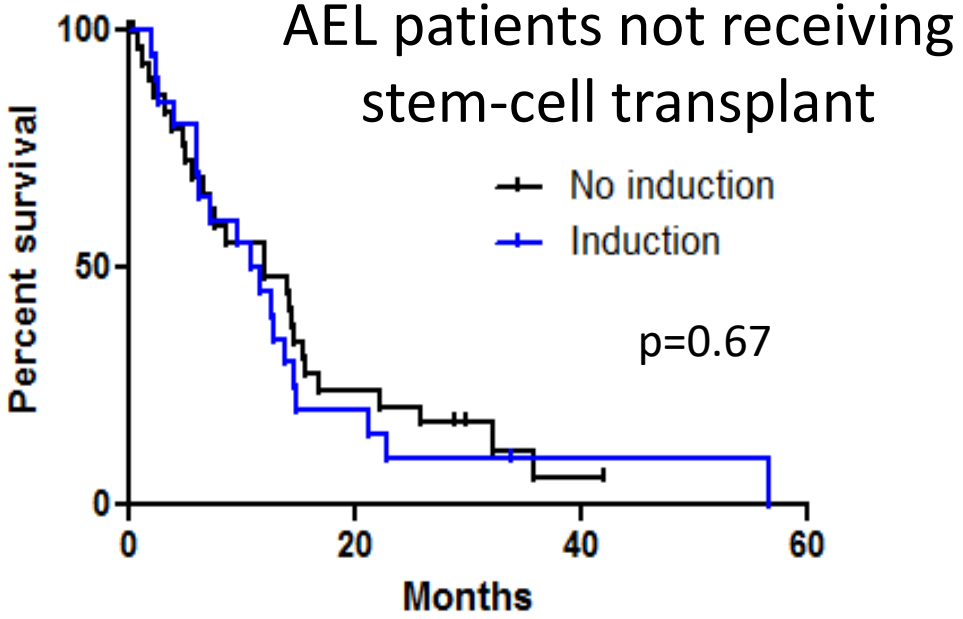
- 'Loophole' in 2008 WHO classification diagnosed acute erythroid leukemia (AEL) if erythroids are ≥50% of marrow cells and blasts are ≥20% of the non-erythroid cells (i.e. excluding erythroids from denominator)
- Small changes in blast or erythroid percentages can change diagnosis, with major clinical impact

MDS with excess blasts or acute erythroid leukemia?



Most AEL cases behave similar to MDS and may not benefit from intensive AML-type chemotherapy





- AEL often occurs as a "progression" of prior MDS
- Morphologic dysplasia is characteristic
- Genetic abnormalities are more similar to MDS than to de novo AML: *TP53* mutation common, *FLT3/NPM1* mutations rare

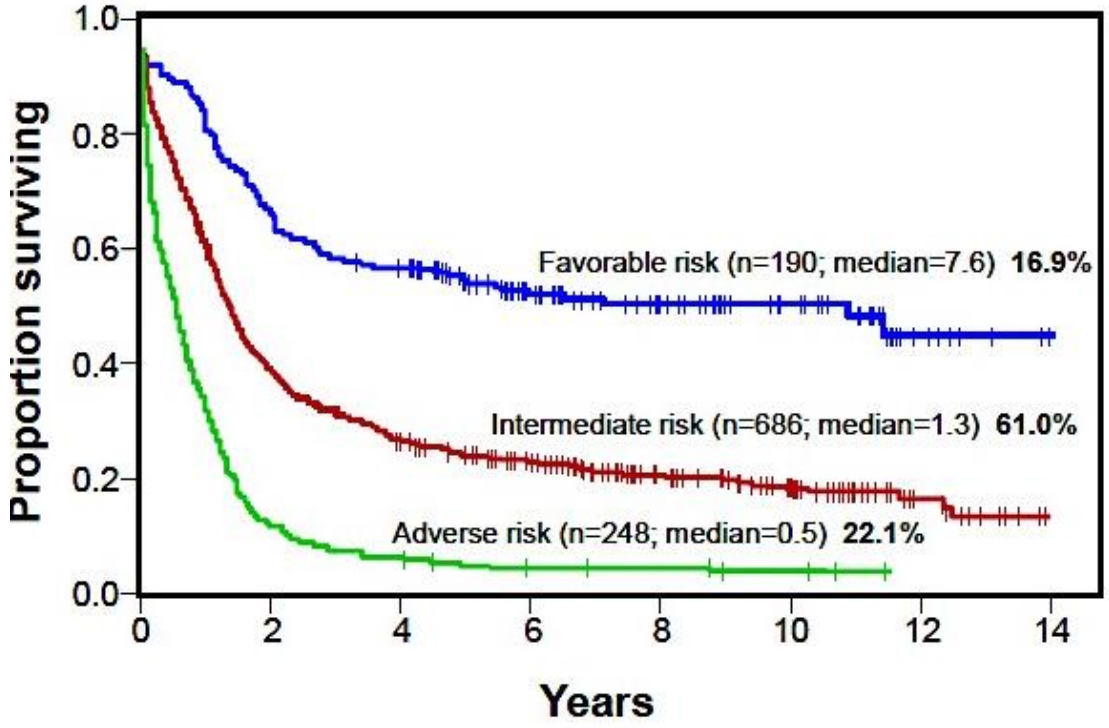
Wang SA et al. Mod Pathol 2016;29:1221, Bacher U et al. Haematologica 2011;96:1284, Zuo Z PLoS One 2012;7:e41485, Wang SA et al. Mod Pathol 2008; 21:1394, Grossman V et al. Leukemia 2013;27:1940, Park S et al. Leukemia 2004;18:888, Honda Y et al. In J Hematol 2008;88:524, Wang SA & Hasserjian RP Hum Pathol 2012;43:153, Porwit A & Vardiman J Haematologica 2011;96:1241

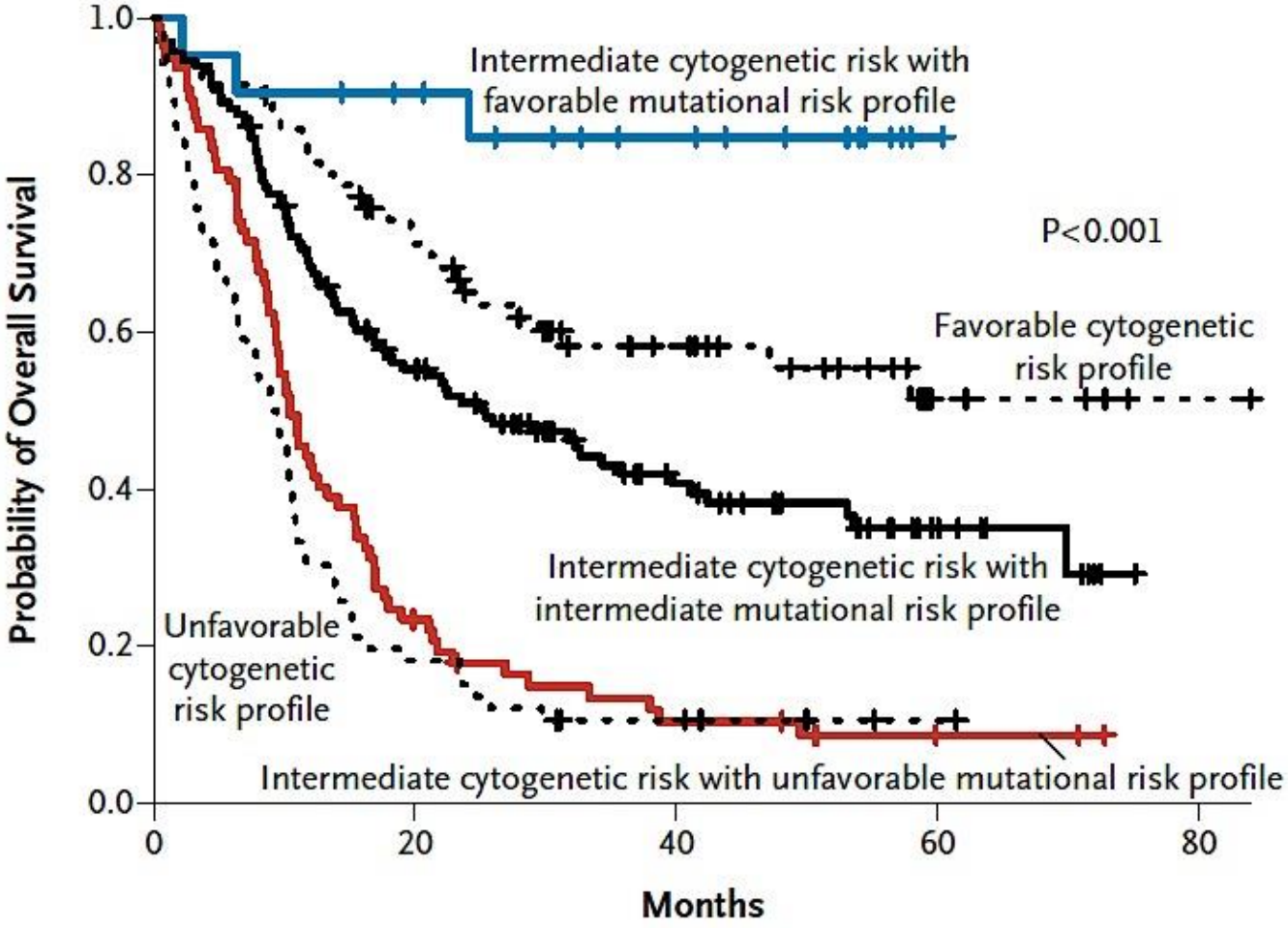
New WHO 2016 recommendations for blast counting

- Blasts in BM are now always counted as % of total cells, never as % of non-erythroid cells
- Myeloid neoplasms with ≥50% erythroids but with blasts <20% all cells are now classified as MDS with excess blasts (not AML) even if blasts are ≥20% of the non-erythroid cells
- This change eliminates the prior WHO 2008 entity of acute erythroid leukemia (erythroid/myeloid subtype) and greatly simplified blast enumeration in myeloid neoplasms

Arber DA et al. Blood 2016;127:2391

Genetic risk stratification in AML





- *NPM1, CEBPA, FLT3*-ITD, *IDH1, IDH2, ASXL1, TET2, PHF6, DNMT3A, MLL*-PTD status

Byrd JC et al. Blood 2002;100:4325, Patel JP et al. NEJM 2012;366:1079

The major challenges in molecular classification of MDS/AML-1

- ~~Mutational testing is not widely available in most practice settings~~
- Many studies have provided *prognostic* data for mutations, but few studies give data that predict response to specific therapeutic regimens (*predictive*)
  - Numerous prospective studies are needed to help establish mutational testing algorithms that direct therapy ("personalized" medicine)
- Most myeloid neoplasms contain multiple mutations whose interactions are unclear
  - Subclones of varying size and relationships to one another are present
  - Different subclones wax and wane during therapy and disease evolution

2016 WHO AML Classification

- Tend to be less genetically complex
- Include entities with relatively favorable prognosis

AML

- Tend to be more genetically complex
- Include entities with poorer prognosis

"De novo"

- APML with *PML-RARA*
- inv(16)/t(16;16), t(8;21)
- *KMT2A* and other gene rearrangements
- AML with mutated *NPM1*
- AML with double-mutated *CEBPA*
- **AML with mutated *RUNX1***

AML with recurrent genetic abnormalities

AML, not otherwise specified

"Secondary"

Therapy-related AML

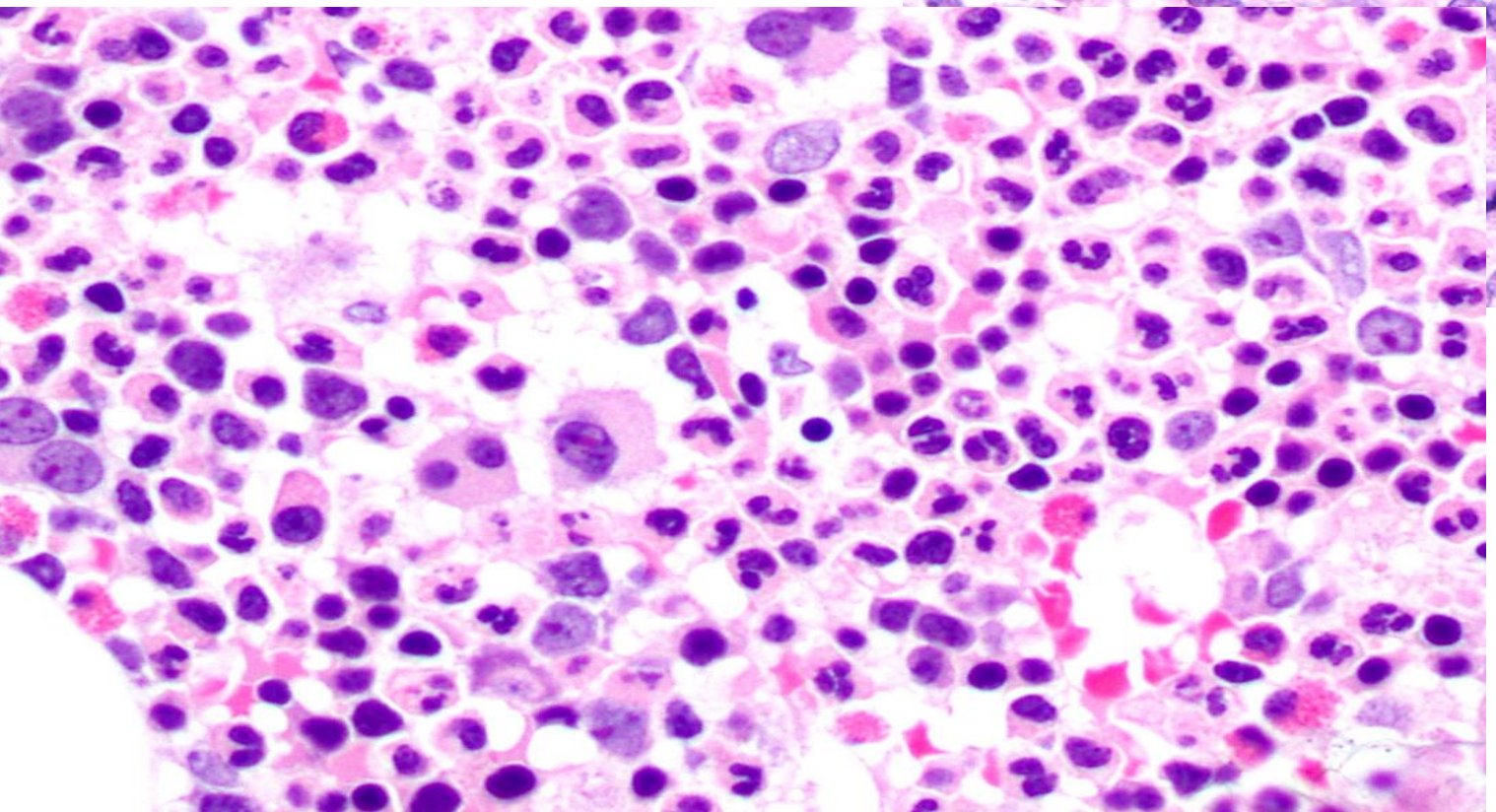
AML with myelodysplasia-related changes

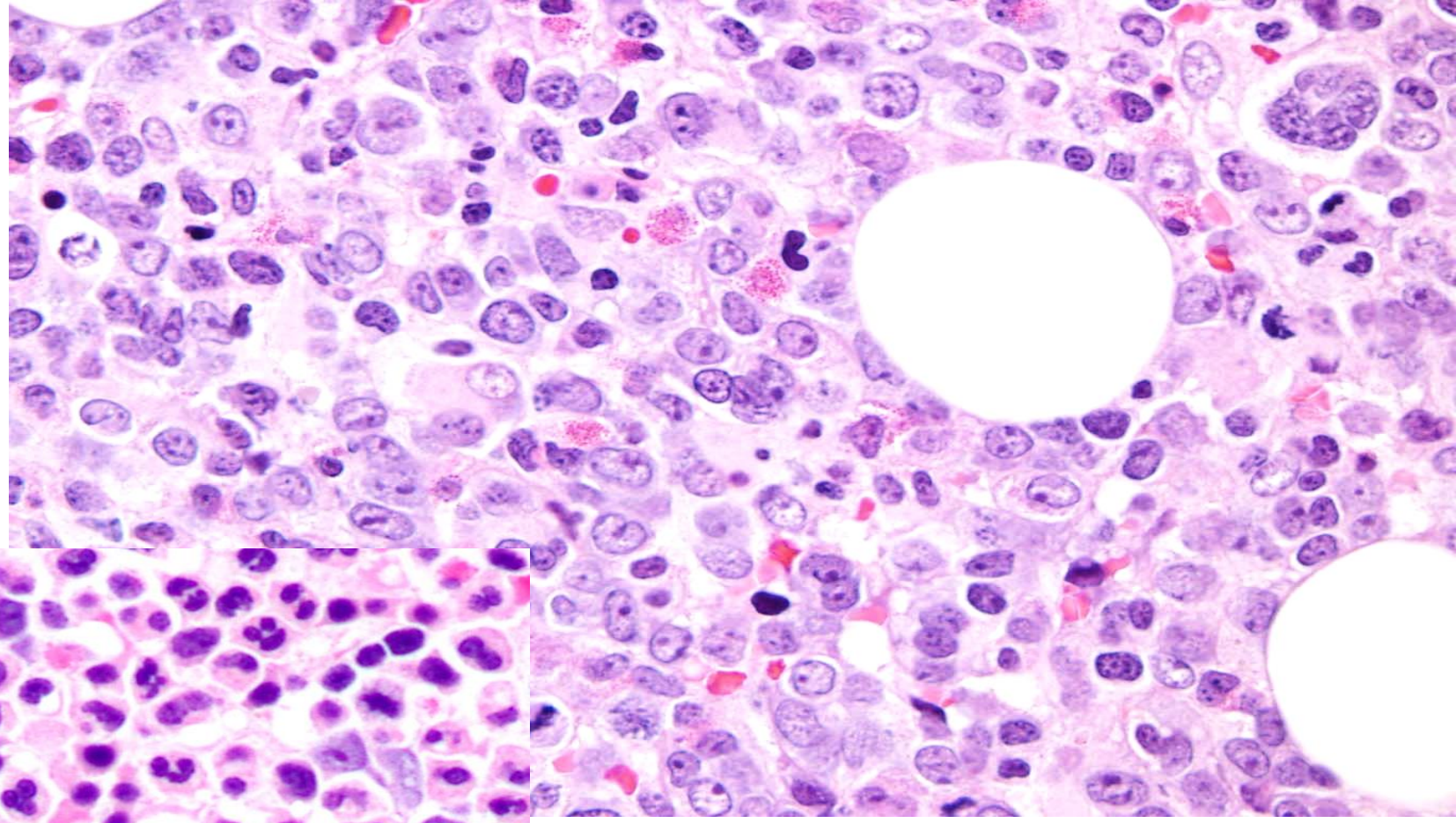
Myeloid proliferations related to Down Syndrome

Myeloid neoplasms with germline predisposition

Myeloid neoplasms with germline predisposition: new WHO category

Thrombocytopenia with germline *ANKRD26* mutation





AML with germline *GATA2* mutation

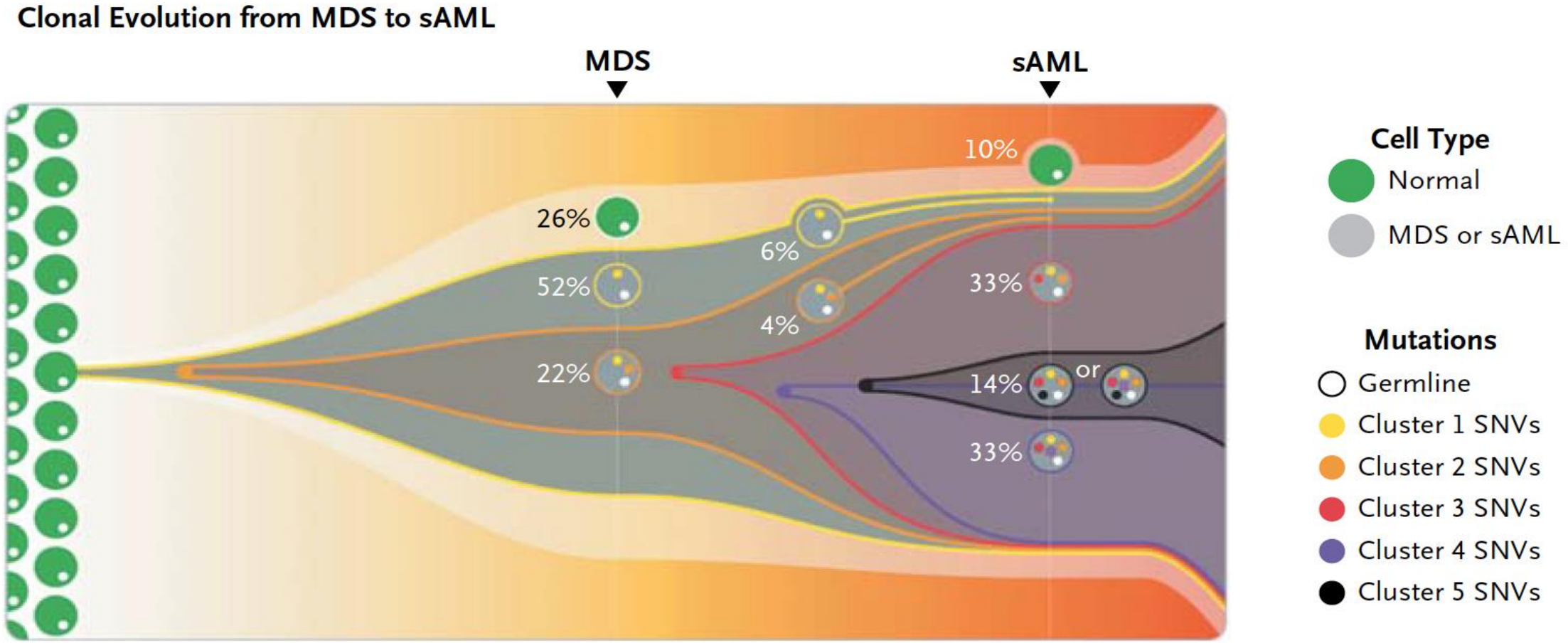
Courtesy of L Peterson and J Vardiman

Challenges in myeloid neoplasms occurring in a background genetic predisposition

- Identifying the germline mutation
  - Need to sequence non-hematopoietic tissue to know for certain that the mutation is germline
  - Need to be alert to the clues: detailed personal and family history (especially thrombocytopenia) and use of experienced genetic counselors
  - Often newly arising mutations where family history is unhelpful
- Entities can present in adulthood without prior clinical clues
  - MDS/AML with *DDX41* mutation
- Implications for family members, especially potential bone marrow donors
- Germline predispositions are underrecognized in clinical practice—we need to do a better job identifying them!

Czuchlewski DR et al. Surg Pathol Clin 2016:9:165, West AH et al. Ann NY Acad Sci 2014;1310:111, Wlodarski MW et al. Blood 2016;127:1387, Lewinsohn M et al. Blood 2016:127:1017.

AML with myelodysplasia-related changes (AML-MRC): "AML with baggage"

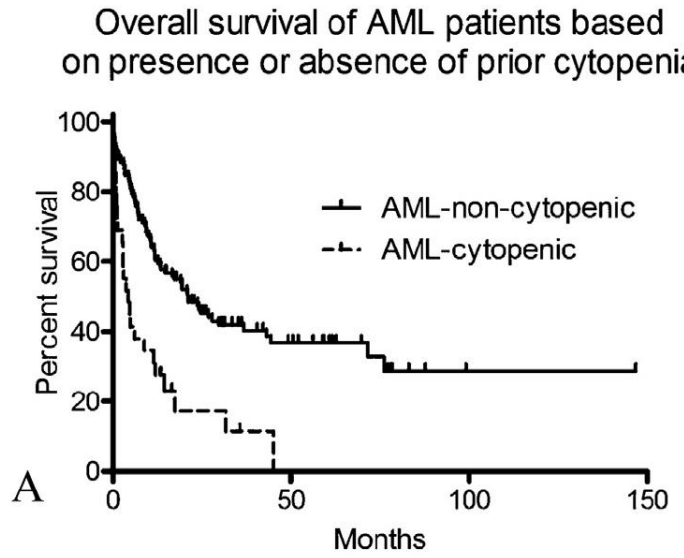


- Mutations in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2* specifically are associated with AML arising from MDS

Walter MJ et al. NEJM 2012;366:1090; Lindsley RC et al. Blood 2015;125:1367

WHO 2016 AML with myelodysplasia-related changes

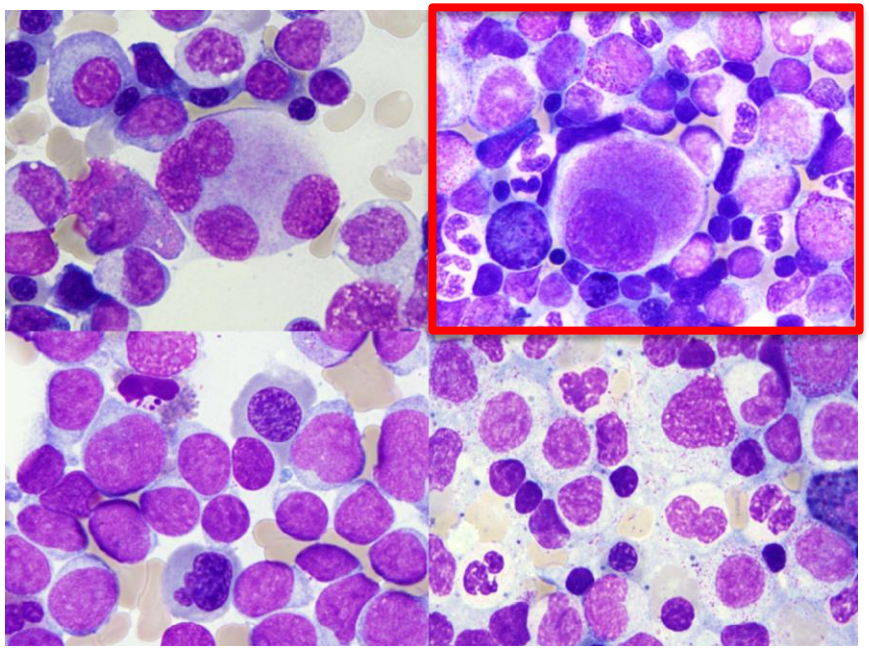
- –Any prior diagnosis of MDS or MDS/MPN
- –MDS-associated cytogenetics
- –Severe morphologic dysplasia
  - >50% of cells from at least 2 lineages are dysplastic



Huck A et al. Leuk Res 2015; 39:1034

Significance of morphologic dysplasia in de novo AML with normal karyotype

- Unclear if morphologic dysplasia alone is independently significant
  - Merely associated with true prognosis drivers (poor-prognosis karyotype and gene mutations)?
- However, WHO criteria for multilineage dysplasia are not evidence-based and may not be optimal

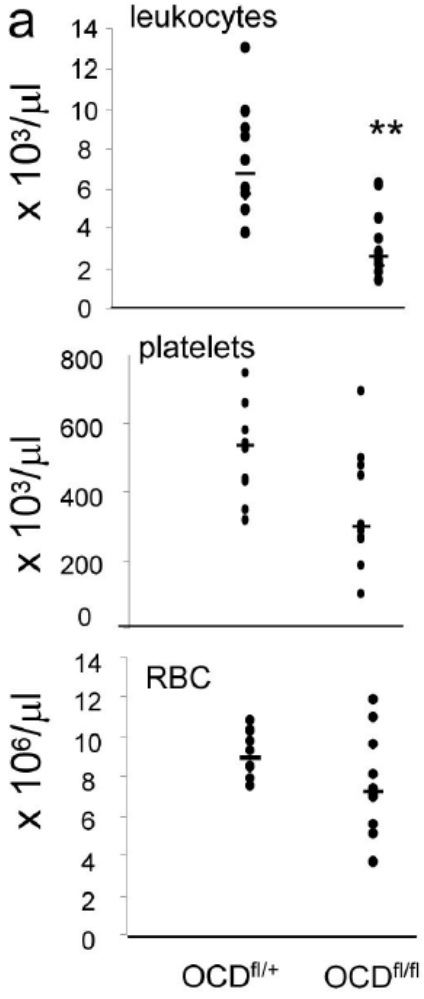


	Coefficient	Exp (coef) Hazard Ratio	SE coefficient	Z value	P value
Stem cell transplant	-0.348	0.706	0.271	-1.283	0.199
Micromegakaryocytes (score ≥3)	0.764	2.146	0.319	2.391	0.017
Subclone present	0.799	2.223	0.248	3.22	0.001
NPM1 mutation	-0.696	0.499	0.248	-2.81	0.005
NF1 mutation	0.756	2.13	0.447	1.69	0.091

Diaz-Beya M Blood 2010;116:6147, Weinberg OK Blood 2009;113:1906, Weinberg OK Mod Pathol 2015;28:965, Devillier R et al. Oncotarget 2015;10:8388, Rozman M et al. Ann Hematol 2014;93:1695, Weinberg OK Haematologica 2018 (Epub)

Can genetics and morphology really convey different and independently relevant types of information?

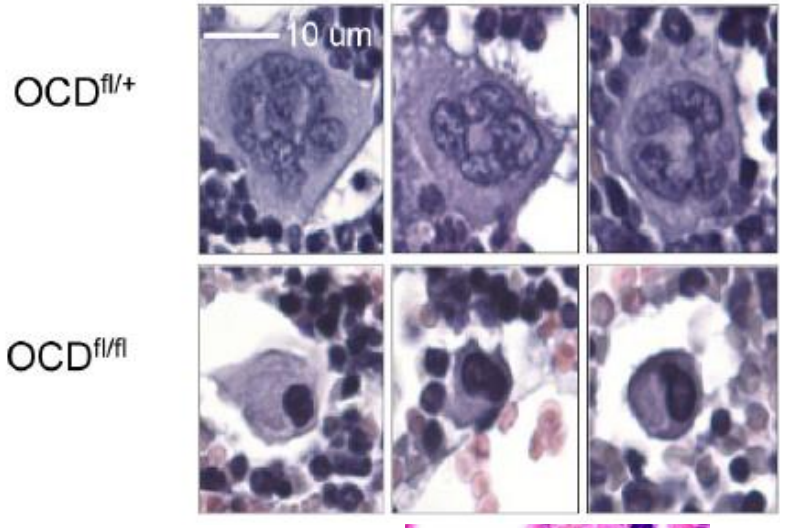
- Genetic changes reflect intrinsic permanent changes to the tumor stem cell's genome
- Morphology and immunophenotype reflect the realization of these changes through translation, protein modification, and interactions with microenvironment



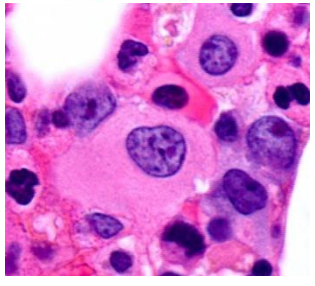
Published in final edited form as:
Nature. 2010 April 8; 464(7290): 852–857. doi:10.1038/nature08851.

Bone progenitor dysfunction induces myelodysplasia and secondary leukemia

Marc H.G.P. Raaijmakers[1,2,3,*], Siddhartha Mukherjee[1,2,3,4,*,#], Shangqin Guo[1,2,3], Siyi Zhang[1,2,3], Tatsuya Kobayashi[5], Jesse A. Schoonmaker[1,2,3], Benjamin L. Ebert[6], Fatima Al-Shahrour[6], Robert P. Hasserjian[7], Edward O. Scadden[1,2,3], Zinmar Aung[1,2,3], Marc Matza[1,2,3], Matthias Merkenschlager[8], Charles Lin[9], Johanna M. Rommens[10], and David. T. Scadden[1,2,3,4]

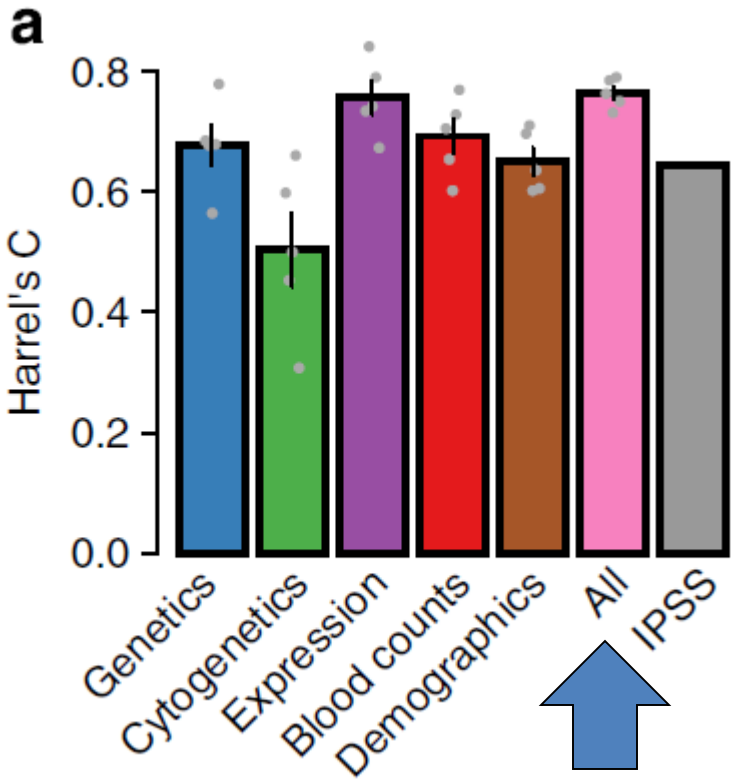


Dysplastic megakaryocytes in human MDS



Conclusion: Optimal diagnosis and classification of myeloid neoplasms must incorporate multiple testing modalities (as emphasized in WHO disease definitions)

- Impact of various factors on outcome in 124 MDS patients
- Optimal prognostic model was achieved by combining all information
- Future work should test existing dogmas and explore the interactions of molecular findings with morphologic findings
- Future models must also take into account response to various therapies



Gerstung M et al. Nature Comm 2015;6:5901