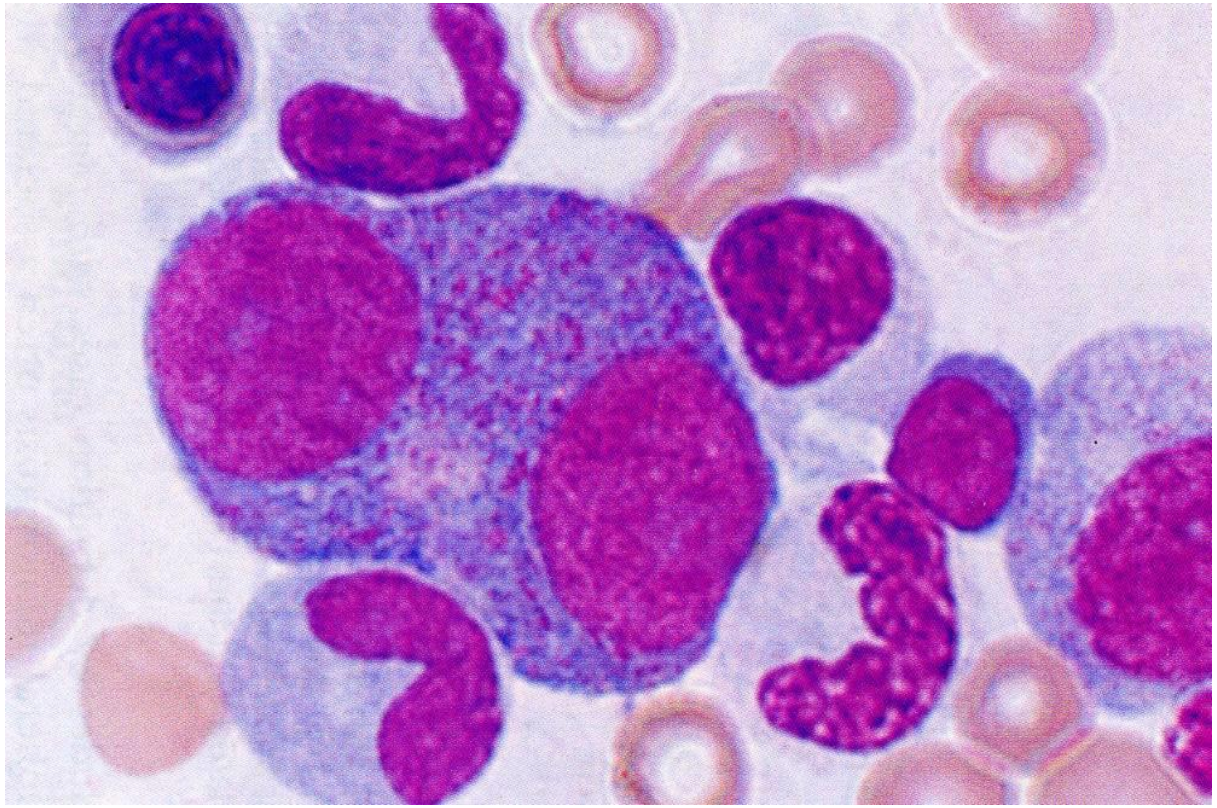
# Sindromi mielodisplastiche

prof. Gian Matteo Rigolin



Castoldi G. Atlas of blood cells. 2003; p 285-98.

# WHO classification of myeloid neoplasms and acute leukemia

1. Myeloproliferative neoplasms (MPN)
2. Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
3. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
4. **Myelodysplastic syndromes (MDS)**
5. Acute myeloid leukemia (AML) and related neoplasms
6. Blastic plasmacytoid dendritic cell neoplasm
7. Acute leukemias of ambiguous lineage
8. B-lymphoblastic leukemia/lymphoma
9. T-lymphoblastic leukemia/lymphoma

**Arber DA et al. Blood. 2016; 127(20):2391-2405**

# MDS: definizione

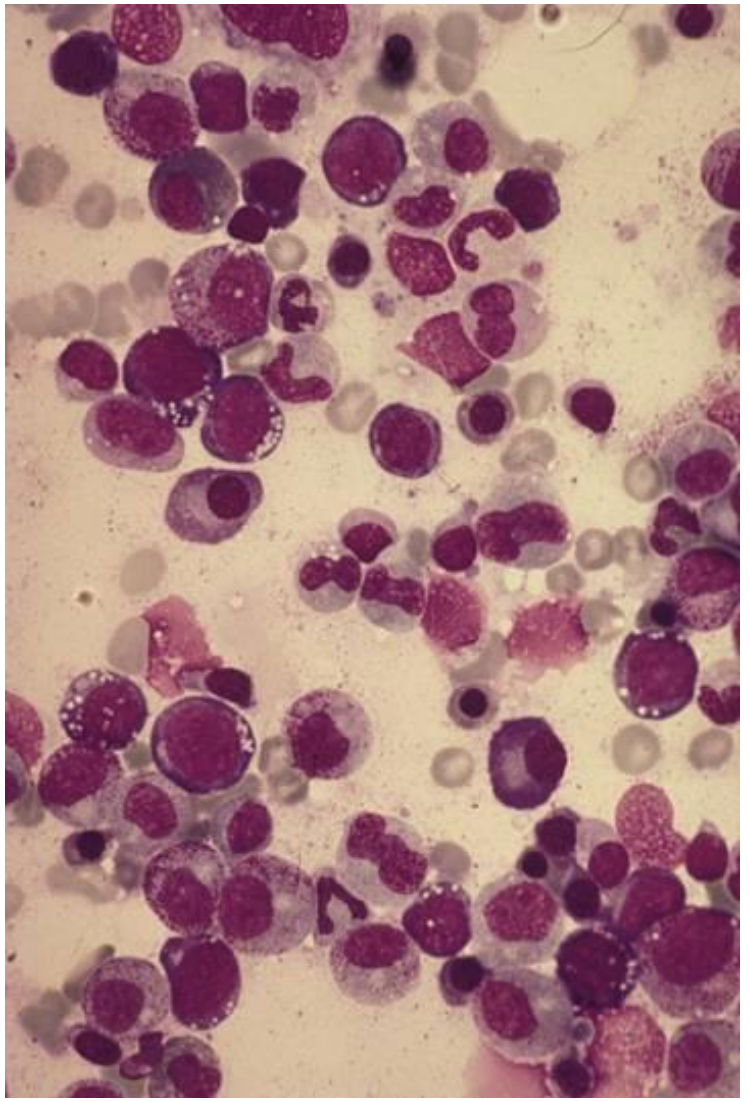
**Gruppo eterogeneo di disordini clonali della cellula staminale, contrassegnati da citopenia periferica e nella maggior parte dei casi da un midollo ipercellulato con evidenti alterazioni maturative (displasia).**

**Le MDS presentano un aumentato rischio di evoluzione in LAM.**

| | MDS | AML | MPD |
|---|---|---|---|
| Differentiation | Impaired | Impaired | Normal ← ← |
| Proliferation/survival | Impaired → → | Preserved | Increased |

Arrows indicate where a second hit could result in progression to AML.

Nimer SD. Blood 2008;111:4841.



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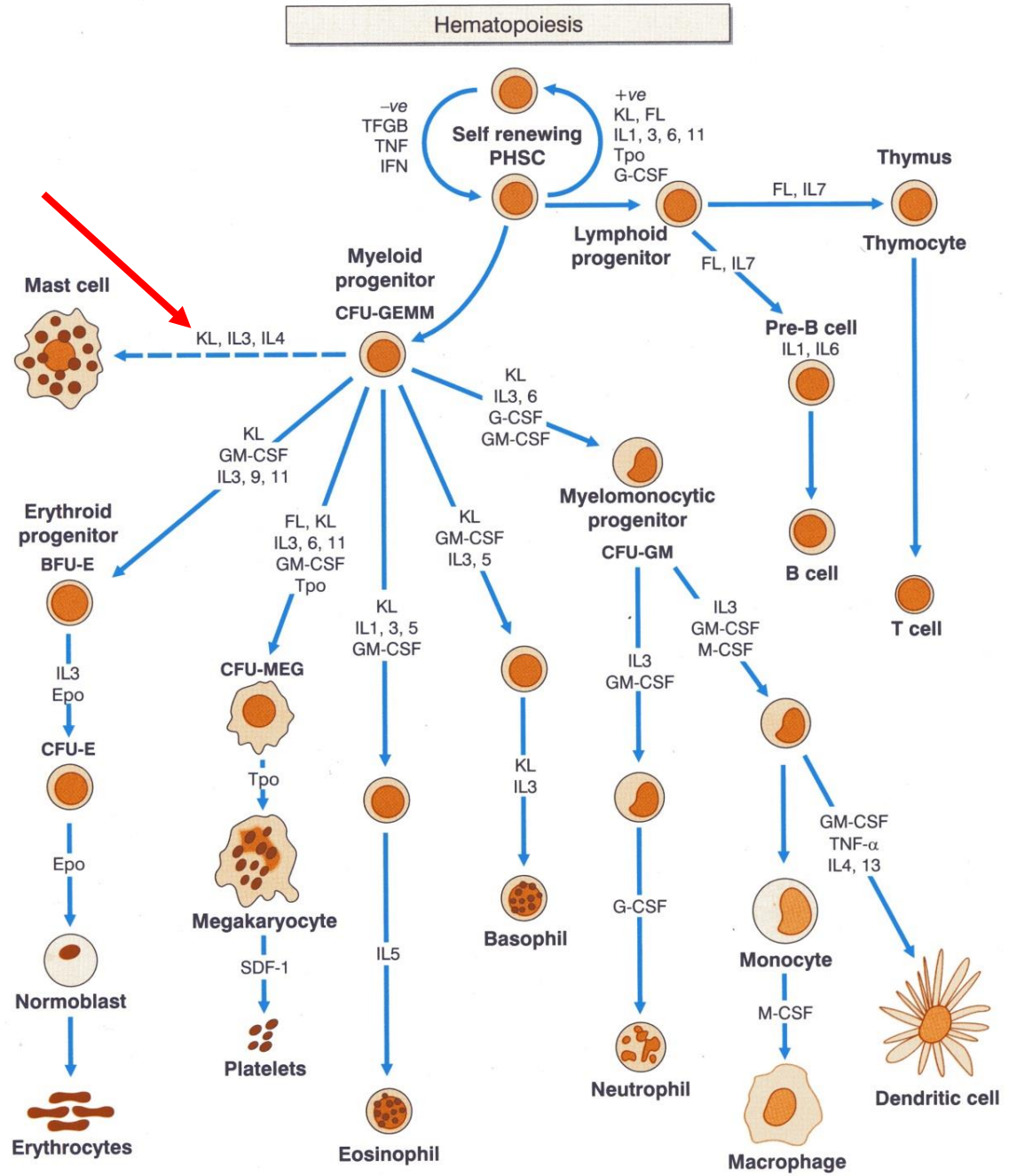
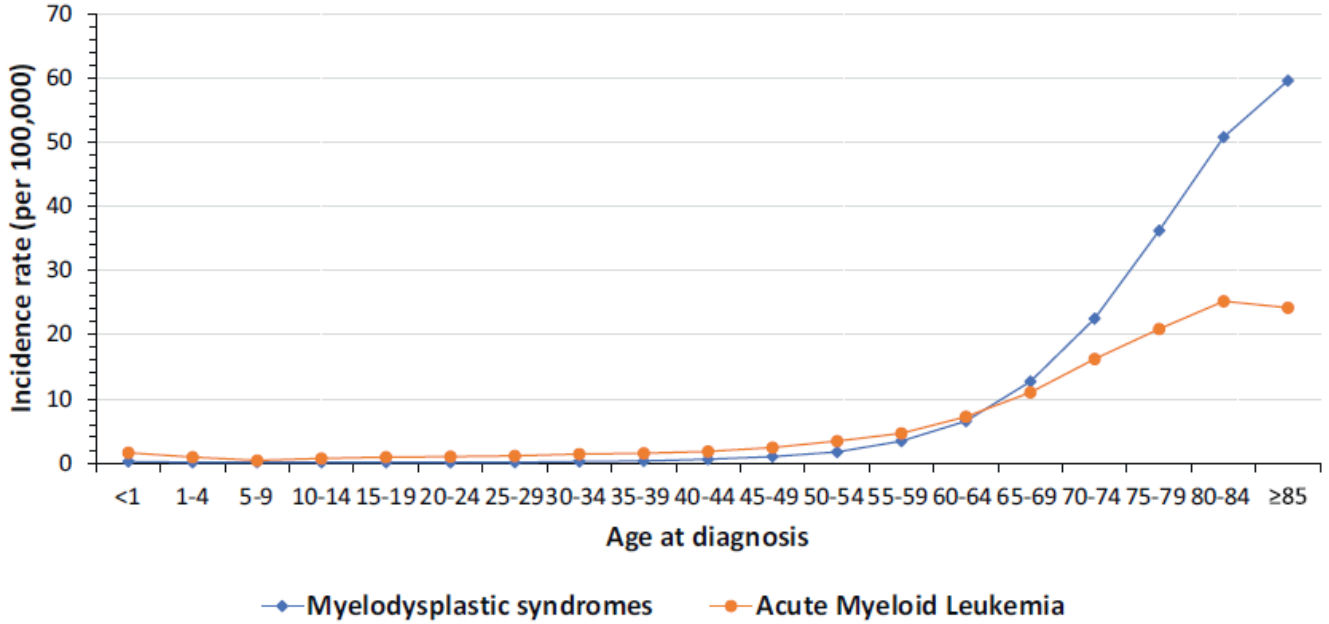
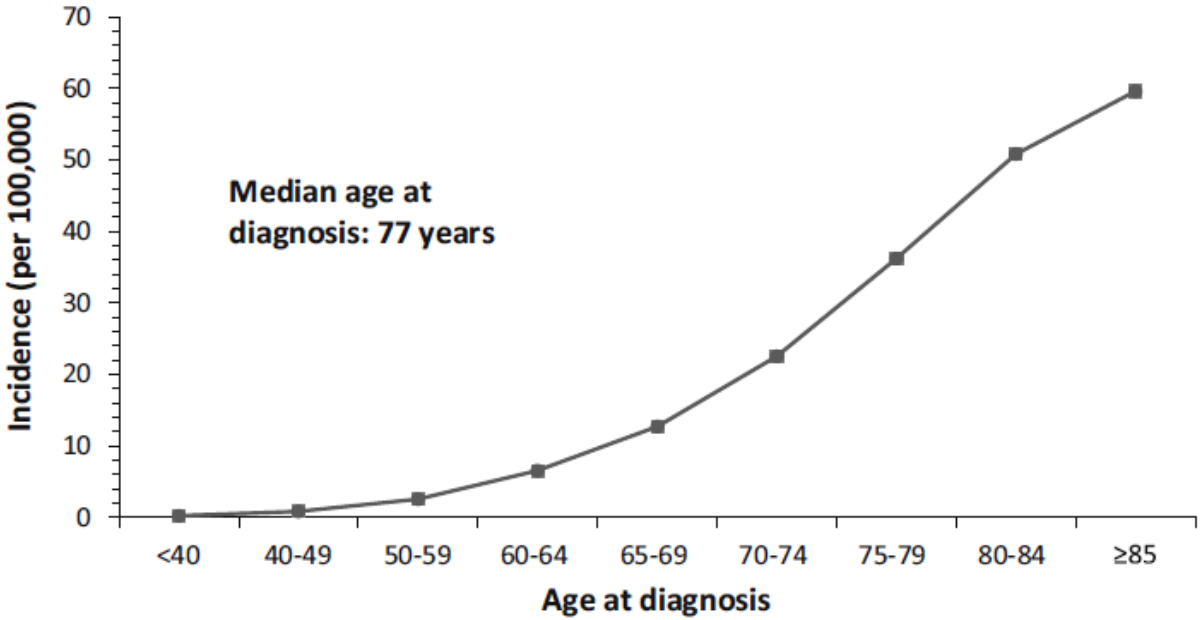
# MDS: definizione



# MDS incidenza

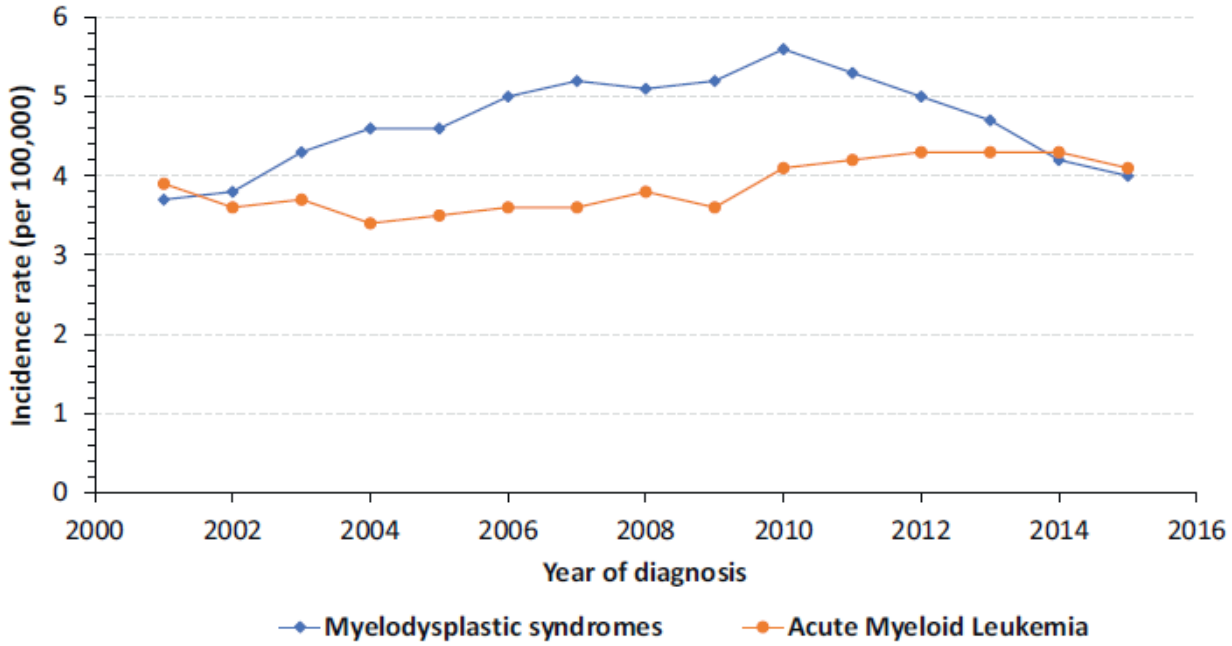


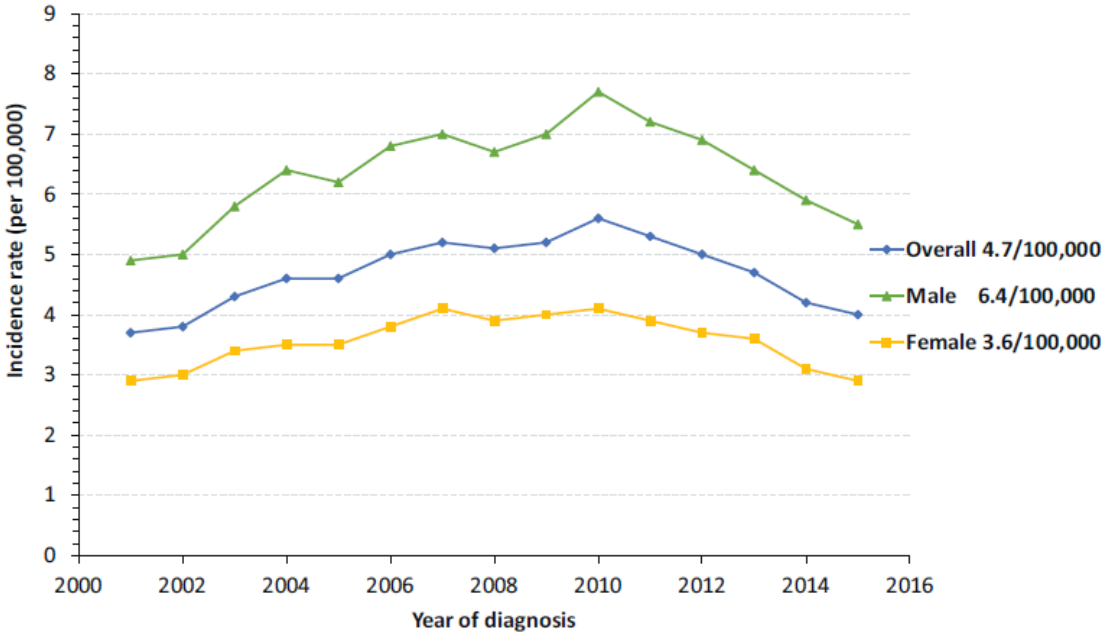




**Incidence of MDS or AML in the USA (Surveillance, Epidemiology, and End Results data, based on the Nov 2017).**

Zeidan et al. Blood Reviews 2018

# MDS: incidenza

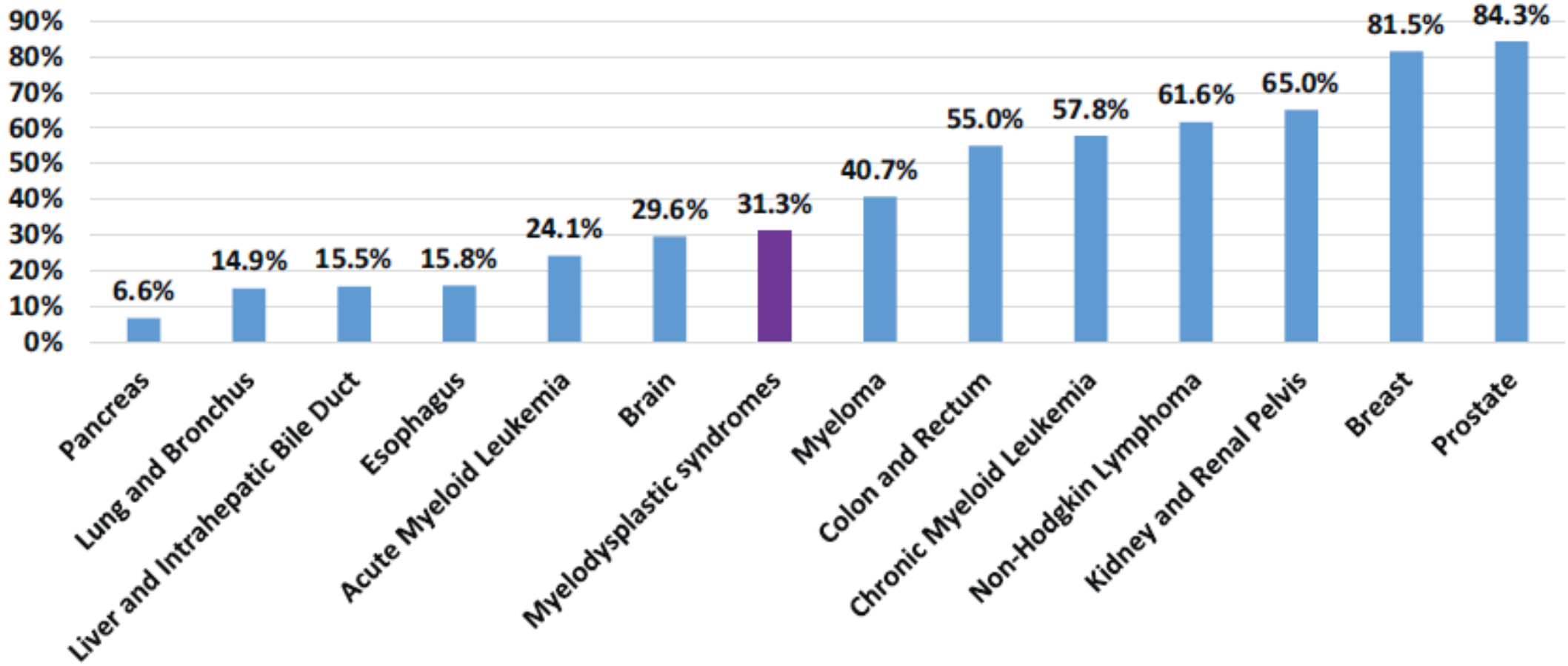



**Incidence of MDS or AML in the USA (Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).**

Zeidan et al. Blood Reviews 2018

# Sopravvivenza a 5 anni



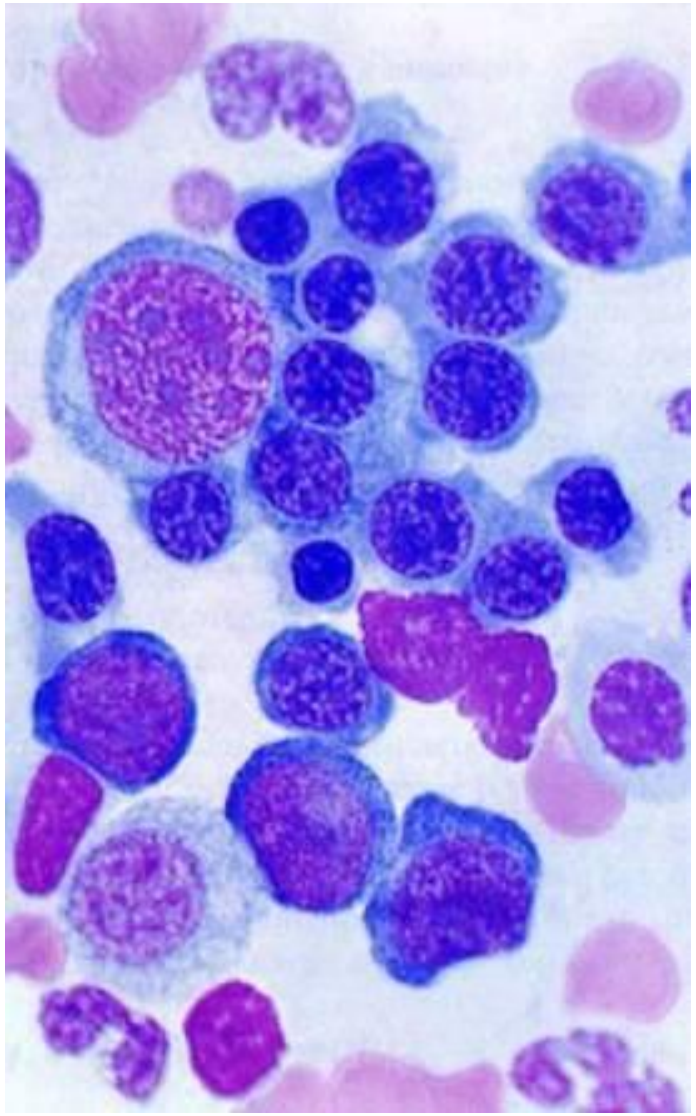

**Five-year overall survival of cancer patients in the United States (Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).**

**Zeidan et al. Blood Reviews 2018**

# Eziologia

- **La causa delle MDS è di solito sconosciuta.**

- **In alcuni casi una MDS può svilupparsi dopo l'esposizione a radiazioni, ad alcuni tossici ambientali quali il benzene o dopo trattamenti con alchilanti o inibitori delle topoisomerasi II per una precedente neoplasia**



Castoldi G. Atlas of blood cells. 2003; p 285-98.

# MDS

- **<u>The cause is known in only 15% of cases</u>**

- **Inherited predisposition**
  - is evident in a third of **paediatric** cases, including in children with Down's syndrome, Fanconi's anaemia, and neurofibromatosis.
  - In **adults**, inherited predisposition is less common but should be investigated in young adults or in families with other cases of MDS, AML, or AA.
- **Environmental factors** include previous use of **chemotherapy**, especially of alkylating agents and purine analogues, radiotherapy, and tobacco smoking.
- Recognised **occupational factors** include exposure to benzene and its derivatives,[7] and an excess of cases is reported in agricultural and industrial workers.

***Panel:*** **Causes of myelodysplastic syndromes**

**Antineoplastic agents**

*Alkylating agents*

- Busulfan
- Carboplatin
- Carmustine
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Dacarbazine
- Lomustine
- Melphalan

*Topoisomerase II inhibitors*

- Daunorubicin
- Doxorubicin
- Etoposide
- Mitoxantrone
- Razoxane

*Purine analogues*

- Fludarabine and others

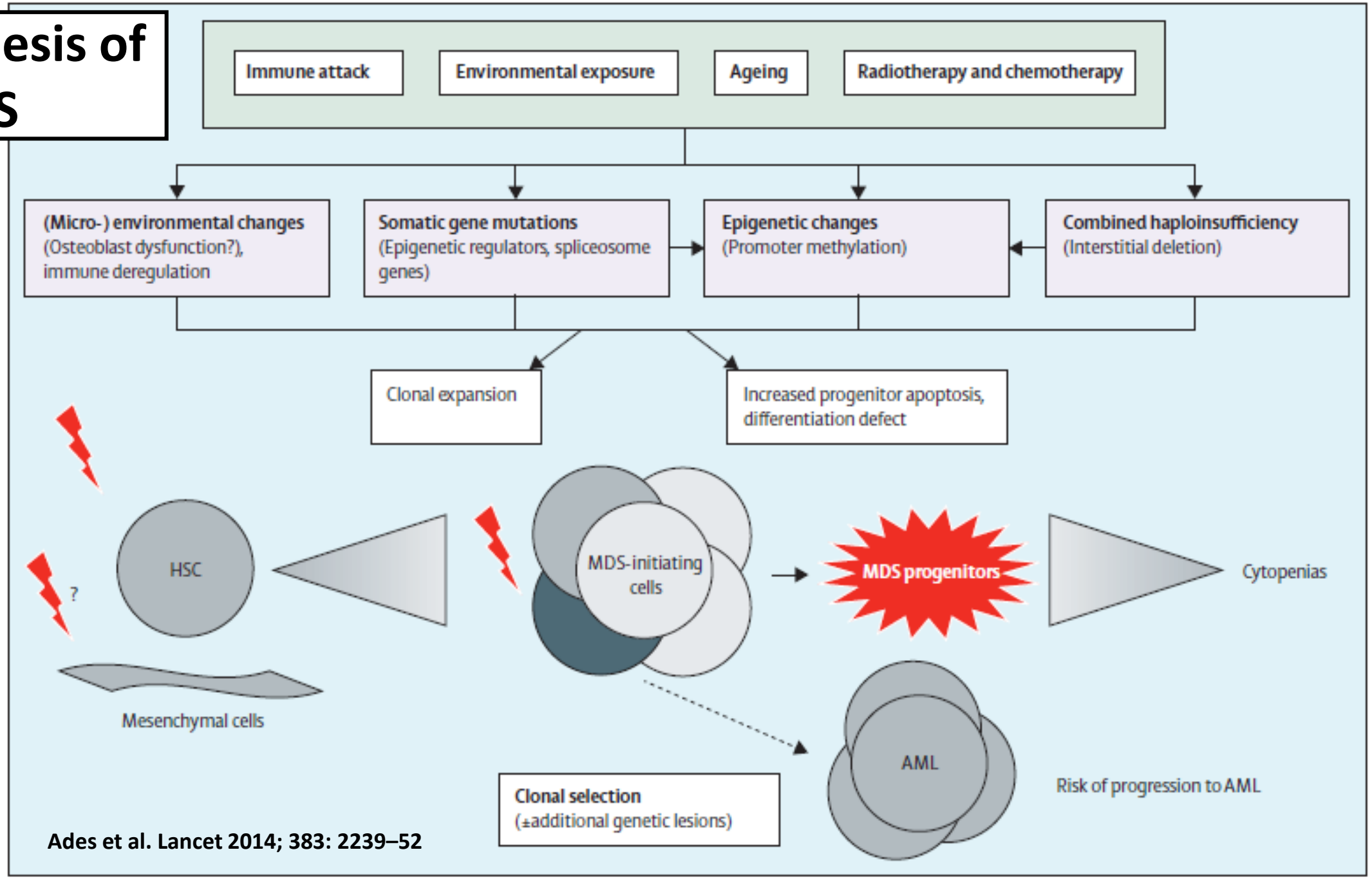
**Radiotherapy**

*Environmental factors*

- Tobacco
- Ionising radiation
- Benzene exposure (and industrial hydrocarbons)
- Agricultural compounds (pesticides, herbicides, fertilisers)

**Ades et al. Lancet 2014; 383: 2239–52**

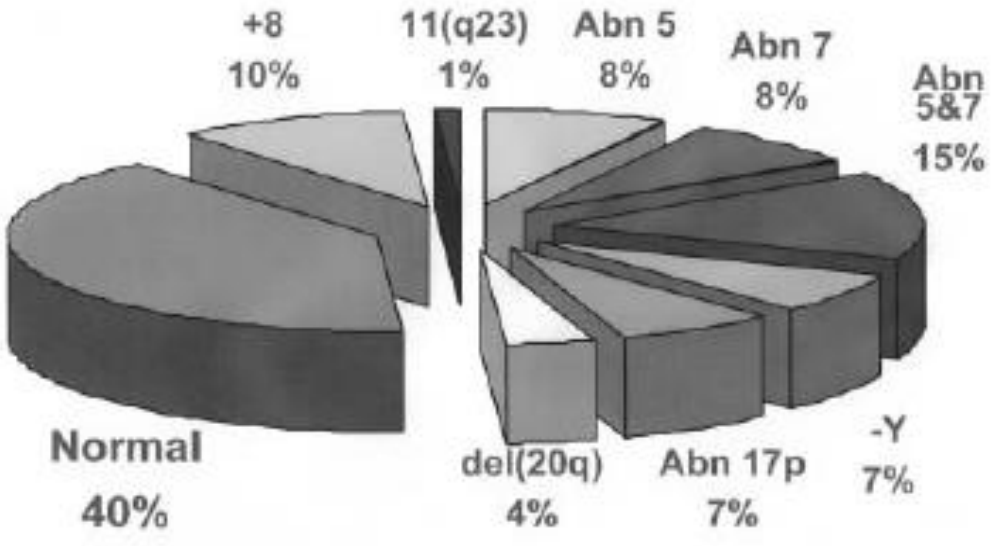
# Pathogenesis of MDS



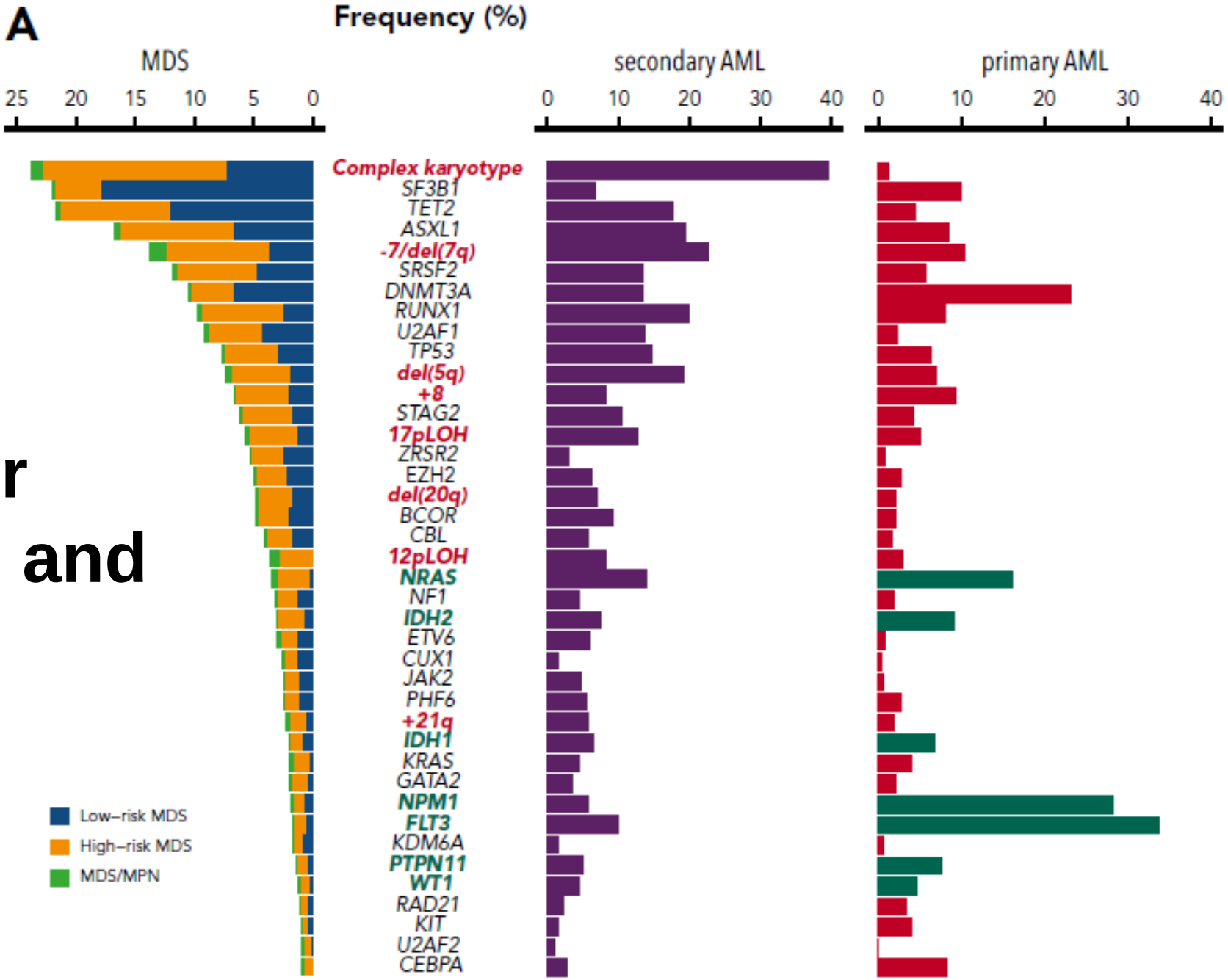

Ades et al. Lancet 2014; 383: 2239–52

# Citogenetica

- Anomalie citogenetiche sono riscontrabili del 40-70% delle MDS de novo e nel 95% delle forme secondarie a chemioterapia (therapy-related)
-

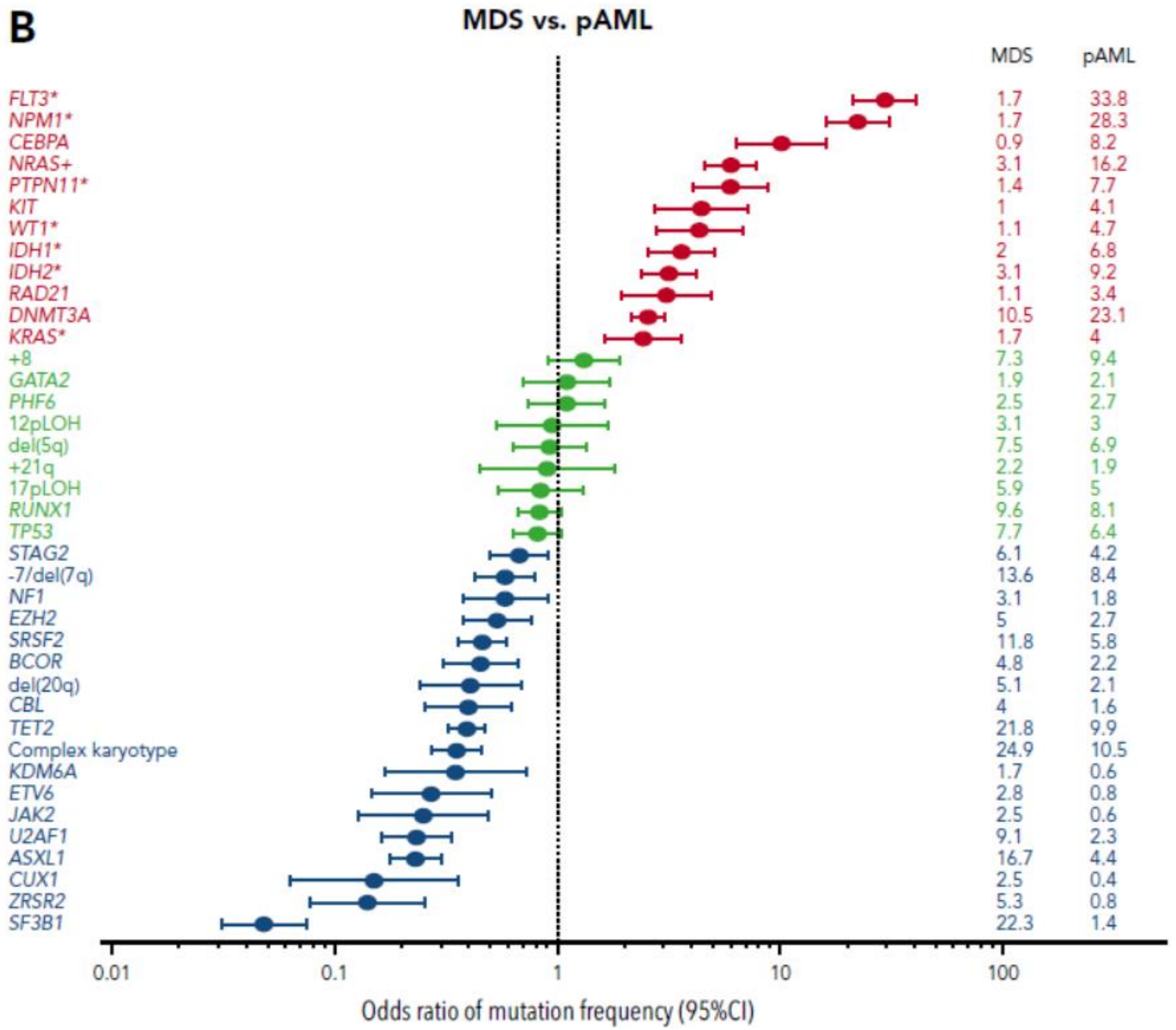


# Common driver alterations in MDS and other myeloid neoplasms.




Ogawa S. Blood. 2019 Mar 7;133(10):1049-1(

# Common driver alterations in MDS and other myeloid neoplasms.

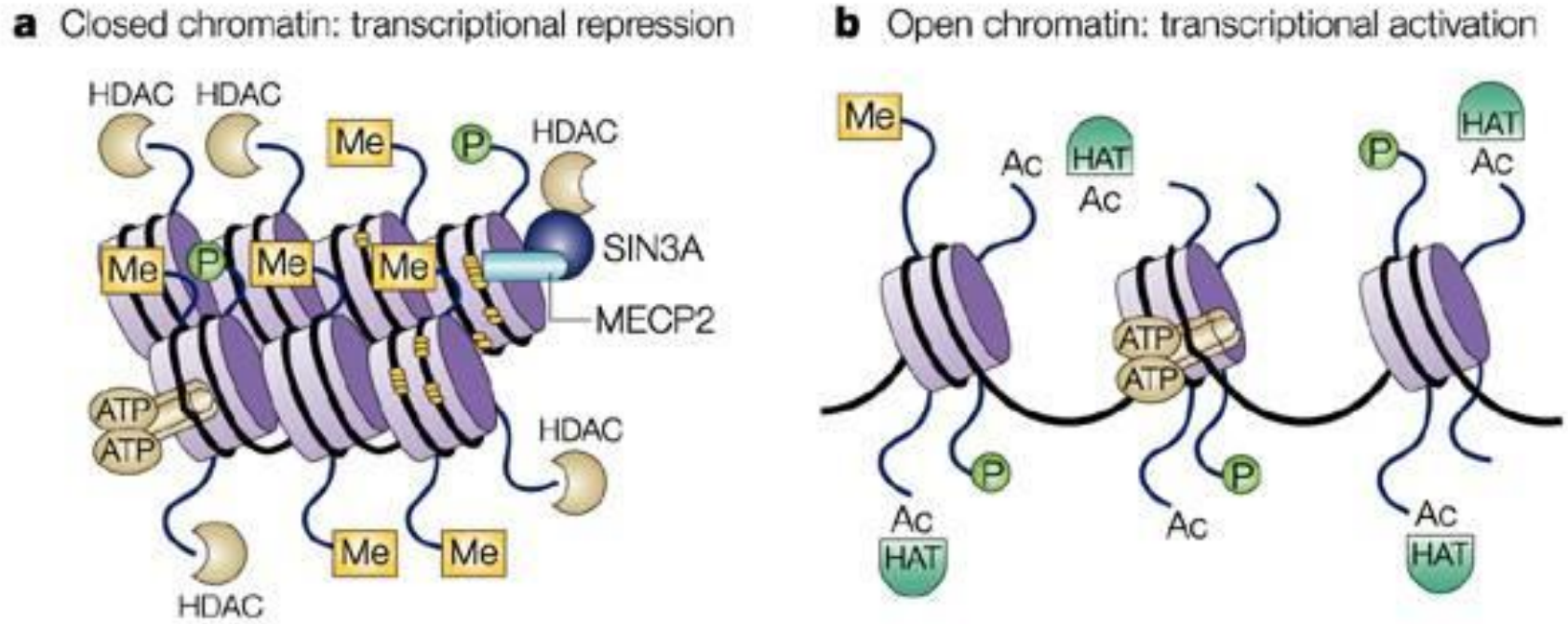



Ogawa S. Blood. 2019 Mar 7;133(10):1049-1059.

# Major driver genes in MDS

| Pathway/functions | Driver genes |
|---|---|
| DNA methylation | *DNMT3A*, *TET2*, *IDH1*,* *IDH2*,* and *WT1* |
| Chromatin modification | *EZH2*, *SUZ12*, *EED*, *JARID2*, *ASXL1*, *KMT2*, *KDM6A*, *ARID2*, *PHF6*, and *ATRX* |
| RNA splicing | *SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, *ZRSR2*, *SF1*, *PRPF8*, *LUC7L2* |
| Cohesin complex | *STAG2*, *RAD21*, *SMC3*, and *SMC1A* (*PDS5B*, *CTCF*, *NIPBL*, and *ESCO2*) |
| Transcription | *RUNX1*,† *ETV6*,† *GATA2*,† *IRF1*, *CEBPA*, *BCOR*, *BCORL1*, *NCOR2*, and *CUX1* |
| Cytokine receptor/tyrosine kinase | *FLT3*, *KIT*, *JAK2*, and *MPL*, *CALR*, and *CSF3R* |
| RAS signaling† | *PTPN11*, *NF1*, *NRAS*, *KRAS*, and *CBL* (*RIT1* and *BRAF*) |
| Other signaling | *GNAS*, *GNB1*, *FBWX7*, and *PTEN* |
| Checkpoint/cell cycle | *TP53* and *CDKN2A* |
| DNA repair | *ATM*, *BRCC3*, and *FANCL* |
| Others | *NPM1*, *SETBP1*, and *DDX41*† |

Ogawa S. Blood. 2019 Mar 7;133(10):1049-1059.




# Epigenetic changes

Nature Reviews | Drug Discovery

Nucleosomes consist of DNA (black line) wrapped around histone octomers (purple).

Post-translational modification of histone tails by methylation (Me), phosphorylation (P) or acetylation (Ac) can alter the higher-order nucleosome structure.

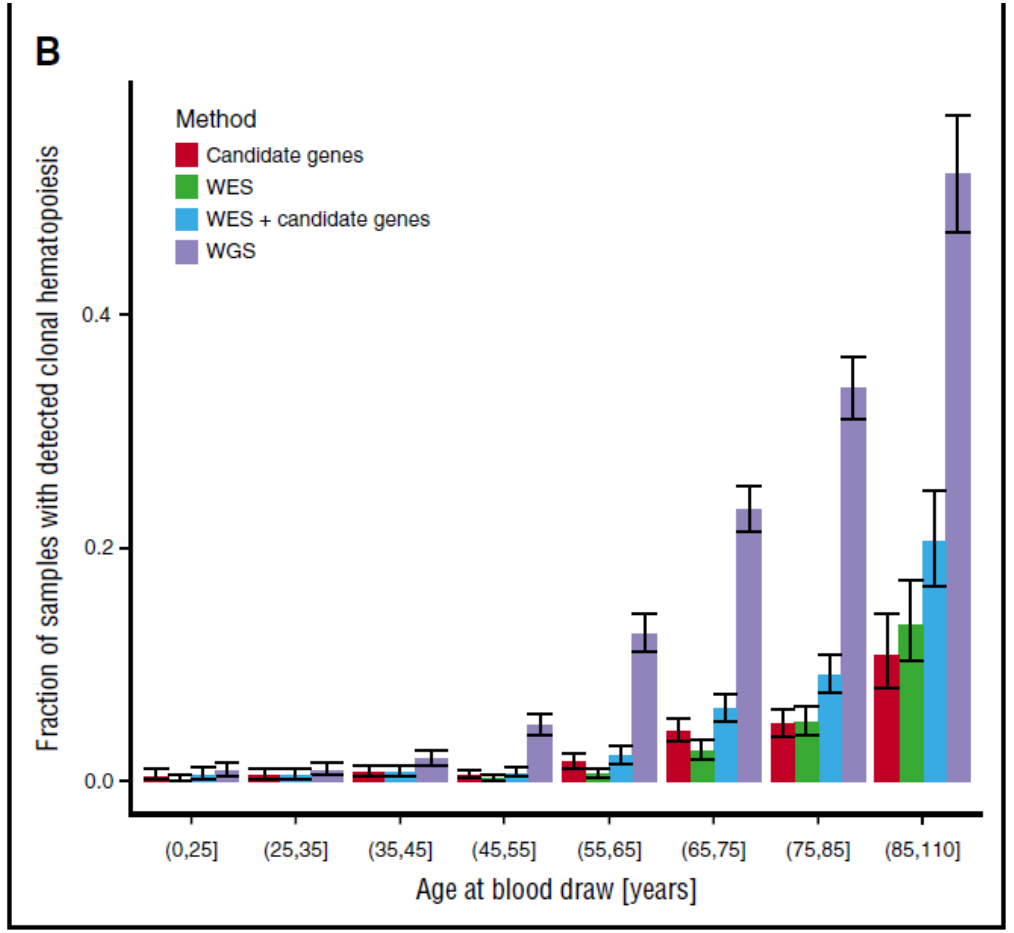
Nucleosome structure can be regulated by ATP-dependent chromatin remodellers (yellow cylinders), and the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Methyl-binding proteins, such as the methyl-CpG-binding protein (MECP2), target methylated DNA (yellow) and recruit HDACs.

**a. DNA methylation and histone deacetylation induce a closed-chromatin configuration and transcriptional repression.**

**b. DNA demethylation and histone acetylation relaxes chromatin, and allows transcriptional activation.**

# Clonal hematopoiesis (CH)

- **WGS of 11.262 Icelanders reveals that CH is very common in the elderly.**
- **Somatic mutation of some genes is strongly associated with CH, but in most cases, no driver mutations were evident (12.6%, 177/1403).**
- **CH is associated with increased mortality rates, risk for hematological malignancy, smoking behavior, telomere length, Y-chromosome loss, and other phenotypic characteristics.**



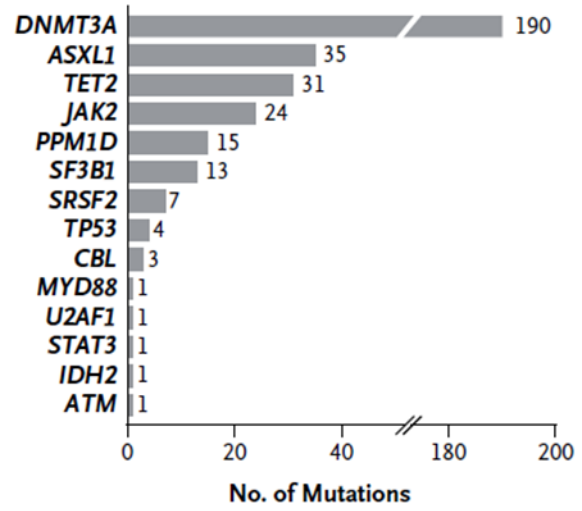

Zink F, et al. Blood. 2017;130(6):742-752.

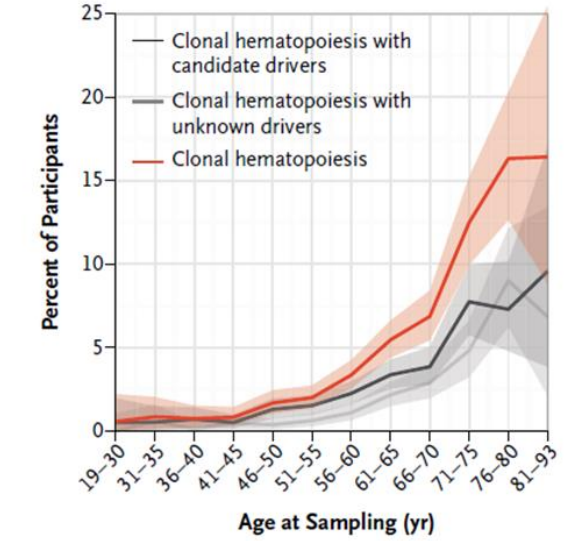
# Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

- whole-exome sequencing of DNA in PB cells from **12,380** persons, unselected for cancer or hematologic phenotypes from Swedish national patient registers.

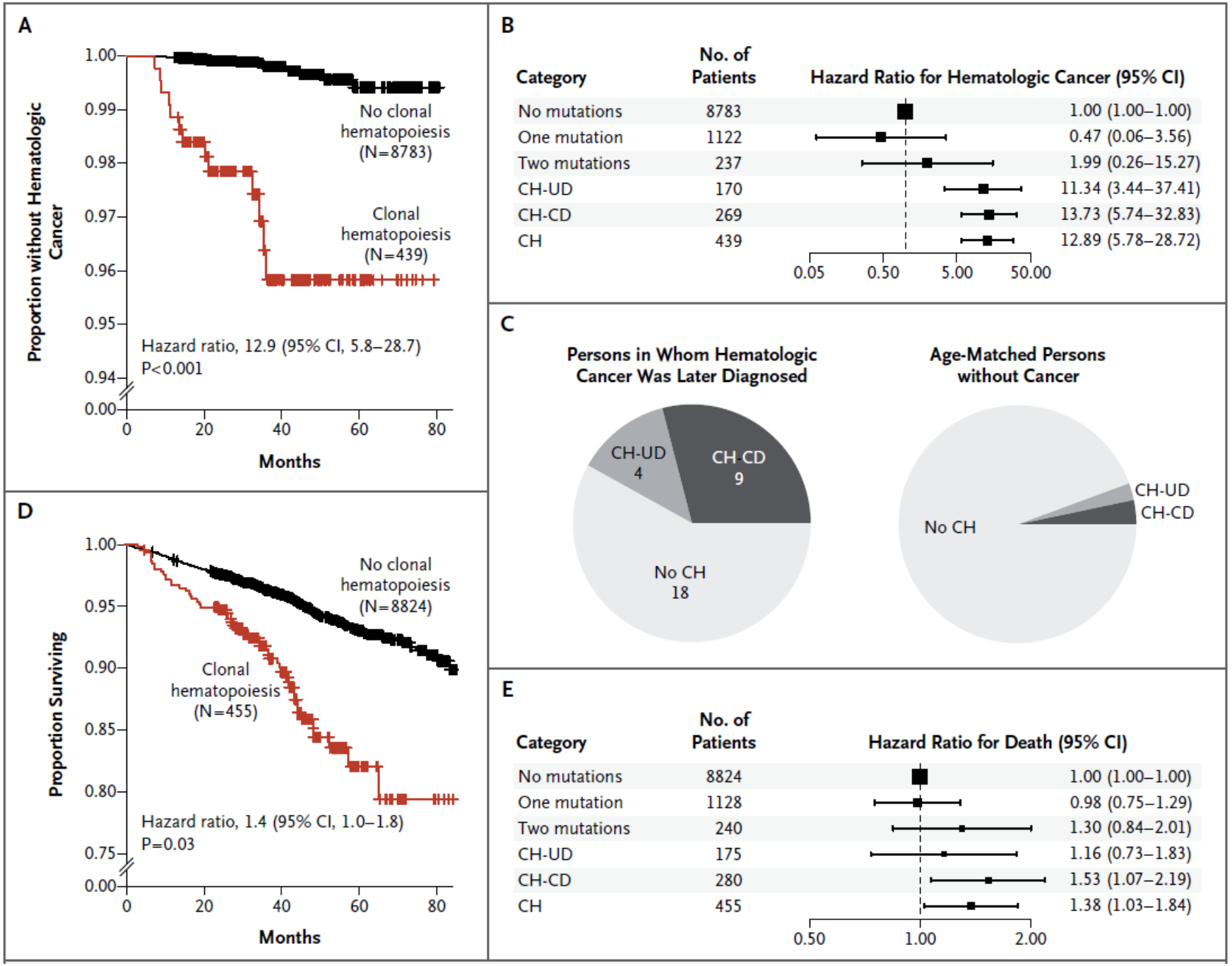
- Clonal hematopoiesis with somatic mutations was observed **in 10% of persons older than 65 years of age** but in only 1% of those younger than 50 years of age.

- **Clonal hematopoiesis was a strong risk factor for subsequent hematologic cancer** (HR, 12.9; 95% confidence interval, 5.8 to 28.7).




Genovese et al, N Engl J Med 2014;371:2477-87.



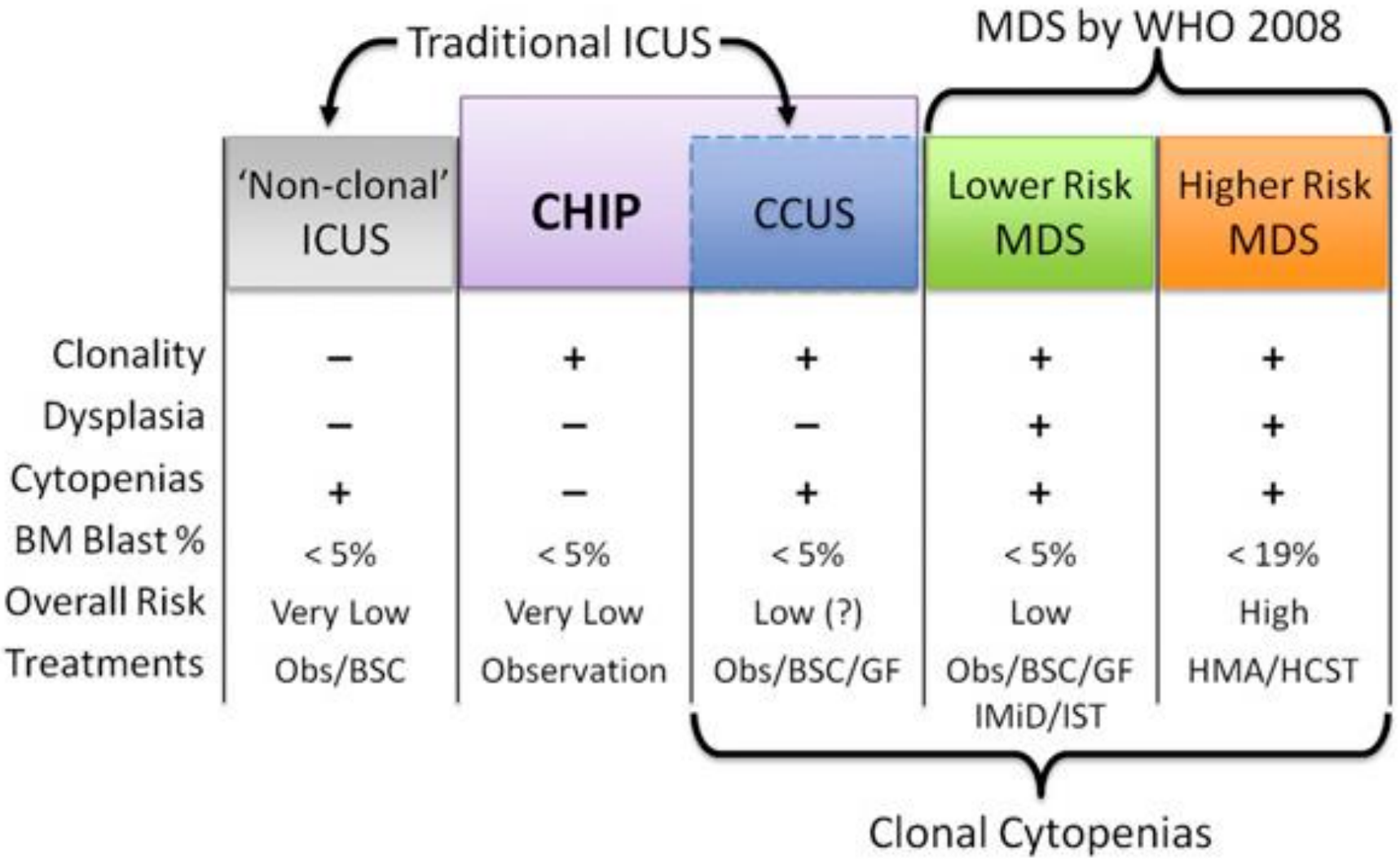

Genovese et al, N Engl J Med 2014;371:2477-87.

## Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele frequency of at least 2% (e.g., *DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, U2AF1, CREBBP, CUX1, SRSF2, MLL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1*)
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

**Steensma et al, Blood 2015;126:9**

# Clonal hematopoiesis of undetermined potetial (CHIP)



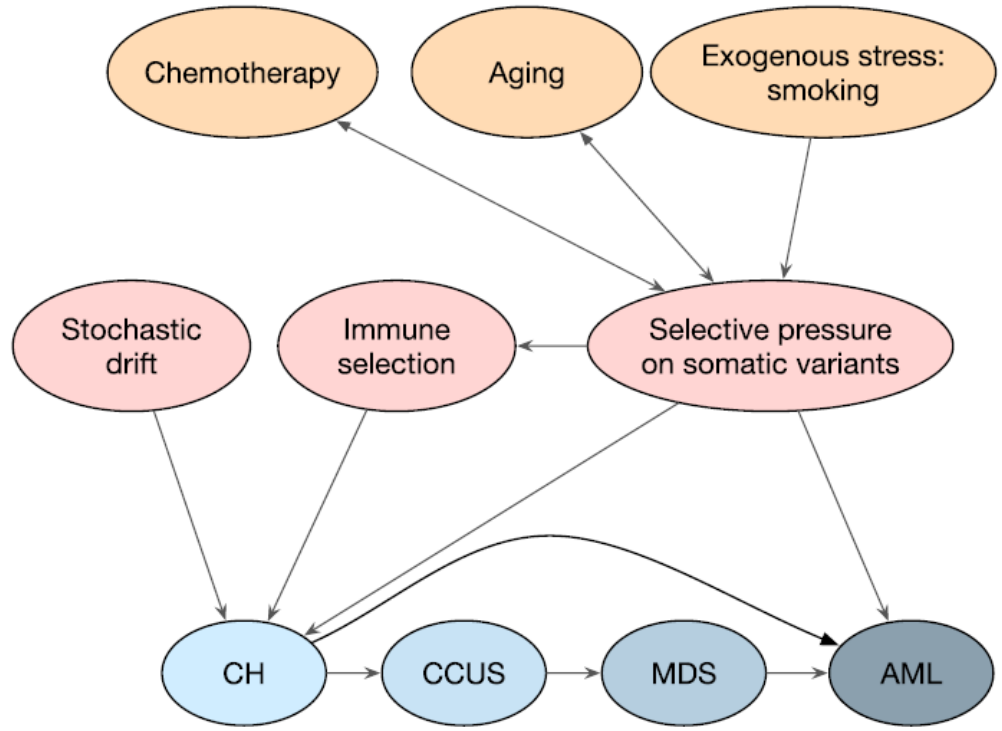

ICUS: idiopatic cytopenia of undetermined significance
CCUS: clonal cytopenia of undetermined signficance

**Steensma et al, Blood 2015;126:9**

# Clonal evolution of CHIP

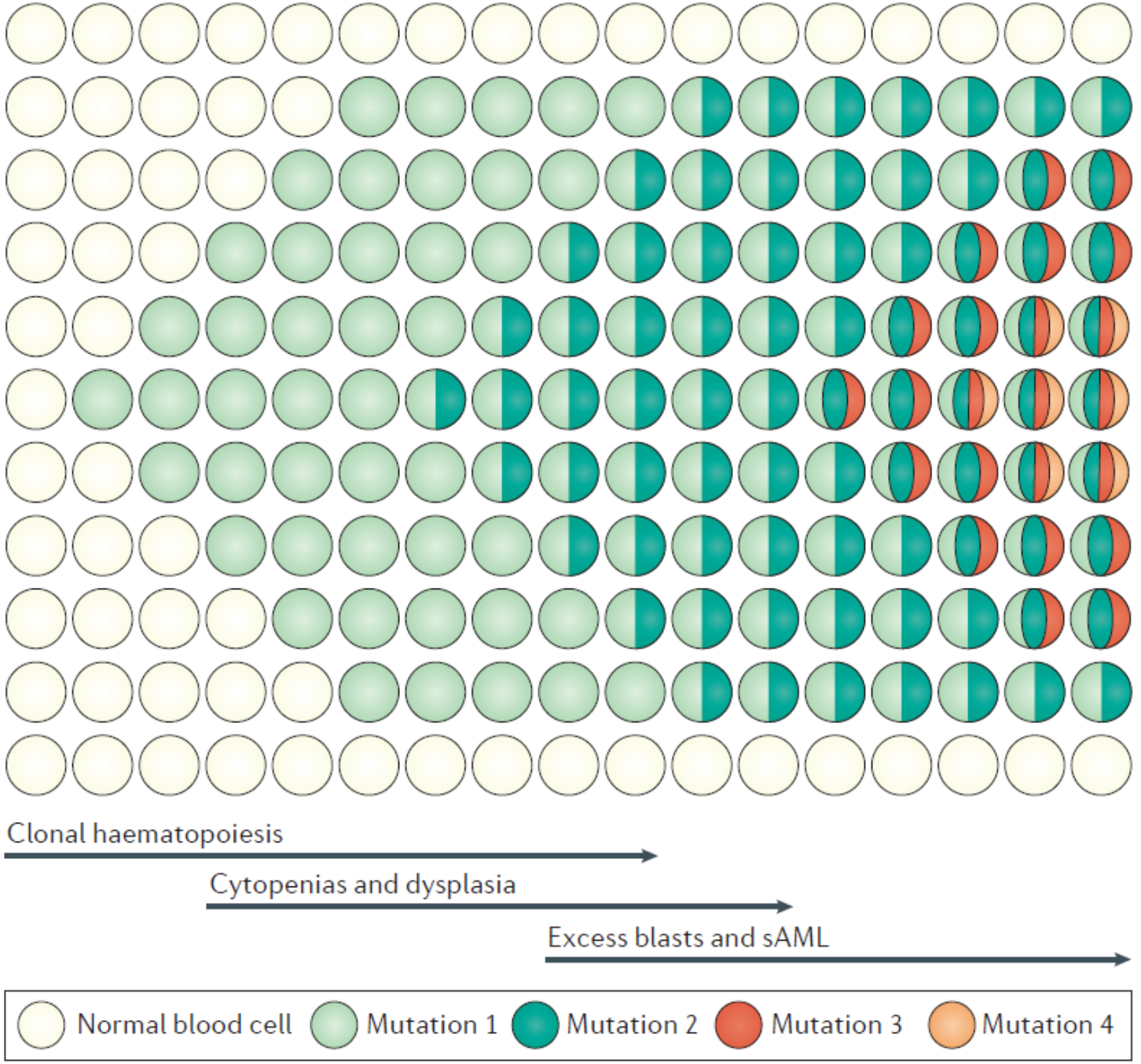
- **Investigators have focused on various MDS- and AML-associated phenomena that may aid and abet clonal evolution.**

- **The primary driver of progression of CHIP to overt neoplasia has been assumed to be acquisition of new mutation in a clonal cell with self-renewal properties.**

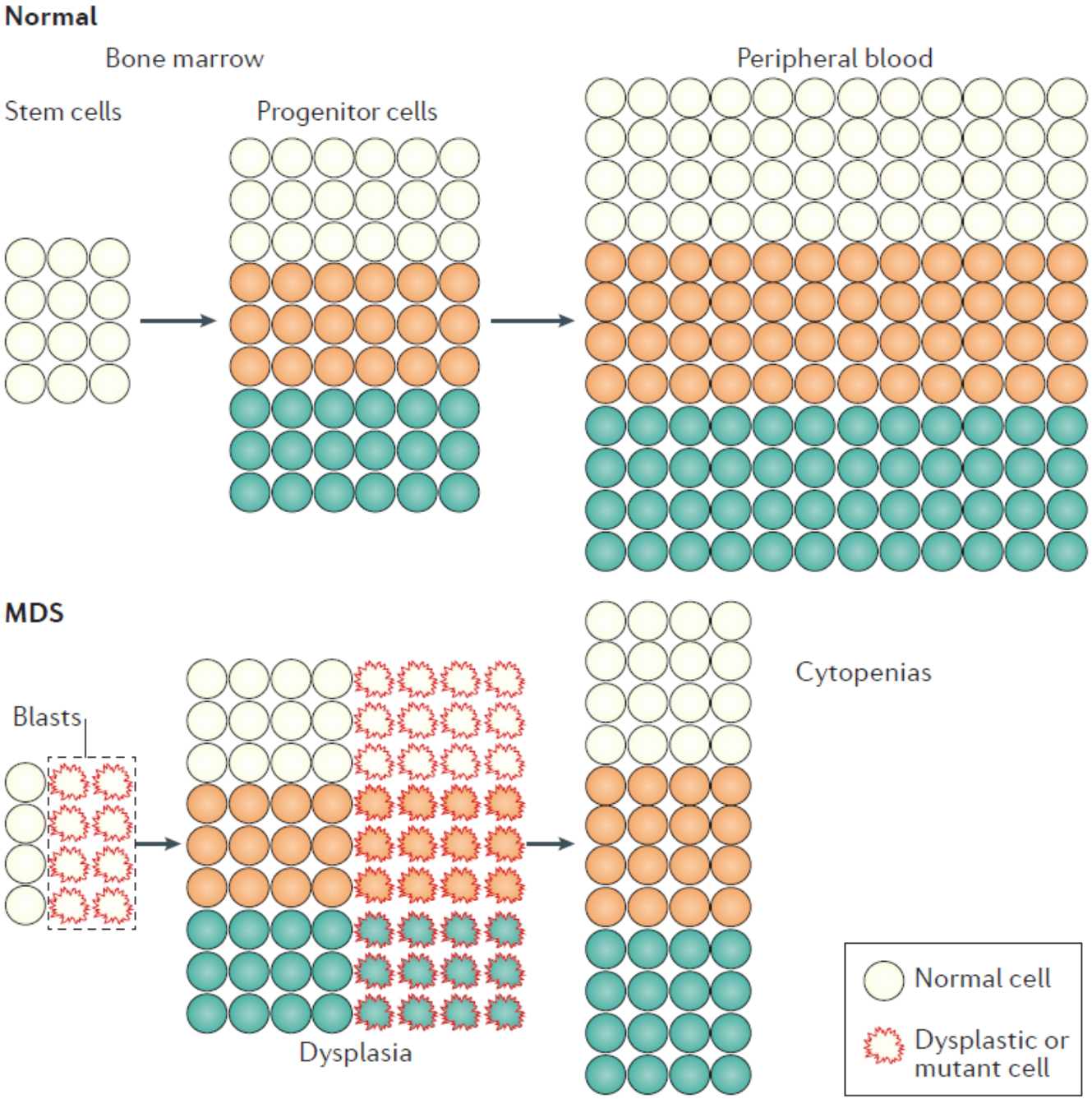



David P. Steensma, ASH 2018

Bowman RL, et al. Cell Stem Cell. 2018;22(2):157-170.

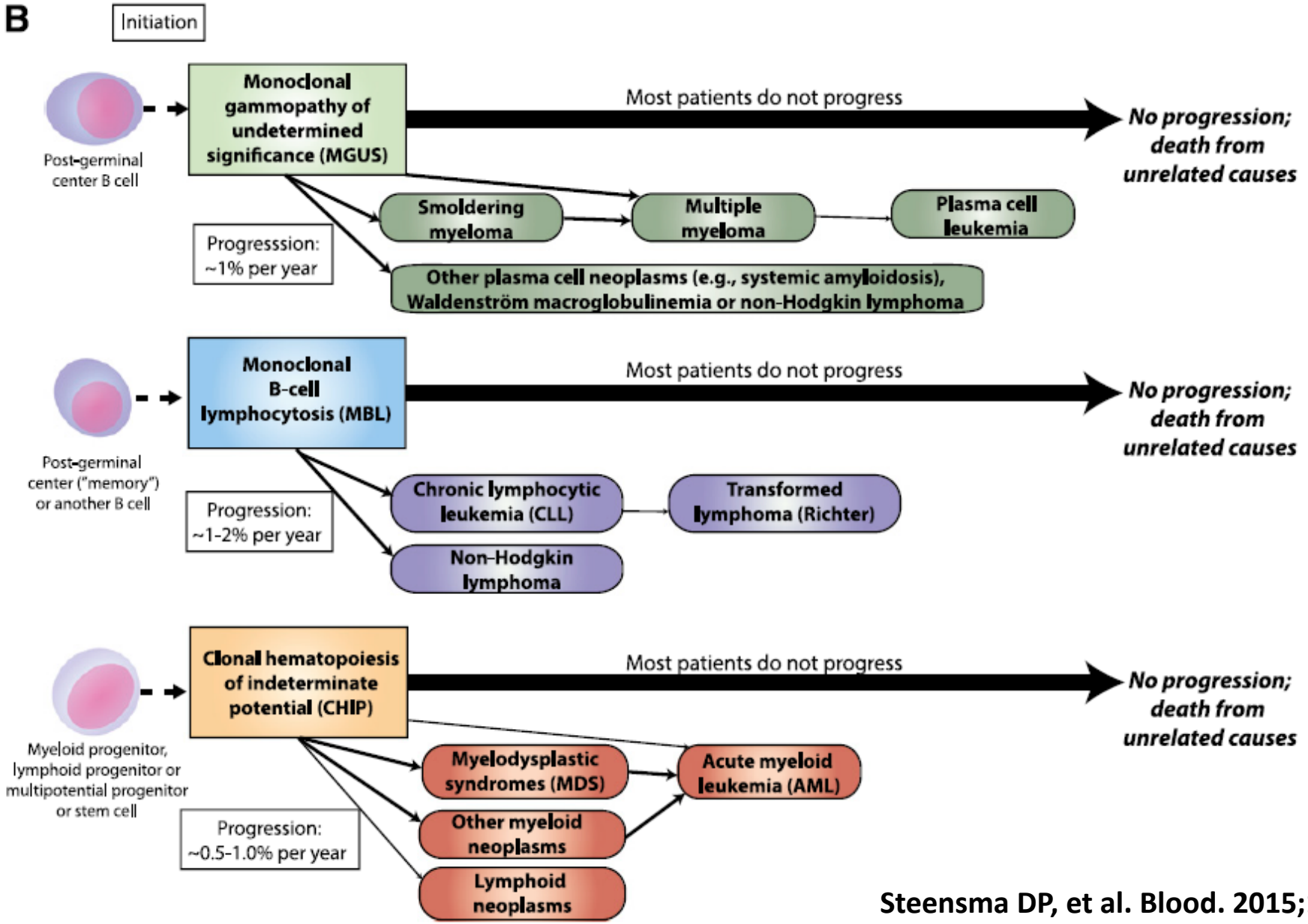



Sperling et al. Nat Rev Cancer 2017



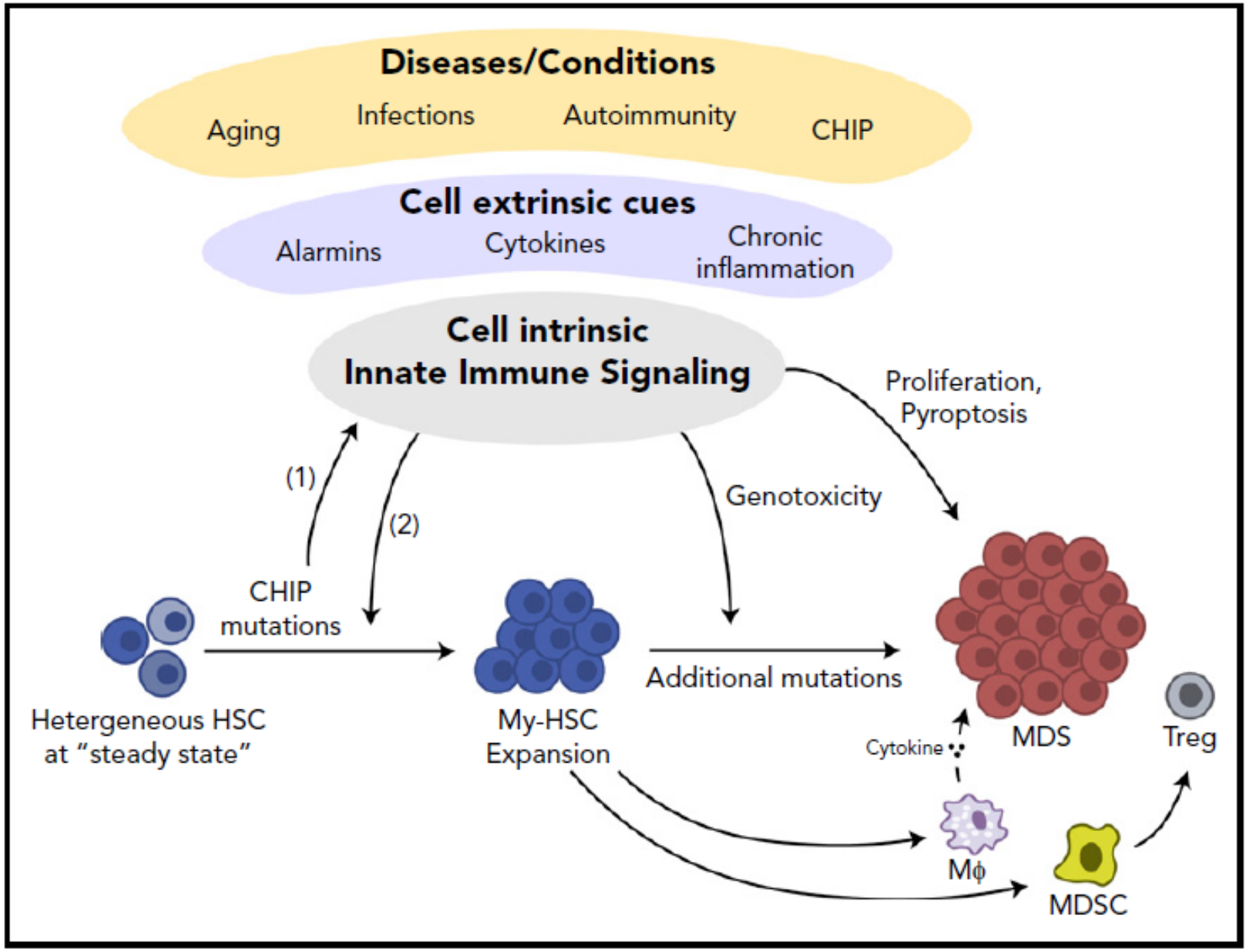

Sperling et al. Nature Reviews Cancer 2017

# CHIP as a precursor state for hematological neoplasms.



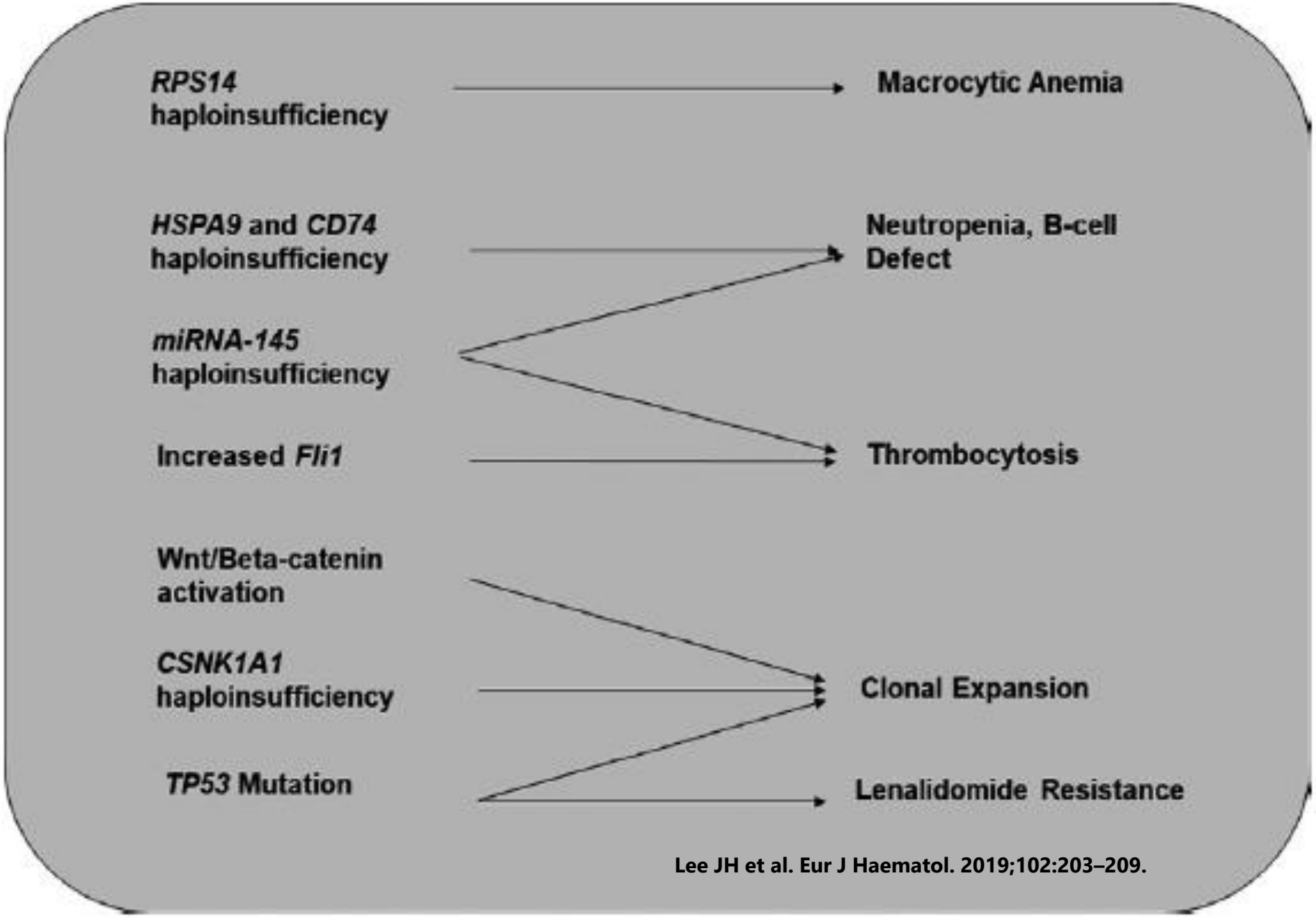

Steensma DP, et al. Blood. 2015;126(1):9-16.

**Figure 2. Model of innate immune signaling dysregulation in the pathogenesis of MDS.** Certain diseases and conditions, such as aging, autoimmune disorders, chronic infections, and/or clonal hematopoiesis of indeterminate potential (CHIP), can induce innate immune signaling dysregulation in HSCs in part by creating an inflammatory BM microenvironment characterized by increased alarmins and/or cytokines. Development of MDS may occur by at least 2 independent mechanisms. (1) CHIP-associated mutations (ie, DNMT3a or TET2) occur in HSCs by innate immune independent mechanisms and drive the expansion of myeloid-biased HSC leading to altered innate immune signaling and development of MDS. (2) Prolonged innate immune signaling caused by clonally expanded myeloid-biased HSCs directly increases the risk of acquiring mutations (ie, CHIP mutations) contributing to MDS. Innate immune signaling dysregulation at the MDS stage occurs through cell-intrinsic (ie, increased cell death via pyroptosis) and cell-extrinsic mechanisms (ie, cytokines and alarmins stimulation from macrophage and myeloid derived suppressor cells [MDSCs]). As a result of altered innate immune signaling, MDSCs also promote regulatory T cell (Treg) activation to limit T-cell surveillance.

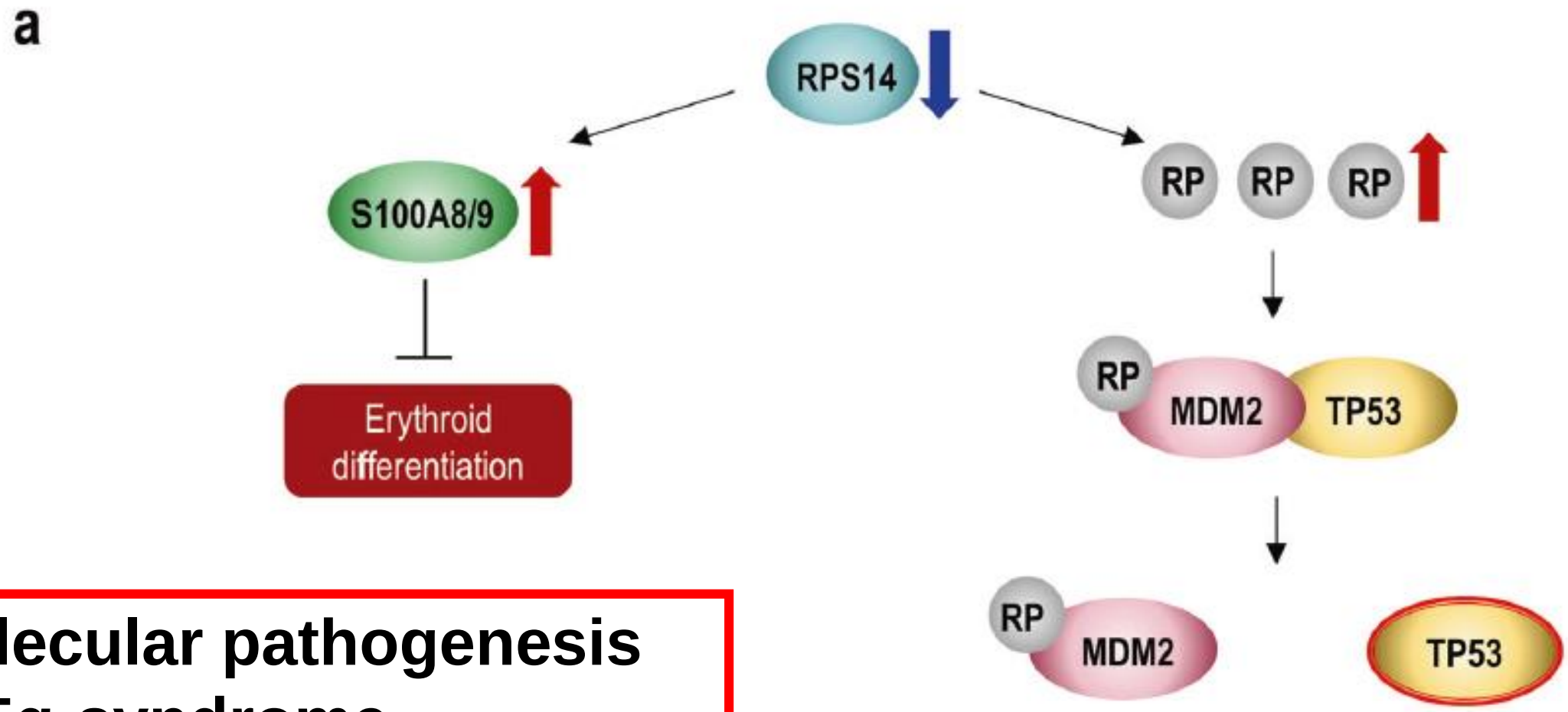



Barreyro et al. Blood. 2018;132(15):1553-1560

# Molecular abnormalities in del(5q) MDS




Lee JH et al. Eur J Haematol. 2019;102:203–209.



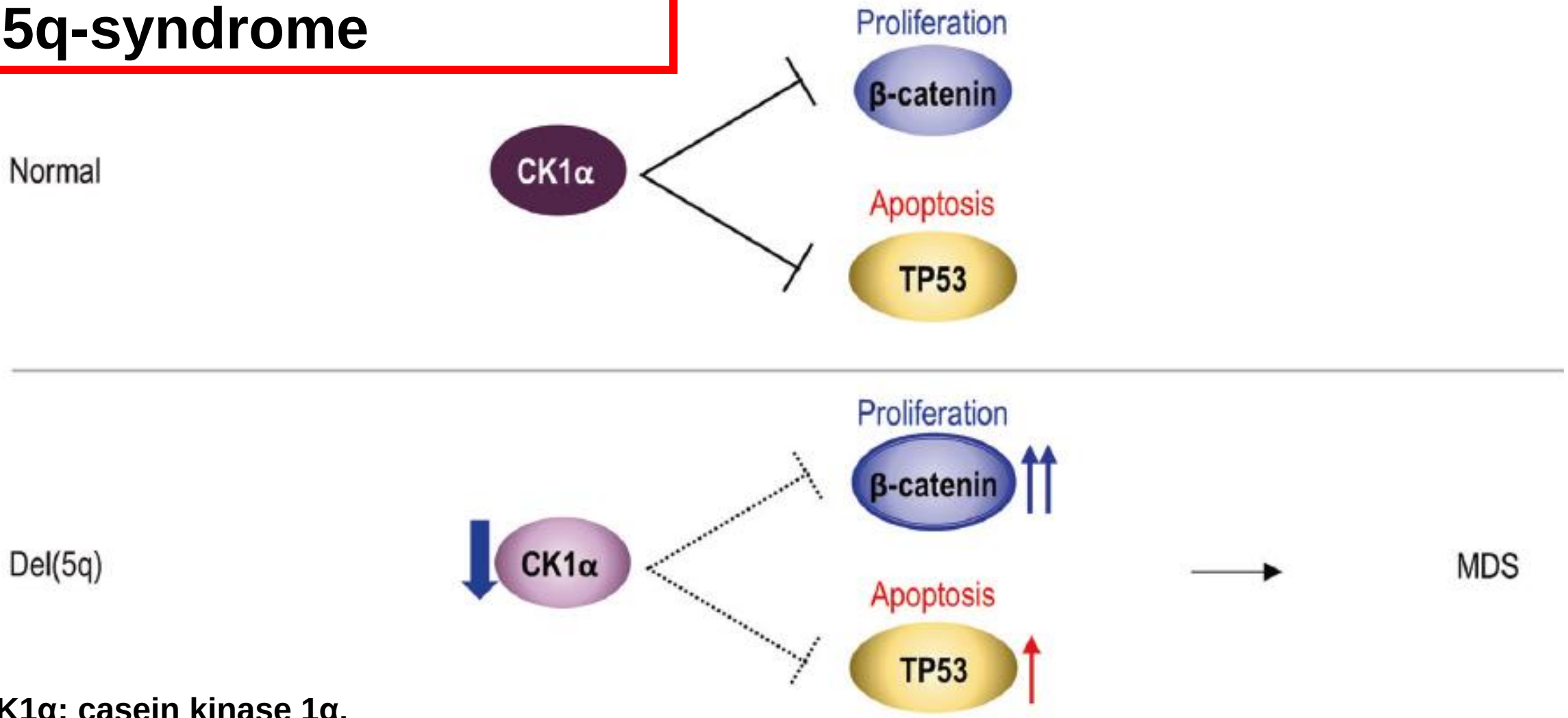

# Molecular pathogenesis of 5q-syndrome

**Decreasing RPS14 expression enhances other ribosomal proteins (RPs) such as RPL11 or RPS19, which sequester MDM2, an E3 ubiquitin ligase that also negatively regulates TP53.**

**Elevated TP53 activation leads to enhanced TP53-dependent apoptosis of erythroid progenitors.**

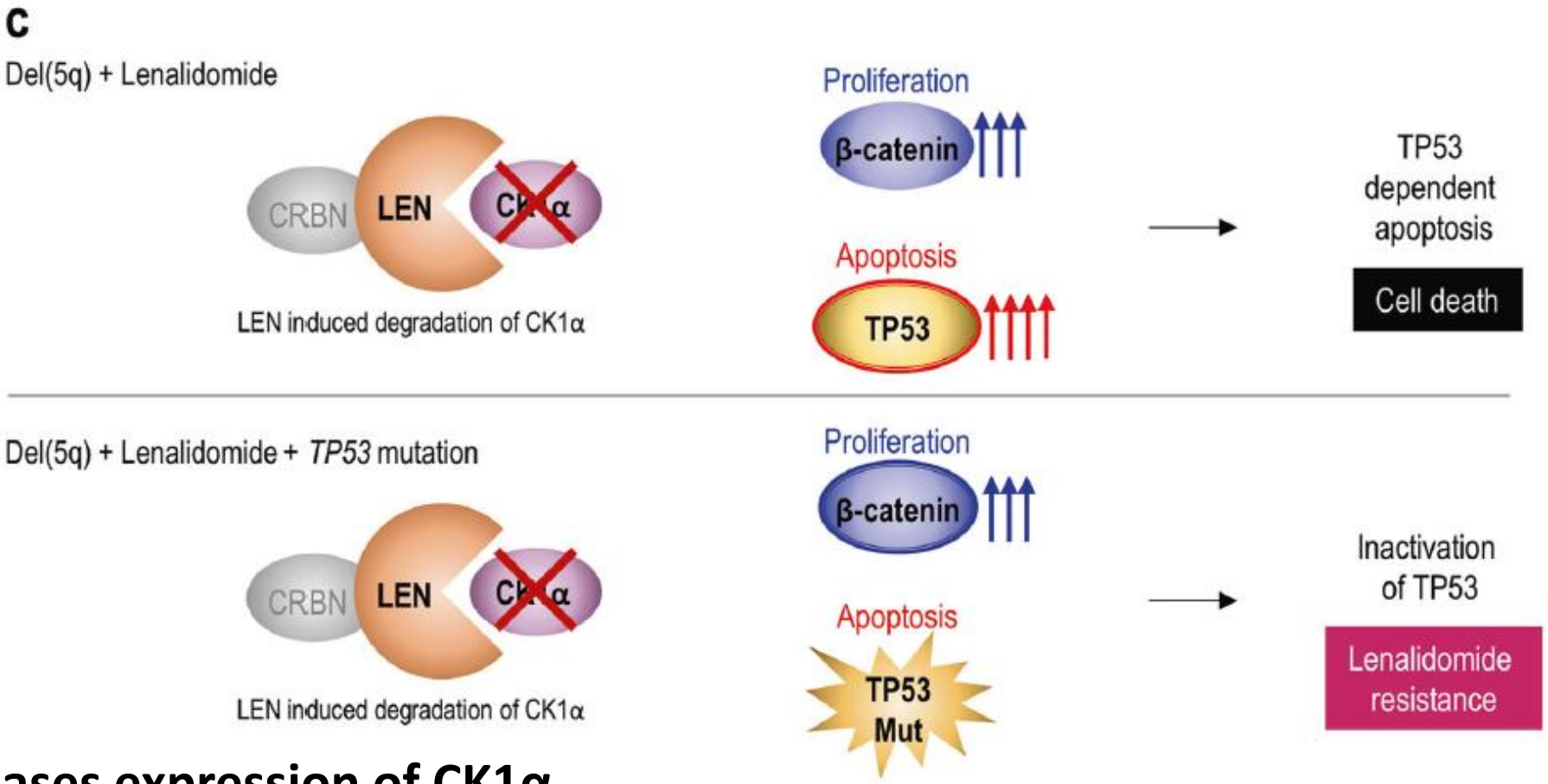
Gagat Y. Leukemia 2019 in press

# Molecular pathogenesis of 5q-syndrome




**CK1α: casein kinase 1α,**

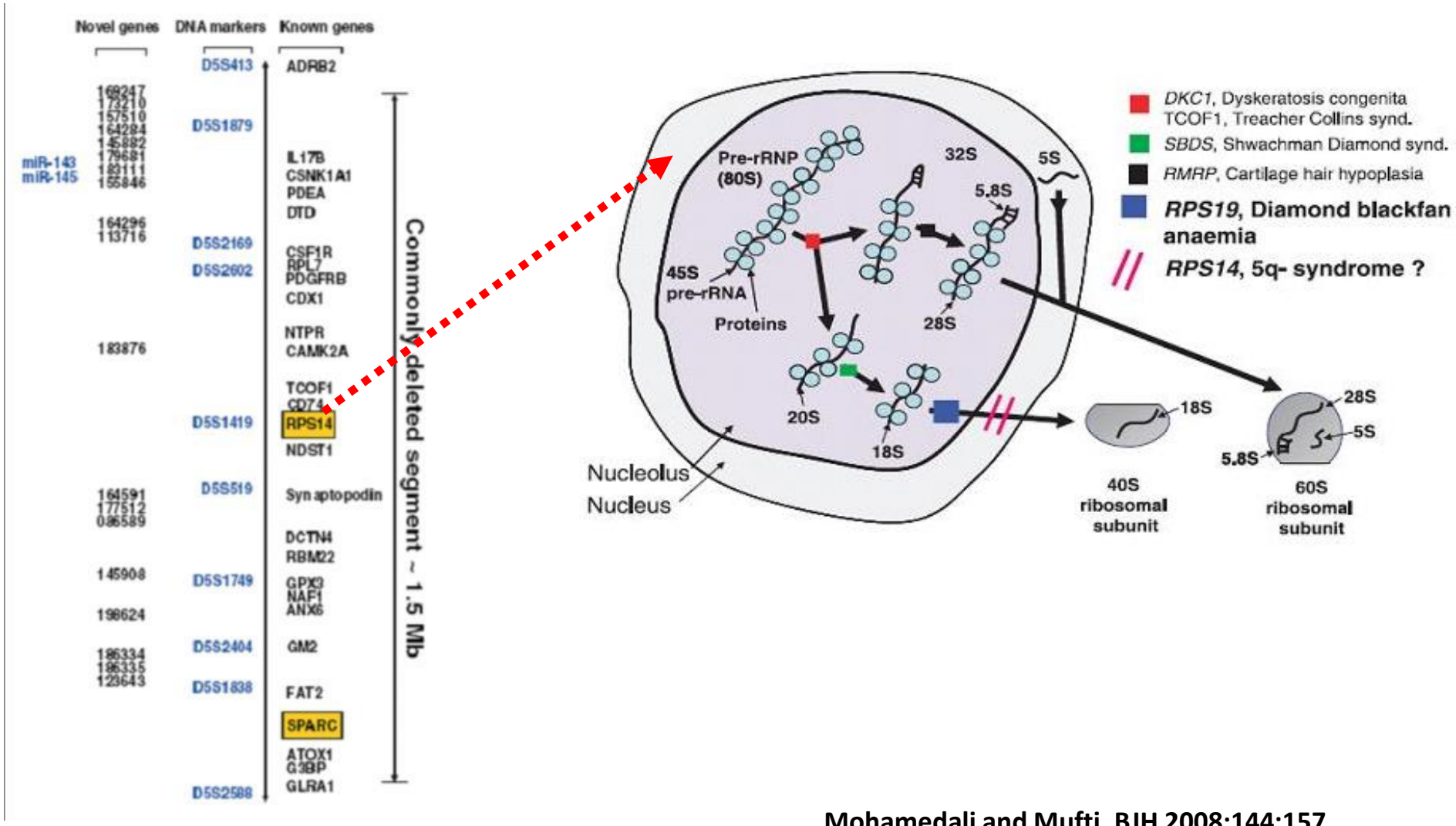
Gagat Y. Leukemia 2019 in press




**LEN decreases expression of CK1α.**
**Normal cells treated with LEN can survive because 50% of CK1α expression remains.**
**In del(5q) cells, CK1α is at 50% due to haploinsufficiency, so LEN treatment is lethal to cells by completely losing CK1α.**
**If del(5q) MDS cells acquire TP53 loss-of-function mutations, they would become resistant to LEN because complete loss of CK1α could not induce TP53-dependent apoptosis**

**Gagat Y. Leukemia 2019 in press**

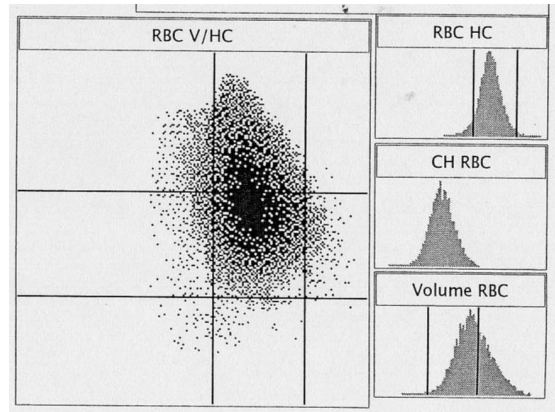
# Ribosomal biogenesis and BM falilure syndromes

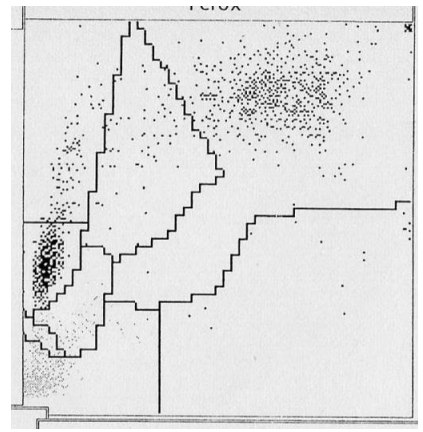



Mohamedali and Mufti, BJH 2008;144:157

| TEST | RISULT | PAT | NORMALI | UNITA' |
|---|---|---|---|---|
| WBC | | 2.41 | ( 5.2 - 12.4 ) | x10.e3 /uL |
| RBC | | 2.35 | ( 4.2 - 6.1 ) | x10.e6 /uL |
| HGB | | 9.0 | ( 12 - 18 ) | g/dL |
| HCT | | 27.3 | ( 37 - 50 ) | % |
| MCV | | 116.3 | ( 80 - 99 ) | fL |
| MCH | | 38.5 | ( 27 - 31 ) | pg |
| MCHC | 33.1 | | ( 33 - 37 ) | g/dL |
| CHCM | 33.4 | | ( 33 - 37 ) | g/dL |
| RDW | | 18.8 | ( 11.5 - 14.5 ) | % |
| HDW | | 3.35 | ( 2.2 - 3.2 ) | g/dL |
| PLT | | 61 | ( 130 - 400 ) | x10.e3 /uL |
| MPV | 9.5 | | ( 7.2 - 11.1 ) | fL |
| %NEUT | | 38.9 | ( 40 - 74 ) | % |
| %LYMPH | | 51.2 | ( 19 - 48 ) | % |
| %MONO | | 3.1 | ( 3.4 - 9 ) | % |
| %EOS | 0.8 | | ( 0 - 7 ) | % |
| %BASO | 0.6 | | ( 0 - 1.5 ) | % |
| %LUC | | 5.4 | ( 0 - 4 ) | % |
| #NEUT | | 0.94 | ( 1.9 - 8 ) | x10.e3 /uL |
| #LYMPH | 1.24 | | ( 0.9 - 5.2 ) | x10.e3 /uL |
| #MONO | | 0.08 | ( 0.16 - 1 ) | x10.e3 /uL |
| #EOS | 0.02 | | ( 0 - 0.8 ) | x10.e3 /uL |
| #BASO | 0.02 | | ( 0 - 0.2 ) | x10.e3 /uL |
| #LUC | 0.13 | | ( 0 - 0.4 ) | x10.e3 /uL |
| LI | | 1.78 | ( 1.90 - 3 ) | |
| MPXI | 3.8 | | ( -10 - 10 ) | |
| WBCPEROX | 2.29 | | | |
| WBC BASO | 2.41 | | | |

| | |
|---|---|
| ANISO | ++ |
| MACRO | +++ |
| HYPO | + |
| LS | ++ |
| ATYP | + |
| BLASTS | + |



# Valutazione morfologica sangue periferico e midollare

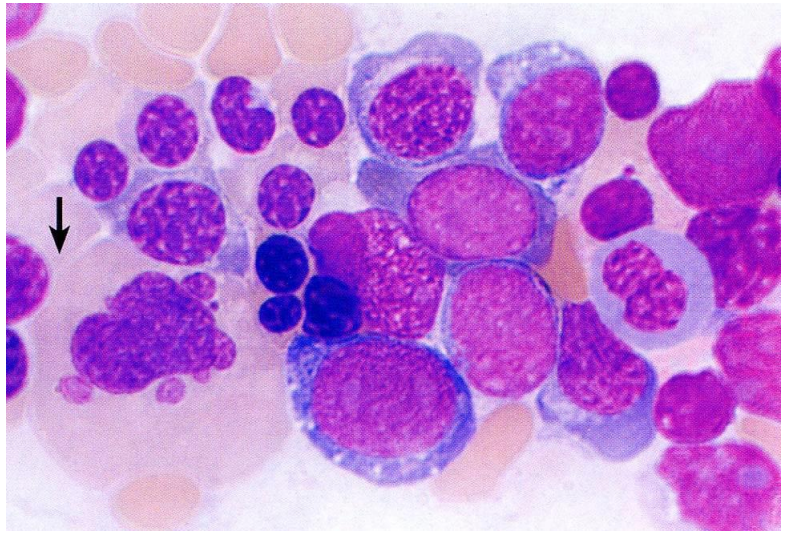
- Valutazione morfologica sangue periferico per orientamento diagnostico
  - diagnosi differenziale, segni di displasia, presenza di blasti

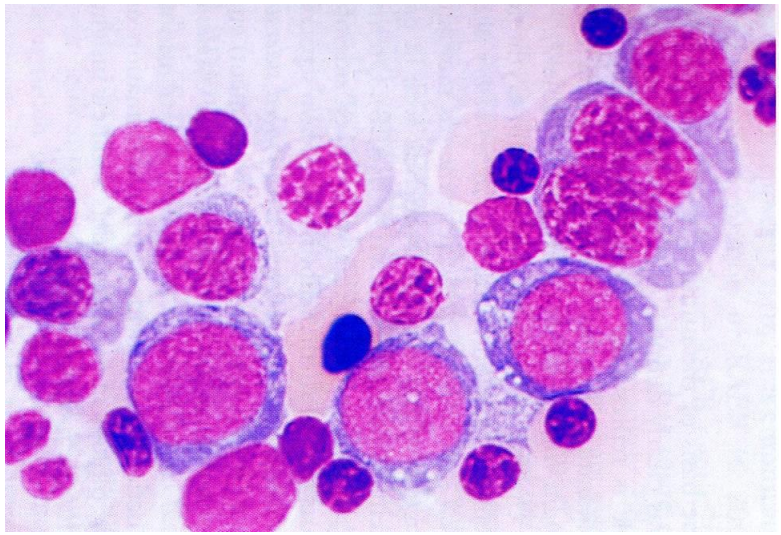
- Valutazione morfologica midollare:
  - Riscontro di segni di displasia
  - La valutazione morfologica dei blasti
    - La % di blasti valutata su almeno 500 cellule (almeno 100 cellule non eritroidi)
    - Non raccomandata la valutazione citofluorimetrica

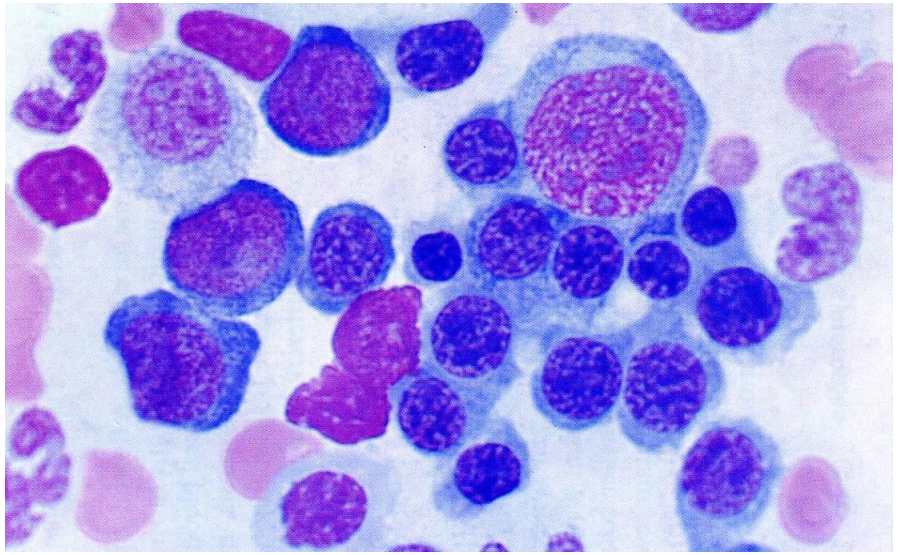
# Caratteristiche morfologiche di displasia

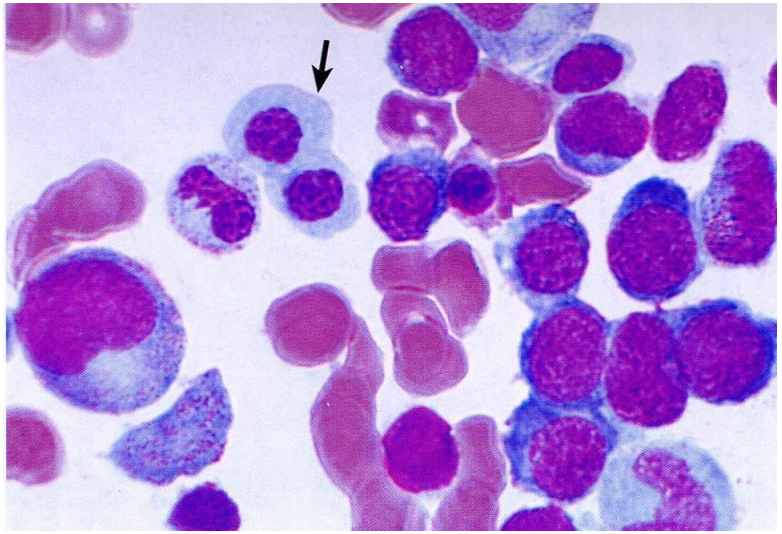
| filiera | Nucleare | Citoplasmatica |
|---|---|---|
| eritroide | Multinuclearità, carioressi, mitosi anomale, megalobastosi | Vacuoli, difetti di emoglobinizzazione, sideroblasti ad anello |
| granulocitaria | Forme Pseudo-Pelger, ipersegmentazione, nuclei ad anello, forme giganti, clumping cromatinico, granulociti binucleati | Ipogranulaione, corpi di Dohle, vacuolizzazioni, difetti di mieloperossidasi |
| megacariocitaria | Micromegacariociti, forme mononucleate, megacariociti con nuclei dispersi | Asincronia nucleo/citoplasmatica, piastrine giganti, piastrine ipogranulate o granulate |
| monocitaria | Ipersegmentazione, nuclei con forme bizzarre | Aumentata basofilia citoplasmatica, granulazioni prominenti |

# Displasia eritroide



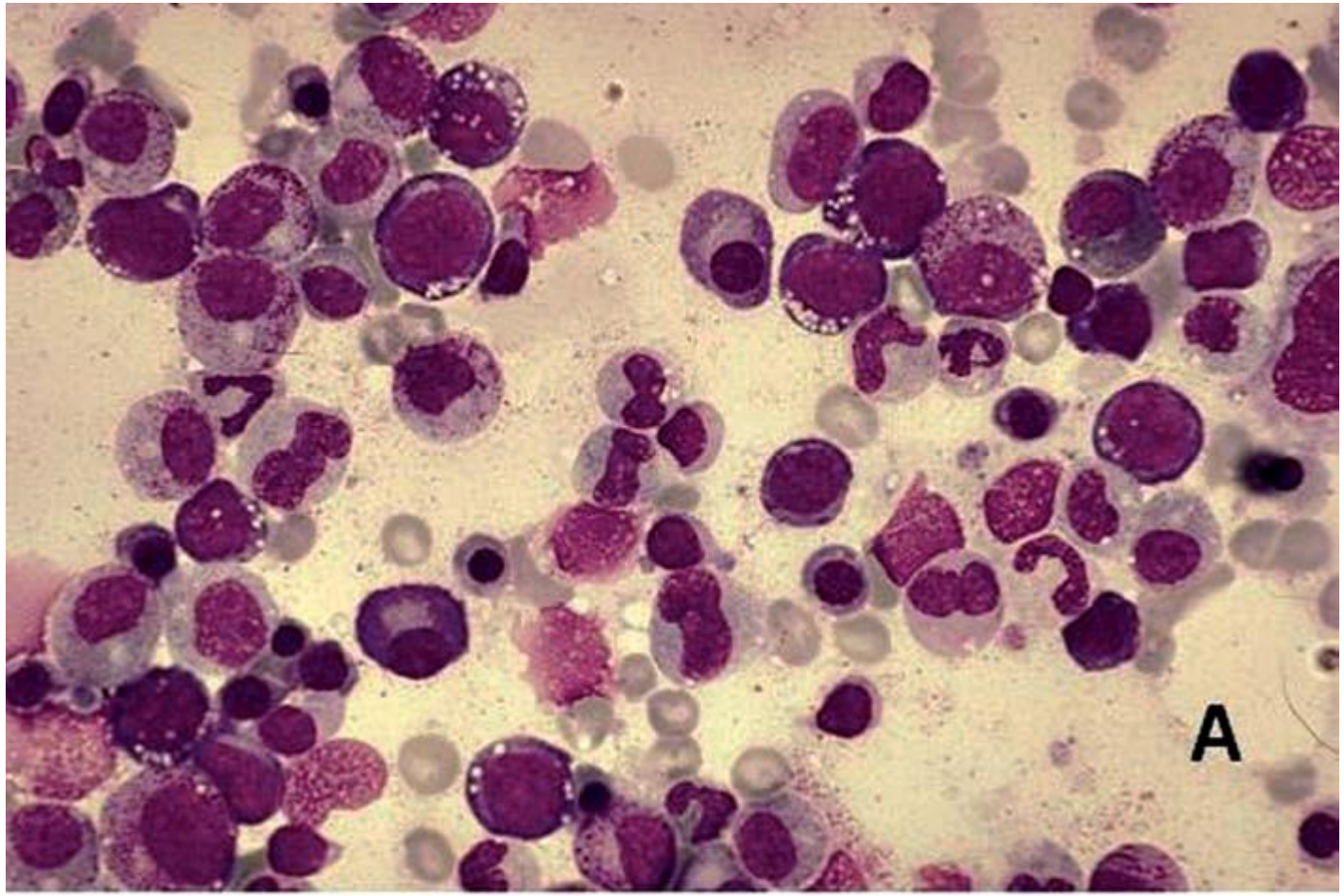


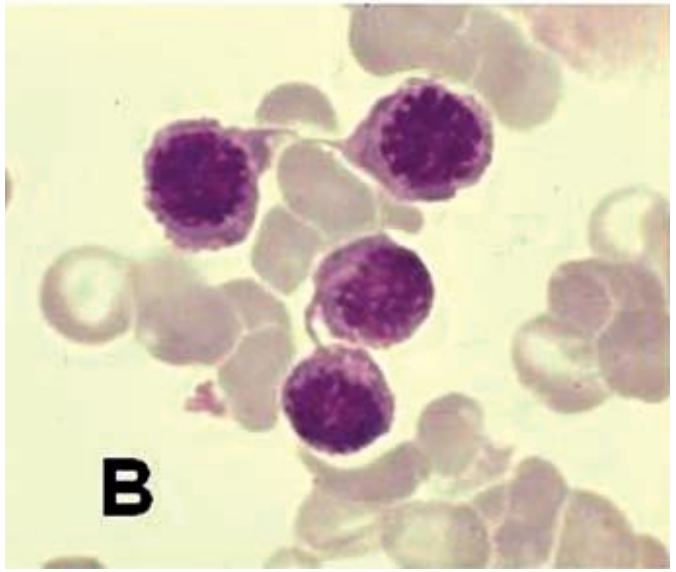




Castoldi G. Atlas of blood cells. 2003; p 285-98.

# Displasia eritroide

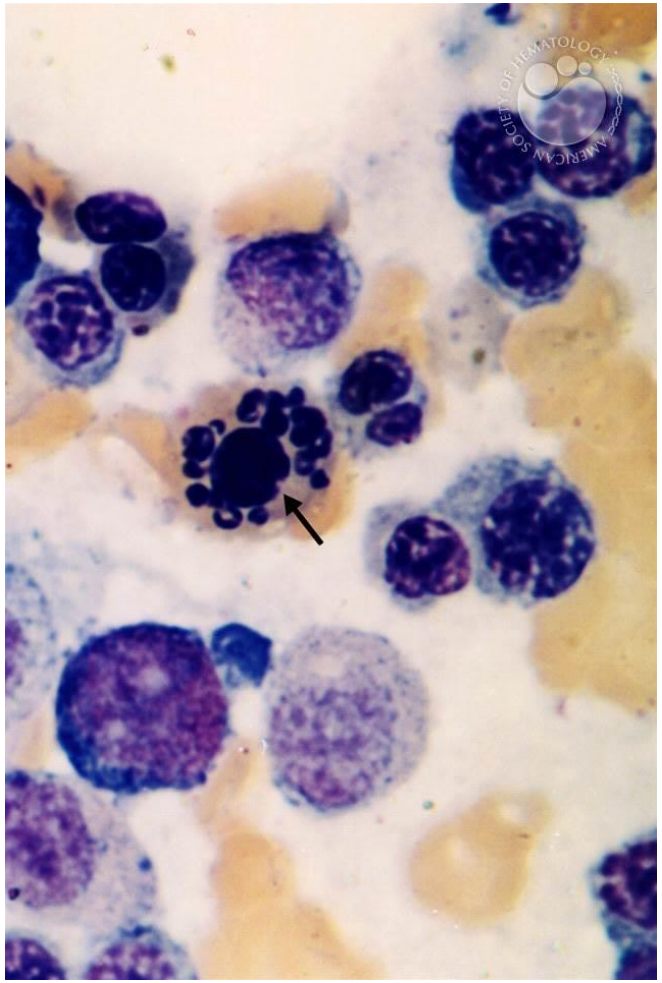


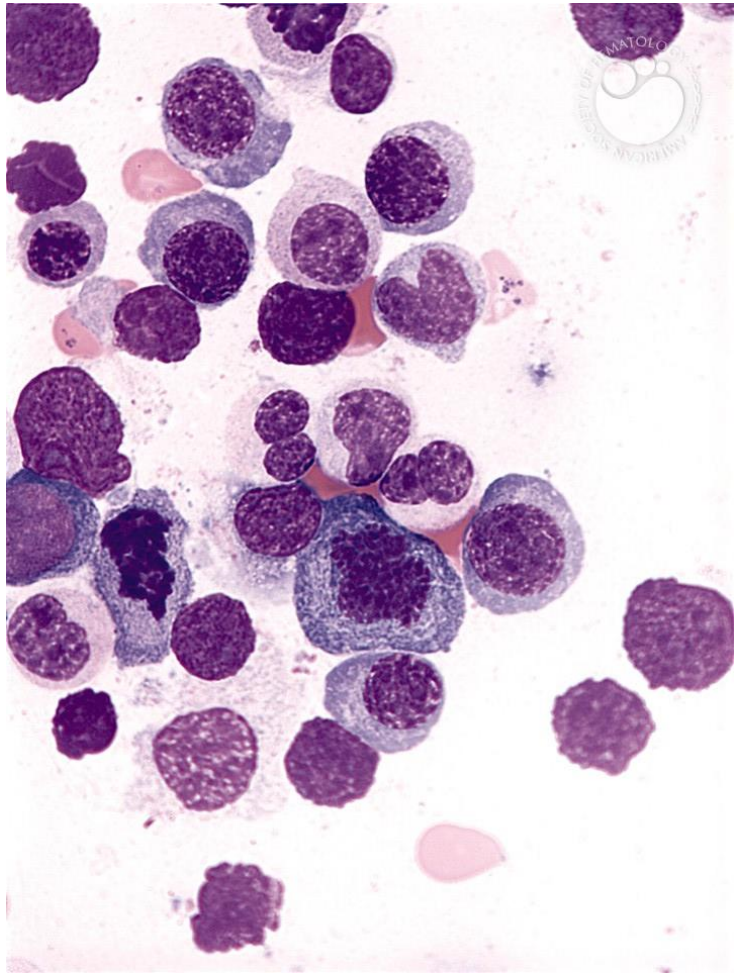




**Rigolin et al seminari di Ematologia Oncologica 2009**

# Displasia eritroide

**Erythroid karyorrhexis in myelodysplasia**





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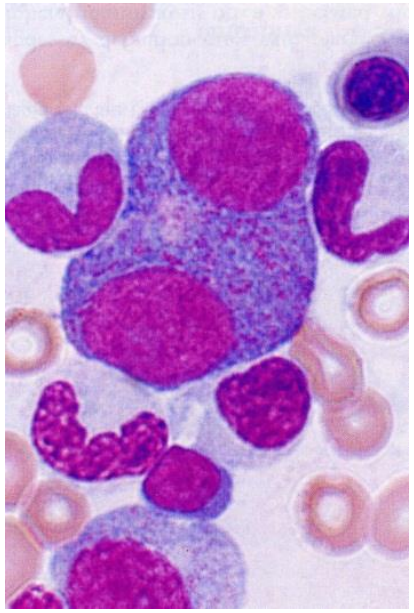
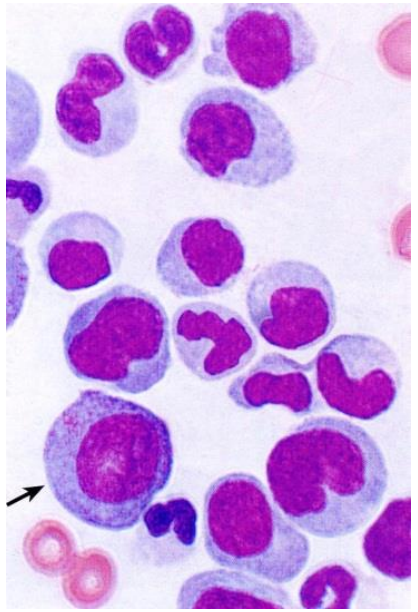
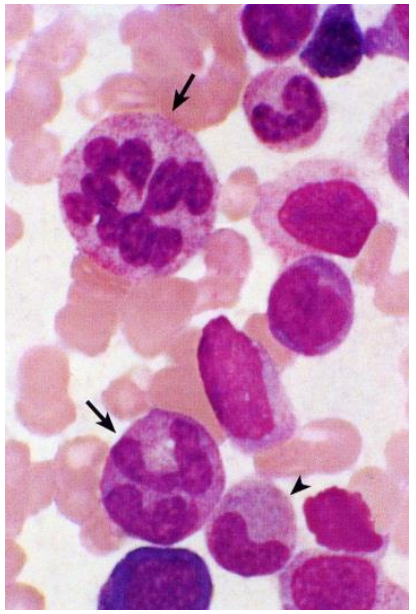
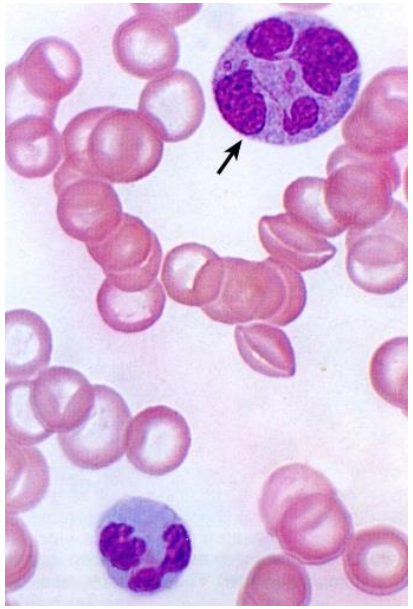
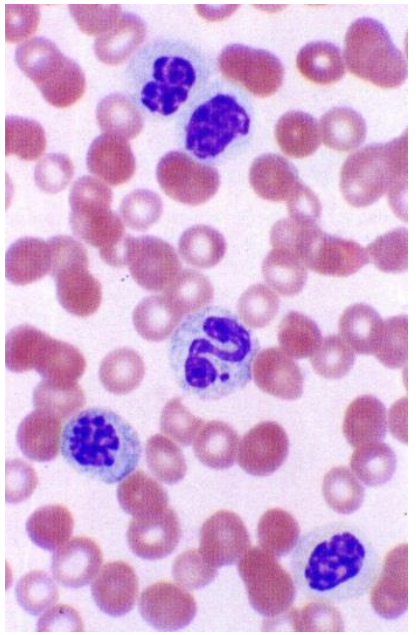
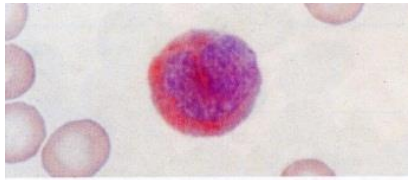
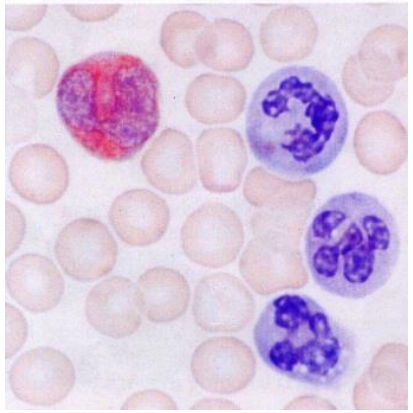
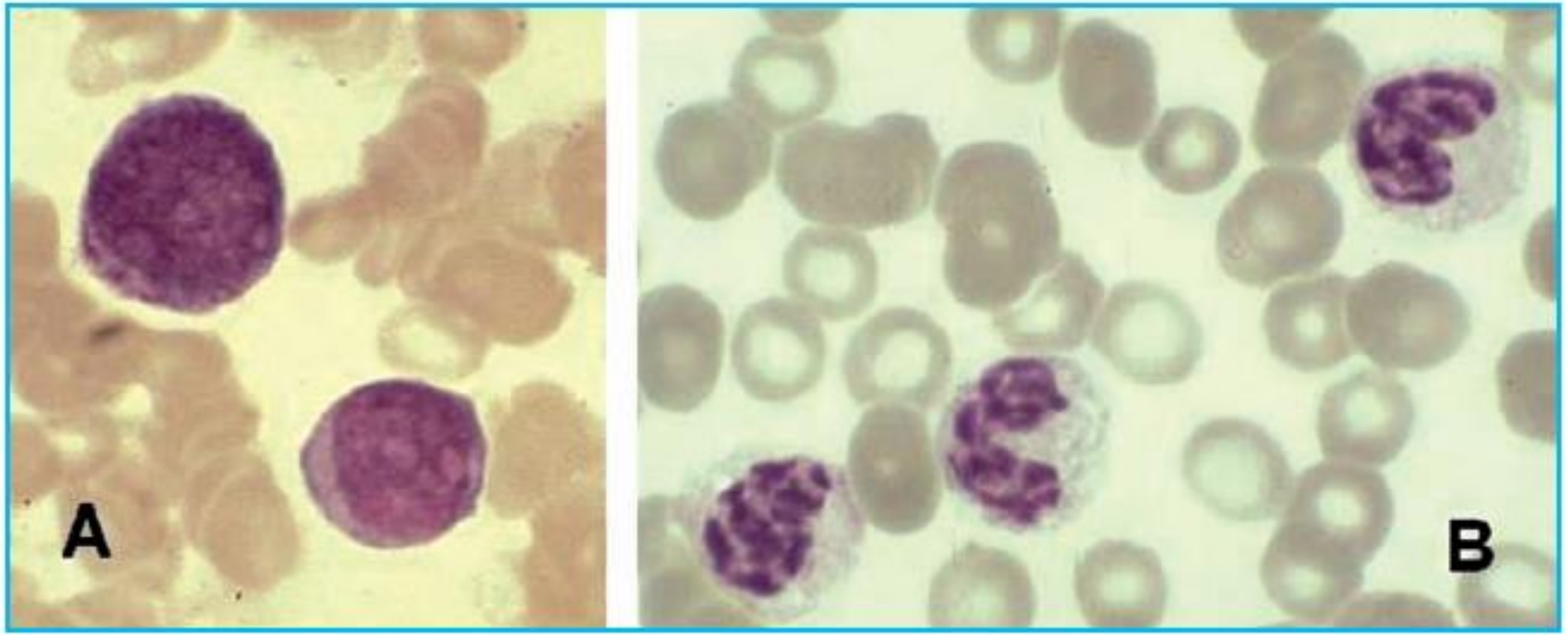
# disgranulopoiesi

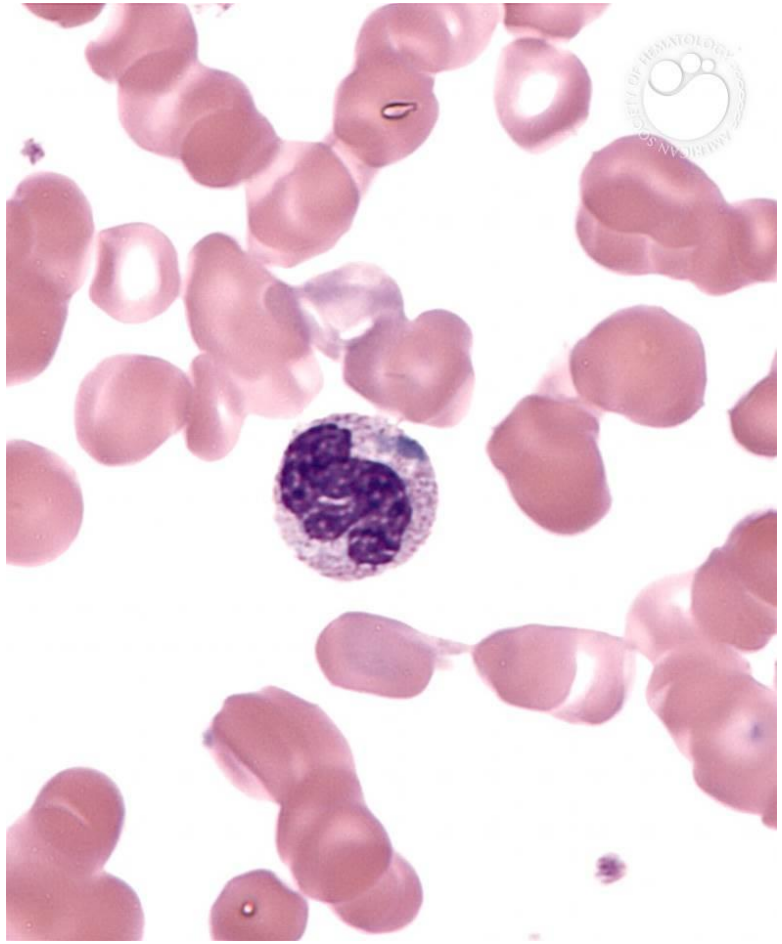
Castoldi G. Atlas of blood cells. 2003; p 285-98.

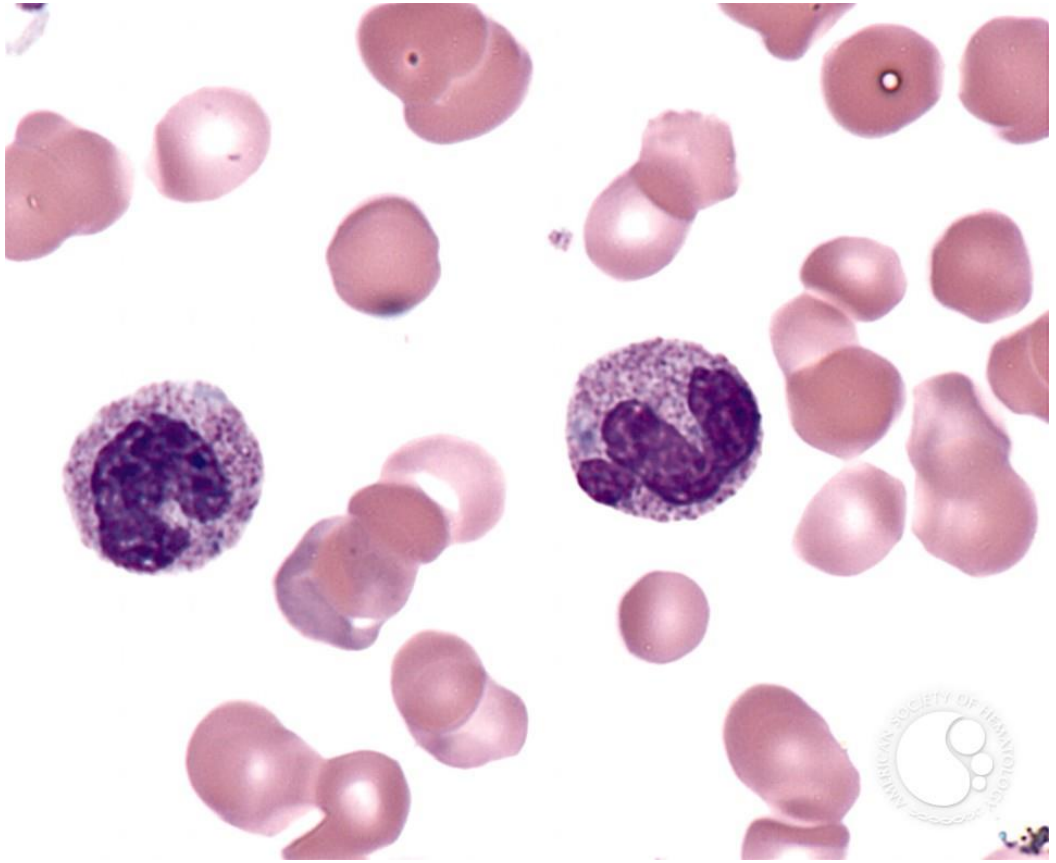
# Blasti e pseudo Pelger




Rigolin et al seminari di Ematologia Oncologica 2009

# Corpi di Dohle





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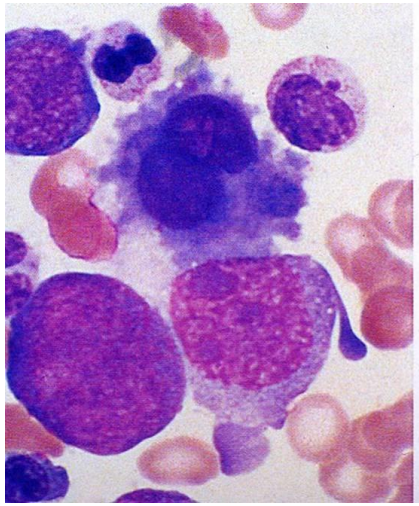
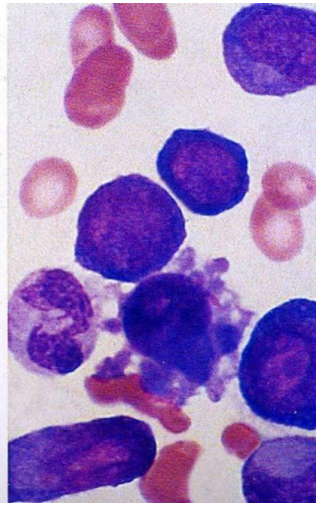
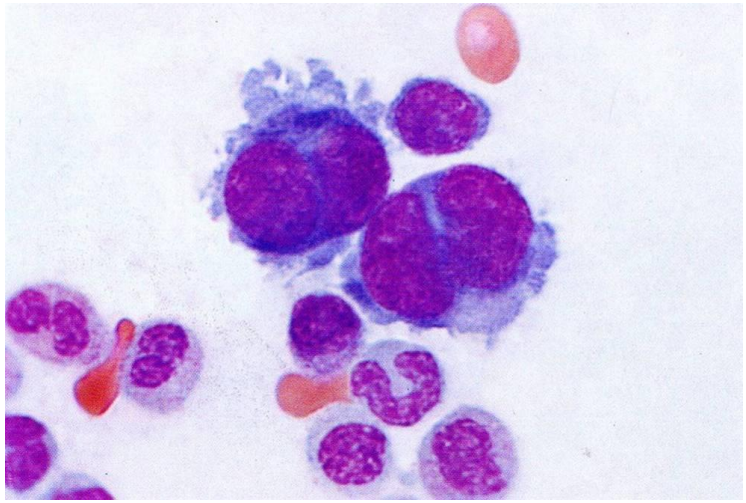
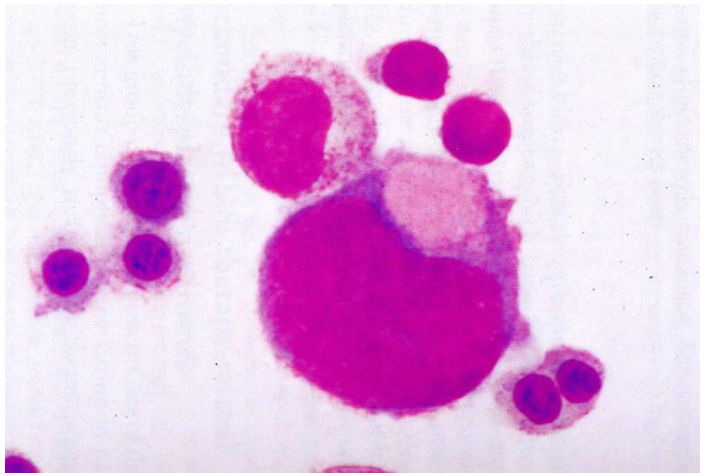
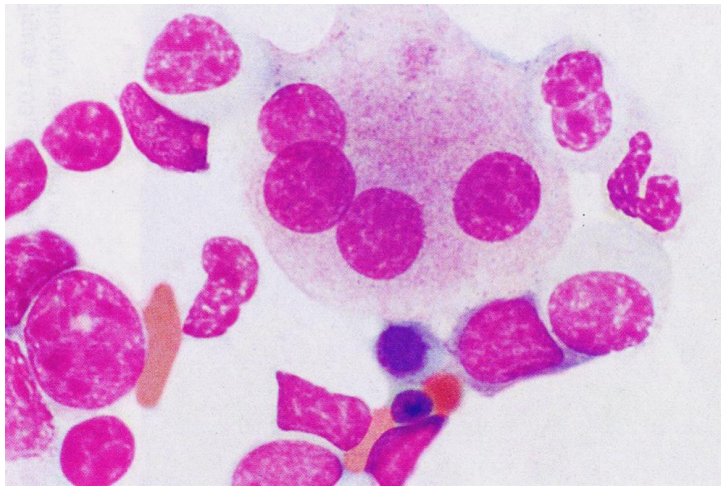
# Displasia megacariocitaria





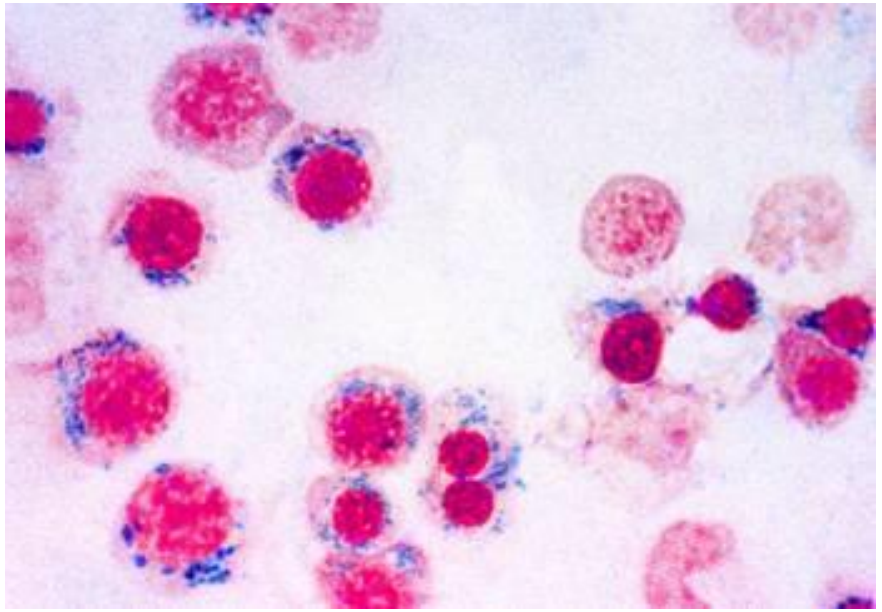






Castoldi G. Atlas of blood cells. 2003; p 285-98.

# Sideroblasti

**Il Working Group ha definito 3 tipi di sideroblasti:**

- **Tipo 1: meno di 5 granuli di ferro nel citoplasma;**
- **Tipo 2: 5 o più granuli di ferro, ma non in una distribuzione perinucleare;**
- **Tipo 3 o sideroblasti ad anello: 5 o più granuli in posizione perinucleare, che circondano il nucleo o interessano almeno un terzo della circonferenza nucleare.**

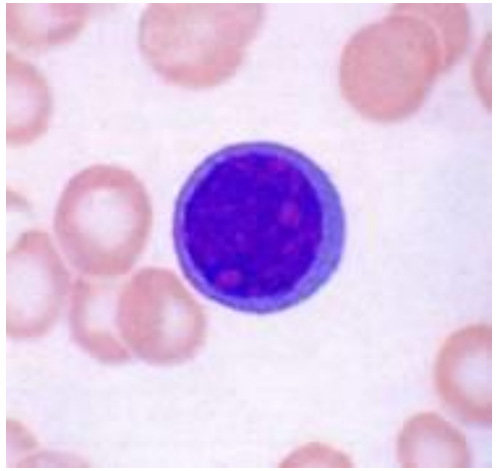
**Nel conteggio dei sideroblasti ad anello, occorre valutare almeno 100 precursori eritroidi nei vari stadi maturativi.**

**La percentuale di sideroblasti ad anello ai fini della classificazione rimane il 15% come per la classificazione FAB e WHO.**

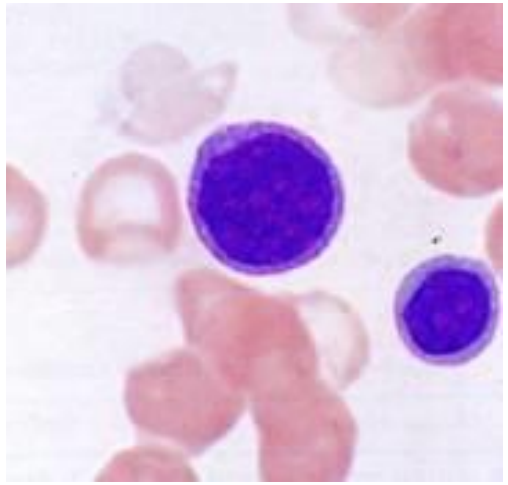
**Haematologica 2008; 93:1712-1717.**

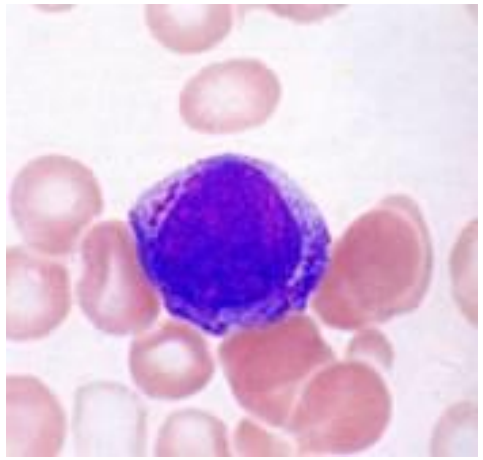
# blasti e promielociti nelle MDS

| Aspetti cellulari | Blasto non granulato | Blasto granulato | Promielocito normale | Promielocito displastico |
|---|---|---|---|---|
| Nucleo | Centrale di forma variabile | Centrale di forma variabile | Ovale, rotondo, indentato Centrale od eccentrico | Ovale, rotondo, indentato in posizione eccentrica |
| Cromatina | fine | fine | Fine od intermedia | Fine o grossolana |
| Nucleolo | 1-2 | 1.2 | Ben riconoscibile | Ben visibile |
| Zona Golgi | Non evidente | Non evidente | Ben visibile | Presente ma poco sviluppata |
| Granuli | Non visibili | Presenti (talora corpi di Auer) | Azzurrofili uniformemente dispersi | irregolare presenza e distribuzione |
| Citoplasmaa | basofilo | basofilo | basofilo | Basofilia ridotta ed irregolare |

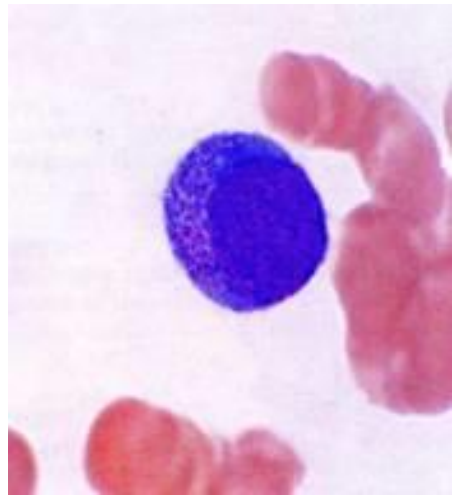


Blasto non granulato





Blasti granulati



promielocito

# Criteri diagnostici minimi nelle MDS

A. **Prerequisiti**
   1. Citopenia costante in una o più delle seguenti filiere: Hb <11 g/dL, ANC < 1500 uL o PLT <100,000 uL
   2. Esclusione di tutti gli altri disordini come causa della citopenia/displasia

B. **Criteri decisivi correlati alla MDS**
   1. Displasia in almeno il 10% di tutte le cellule o >15% di sideroblasti ad anello
   2. 5–19% di cellule blastiche nello striscio midollare
   3. Anomalie cromosomiche tipiche (citogenetica o FISH)

C. **Co-criteri (per i pazienti che soddisfano i criteri A ma non quelli B)**
   1. Anomalo fenotipo mediante citometria a flusso
   2. Anomalie molecolari (gene chip profiling, o mutazioni puntiformi (RAS, etc)
   3. Anomalie colturali dei progenitori midollari e/o circolanti (CFU-assay)

- **La diagnosi di MDS può essere formulata quando entrambi i prerequisiti ed almeno un criterio decisivo sono soddisfatti.**

- **Se nessun criterio decisivo è soddisfatto, ma è molto probabile che il paziente sia affetto da una neopasia mieloide clonale, i co-criteri devono essere applicati e possono aiutare nel raggiungimento della diagnosi di MDS o di una condizione definita 'fortemente sospetta di MDS'.**

Valent P Leuk Res 2007; 31: 727

## Diagnosis of MDS requires:

(A) Persistent blood cytopenia(s) as defined by local laboratory ranges (with consideration of patient factors, such as ethnic background, altitude of residence, etc), without another reversible cause, such as nutritional deficiency or the effect of a drug, and

(B1) Increased myeloblasts (5%-19%), or

(B2) Extensive dysplasia (>10% of marrow cells in at least 1 lineage: erythroid, granulocytic, or megakaryocytic), or

(B3) Karyotypic evidence of clonality with a typical MDS-associated alteration, such as del(5q) or monosomy 7 (excluding nonspecific alterations, such as trisomy 8, loss of the Y chromosome, isolated del(20q), or trisomy 15[53])

## Supplemental "co-criteria" include

(C1) Abnormal findings on histologic or immunochemical studies of marrow biopsy that could be consistent with MDS, such as abnormally localized immature precursors, clusters of CD34-positive blast cells, or >10% dysplastic micromegakaryocytes detected by immunohistochemistry

(C2) Abnormal immunophenotype of marrow cells by flow cytometry with multiple MDS-associated phenotypic aberrancies

(C3) Evidence of a clonal population of myeloid cells by molecular genetic testing, which is the subject of this article

If (A) is present, but not (B1-B3), then the case might be termed "idiopathic cytopenias of undetermined significance" (ICUS): a term that is agnostic about clonality

C1-C3 alone are generally not yet considered specific enough by themselves to be confident about the diagnosis of MDS, but can help confirm the diagnosis if other criteria are present

**Steensma DP, Blood. 2018;132:1657-63**

# Citopenia idiopatica di incerto (indeterminato) significato (ICUS)

**Definizione**

Citopenia in una o più delle seguenti filiere (per più di 6 mesi):

Hb < 11 g/dL; neutrofili <1500 uL; piastrine <100,000 uL

Esclusa una MDS

Escluse tutte le altre possibili cause di citopenia

**Indagini iniziali richieste per la diagnosi di ICUS**

Anamnesi dettagliata (farmaci, tossici, mutageni, etc.)

Attento esame clinico comprendente indagini radiologiche ed ecografia splenica

Emocromo con conteggio differenziale al microscopio e completa valutazione biochimica clinica

Biopsia osteomidollare ed immunistochimica

Aspirato midollare e colorazione per il ferro.

Citometria a flusso midollare e sangue periferico

Analisi cromosomica con FISH (pannello standard minimo: 5q31, CEP7, 7q31, CEP8, 20q,CEPY, p53)

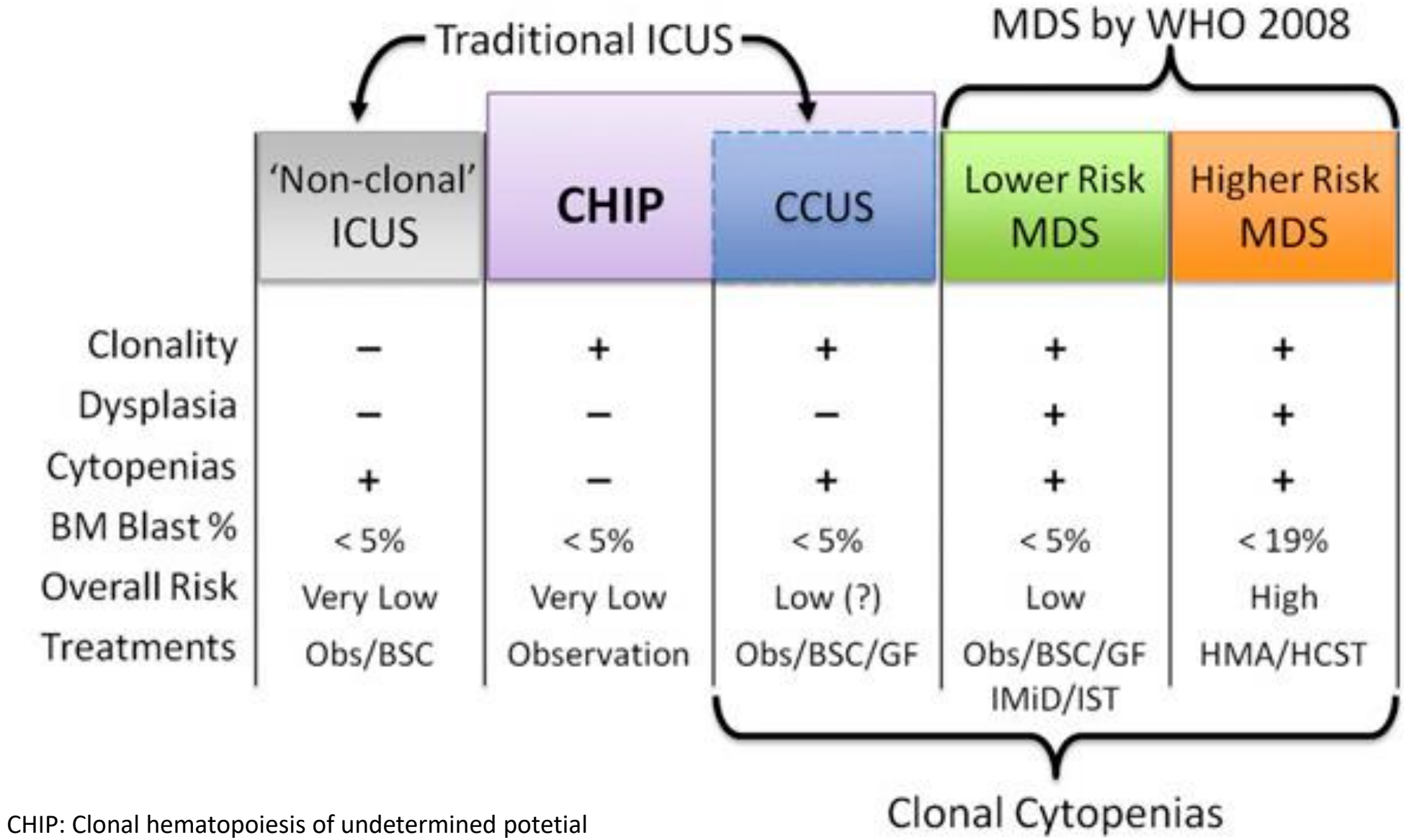
Analisi molecolare se appropriato

Esclusione di infezioni virali (HCV, HIV, CMV, EBV, altre)

**Indagini raccomandate nel follow-up**

Emocromo con formula e biochimica clinica ad intervalli di 1–6 mesi

In caso di evidente sospetto di MDS: esame midollare



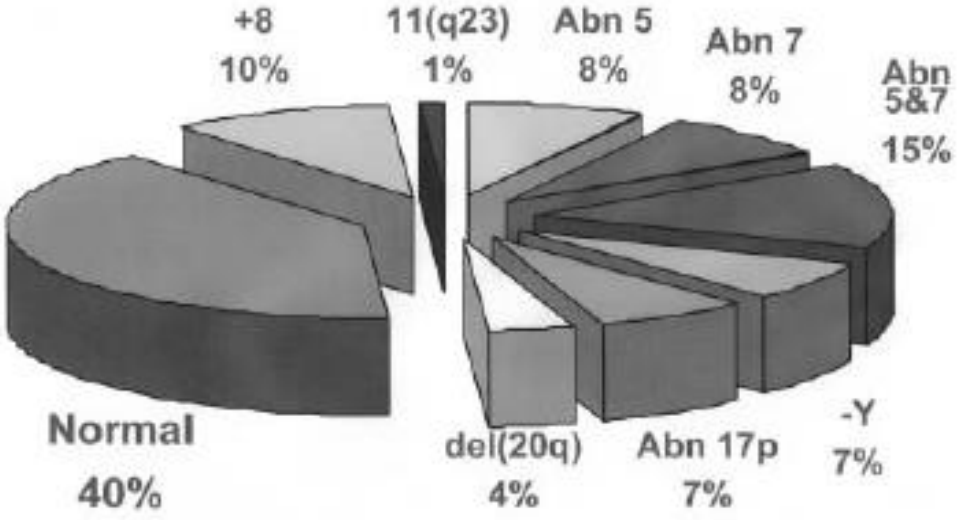

CHIP: Clonal hematopoiesis of undetermined potetial
ICUS: idiopatic cytopenia of undetermined significance
CCUS: clonal cytopenia of undetermined signficance

**Steensma et al, Blood 2015;126:9**

# Citogenetica

- La citogenetica ha un ruolo decisivo nella diagnosi e nella definizione della prognosi

- Anomalie citogenetiche sono riscontrabili del 40-70% delle MDS de novo e nel 95% delle forme secondarie a chemioterapia (therapy-related)

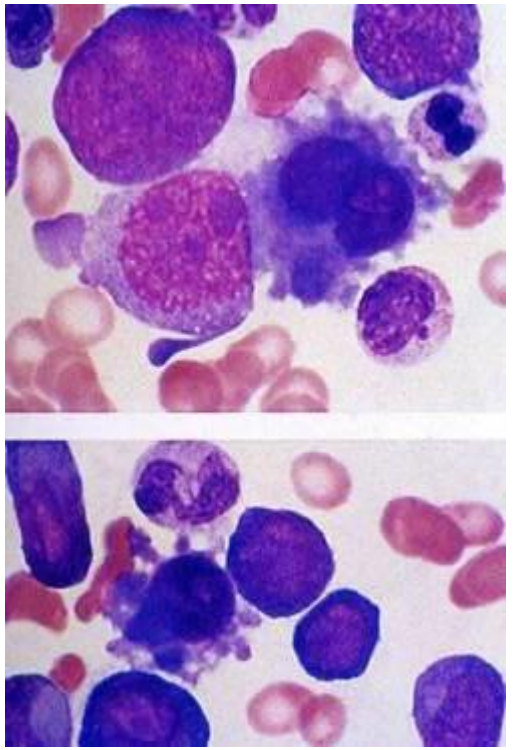


# Anomalie cromosomiche e MDS

Table 6. Recurring chromosomal abnormalities considered as presumptive evidence of MDS in the setting of persistent cytopenia of undetermined origin, but in the absence of definitive morphologic features of MDS

| Unbalanced abnormalities | Balanced abnormalities |
|---|---|
| −7 or del(7q) | t(11;16)(q23;p13.3) |
| −5 or del(5q) | t(3;21)(q26.2;q22.1) |
| i(17q) or t(17p) | t(1;3)(p36.3;q21.1) |
| −13 or del(13q) | t(2;11)(p21;q23) |
| del(11q) | inv(3)(q21q26.2) |
| del(12p) or t(12p) | t(6;9)(p23;q34) |
| del(9q) | |
| idic(X)(q13) | |

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.



Vardiman JW et al Blood 2009;114:937

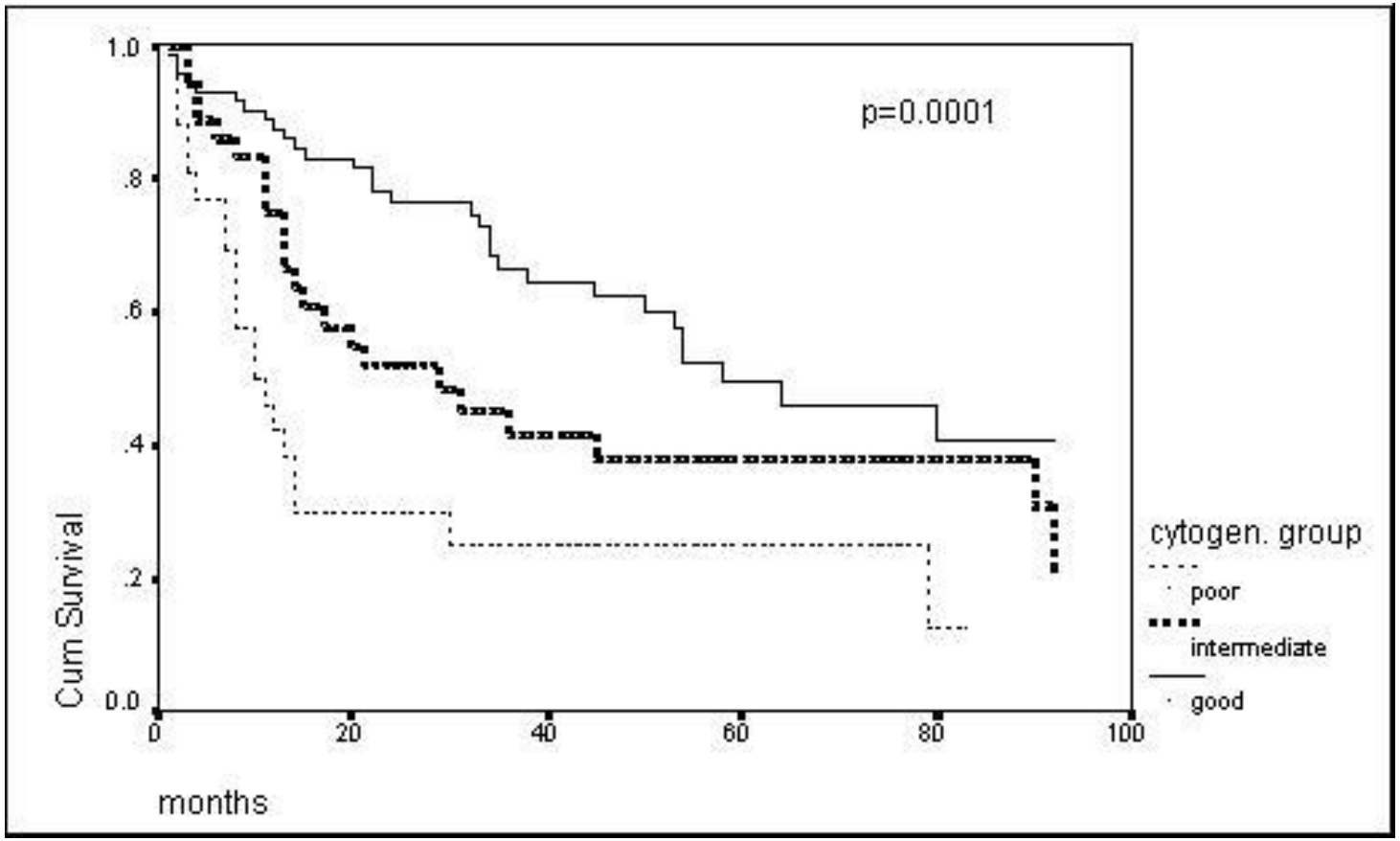
Castoldi G. Atlas of blood cells. 2003; p 285-98.

# Recurrent cytogenetic abnormalities in MDS

| Chromosomal abnormality | Key genes deleted* | IPSS-R risk category[6] | Clinical features |
|---|---|---|---|
| Normal | NA | Good | NA |
| del(5q) | *CSNK1A1*, *RPS14*, *EGR1*, *APC*, *DDX41*, *HSPA9*, *NPM1*, *TIFAB*, *DIAPH1*, *miR-145* and *miR-146a*[130–140] | Good | Sensitive to lenalidomide[196] |
| Monosomy 7 or del(7q) | *EZH2*, *MLL3* and *CUX1* (REFS 148–150) | Poor | Monosomy 7 may have a worse prognosis than del(7q)[197] |
| Trisomy 8 | Unknown | Intermediate | High response rate to immunosuppression[190] |
| Trisomy 19 | Unknown | Intermediate | Unknown |
| del(20q) | *MYBL2*, *TP53RK* and *TP53TG5* (REF. 198) | Good | Often associated with mutations in splicing factors[198] |
| del(17p) | *TP53* (REF. 109) | N/A | Poor response to alloHSCT[35]. |
| Complex‡ and monosomal§ | *TP53* (REF. 109) | Poor to very poor | Associated with *TP53* mutation[35] |
| del(11q) | *MLL* and *ATM*[199] | Very good | Unknown |
| Y chromosome loss (–Y) | Unknown | Very good | May not be pathogenic, but instead may be lost during normal ageing[200] |

Sperling et al. Nature Reviews Cancer 2017

# Citogenetica e sopravvivenza




**Karyotype**

- **Good:** normal, -Y, del(5q), del(20q)
- **Intermediate:** other abnormalities
- **Poor:** complex (>= 3 abnorm) or chrom 7 abnorm

| | Proportion of patients (%) | Karyotype | Median survival (years) | Time to 25% AML evolution (years) |
|---|---|---|---|---|
| Very good | 4% | –Y, del(11q) | 5·4 | NR |
| Good | 72% | Normal, del(5q), del(12p), del(20q), double including del(5q) | 4·8 | 9·4 |
| Intermediate | 13% | del(7q), +8, +19, i(17q), any other single or double independent clones | 2·7 | 2·5 |
| Poor | 4% | –7, inv(3)/t(3q)/del(3q), double including –7/del(7q); complex: 3 abnormalities | 1·5 | 1·7 |
| Very poor | 7% | Complex >3 abnormalities | 0·7 | 0·7 |

AML=acute myeloid leukaemia. NR=not reached.

*Table 2:* **Cytogenetic findings in patients with myelodysplastic syndromes, by their prognostic value[8,68]**

**Ades et al. Lancet 2014; 383: 2239–52**

| | Blood findings | Bone-marrow findings |
|---|---|---|
| **Myelodysplastic syndrome** | | |
| Refractory cytopenia with unilineage dysplasia (refractory anaemia; refractory neutropenia; refractory thrombocytopenia) | One or two cytopenias; no or rare blasts (<1%) | One lineage dysplasia ≥10% of cells in one myeloid lineage; <5% blasts; <15% of erythroid precursors ring sideroblasts |
| Refractory anaemia with ring sideroblasts | Anaemia; no blasts | ≥15% of erythroid precursors ring sideroblasts; erythroid dysplasia only; <5% blasts |
| Refractory cytopenia with multilineage dysplasia | Cytopenia(s); no or rare blasts (<1%); no auer rods; $<1 \times 10^9$ cells per L monocytes | Dysplasia in ≥10% of cells in at least two myeloid lineages (neutrophil, erythroid precursors, or megakaryocytes); <5% blasts in marrow; no auer rods; with or without 15% ring sideroblasts |
| Refractory anaemia with excess blasts 1 | Cytopenia(s); <5% blasts; no auer rods; $<1 \times 10^9$/L monocytes | Dysplasia in one or several lineages; 5–9% blasts; no auer rods |
| Refractory anaemia with excess blasts 2 | Cytopenia(s); 5–19% blasts; with or without auer rods; $<1 \times 10^9$/L monocytes | Dysplasia in one or several lineages ; 10–19% blasts; with or without auer rods |
| Myelodysplastic syndrome unclassified | Cytopenias; <1% blasts | Unequivocal dysplasia in <10% of cells in one or more myeloid lineages accompanied by a cytogenetic abnormality is presumptive evidence for diagnosis; <5% blasts |
| MDS associated with isolated del(5q) | Anaemia; normal or increased platelet count in most cases; no or rare blasts (<1%) | Normal to increased megakaryocytes with hypolobated nuclei; <5% blasts; isolated del(5q) cytogenetic abnormality; no auer rods |
| **Myelodysplastic–myeloproliferative neoplasms** | | |
| Chronic myelomonocytic leukaemia 1 | Persistent peripheral blood monocytosis ($>1 \times 10^9$/L); no Philadelphia chromosome or *BCR-ABL1* fusion gene; <5% blasts | Dysplasia in one or more cell lines; <10% blasts |
| Chronic myelomonocytic leukaemia 2 | Persistent peripheral blood monocytosis ($>1 \times 10^9$/L); no Philadelphia chromosome or *BCR-ABL1* fusion gene; <19% blasts | Dysplasia in one or more cell lines; 10–19% blasts |
| Myelodysplastic or myeloproliferative disease, unclassifiable | Morphological features of myelodysplastic syndrome; prominent myeloproliferative features (platelets $>600 \times 10^9$ cells per L, leucocytes $>13 \times 10^9$/L, splenomegaly); no Philadelphia chromosome or *BCR-ABL1* fusion gene; no del(5q), t(3;3)(q21;q26), inv3(q21;q26); no underlying myeloproliferative disease | .. |
| Provisional entity: refractory anaemia with ring sideroblasts and thrombocytosis | Similar to refractory anaemia with ring sideroblasts; platelet $>600 \times 10^9$ cells per L | Similar to refractory anaemia with ring sideroblasts; without del(5q) |
| **Therapy-related neoplasm** | | |
| Acute myeloid leukaemia or myelodysplastic syndrome in individuals exposed to cytotoxic agents | .. | .. |

*Table 3:* **WHO 2008 classification[6]**

# 2016 WHO classification of myeloid neoplasms and acute leukemia

| Myelodysplastic syndromes (MDS) |
| --- |
| MDS with single lineage dysplasia |
| MDS with ring sideroblasts (MDS-RS) |
| MDS-RS and single lineage dysplasia |
| MDS-RS and multilineage dysplasia |
| MDS with multilineage dysplasia |
| MDS with excess blasts |
| MDS with isolated del(5q) |
| MDS, unclassifiable |
| *Provisional entity: Refractory cytopenia of childhood* |

**Blood. 2016;127(20):2391-2405**

**Table 15. PB and BM findings and cytogenetics of MDS**

| Name | Dysplastic lineages | Cytopenias* | Ring sideroblasts as % of marrow erythroid elements | BM and PB blasts | Cytogenetics by conventional karyotype analysis |
|---|---|---|---|---|---|
| MDS with single lineage dysplasia (MDS-SLD) | 1 | 1 or 2 | <15%/<5%† | BM <5%, PB <1%, no Auer rods | Any, unless fulfills all criteria for MDS with isolated del(5q) |
| MDS with multilineage dysplasia (MDS-MLD) | 2 or 3 | 1-3 | <15%/<5%† | BM <5%, PB <1%, no Auer rods | Any, unless fulfills all criteria for MDS with isolated del(5q) |
| **MDS with ring sideroblasts (MDS-RS)** | | | | | |
| MDS-RS with single lineage dysplasia (MDS-RS-SLD) | 1 | 1 or 2 | ≥15%/≥5%† | BM <5%, PB <1%, no Auer rods | Any, unless fulfills all criteria for MDS with isolated del(5q) |
| MDS-RS with multilineage dysplasia (MDS-RS-MLD) | 2 or 3 | 1-3 | ≥15%/≥5%† | BM <5%, PB <1%, no Auer rods | Any, unless fulfills all criteria for MDS with isolated del(5q) |
| MDS with isolated del(5q) | 1-3 | 1-2 | None or any | BM <5%, PB <1%, no Auer rods | del(5q) alone or with 1 additional abnormality except −7 or del (7q) |
| **MDS with excess blasts (MDS-EB)** | | | | | |
| MDS-EB-1 | 0-3 | 1-3 | None or any | BM 5%-9% or PB 2%-4%, no Auer rods | Any |
| MDS-EB-2 | 0-3 | 1-3 | None or any | BM 10%-19% or PB 5%-19% or Auer rods | Any |
| **MDS, unclassifiable (MDS-U)** | | | | | |
| with 1% blood blasts | 1-3 | 1-3 | None or any | BM <5%, PB = 1%,‡ no Auer rods | Any |
| with single lineage dysplasia and pancytopenia | 1 | 3 | None or any | BM <5%, PB <1%, no Auer rods | Any |
| based on defining cytogenetic abnormality | 0 | 1-3 | <15%§ | BM <5%, PB <1%, no Auer rods | MDS-defining abnormality |
| Refractory cytopenia of childhood | 1-3 | 1-3 | None | BM <5%, PB <2% | Any |

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

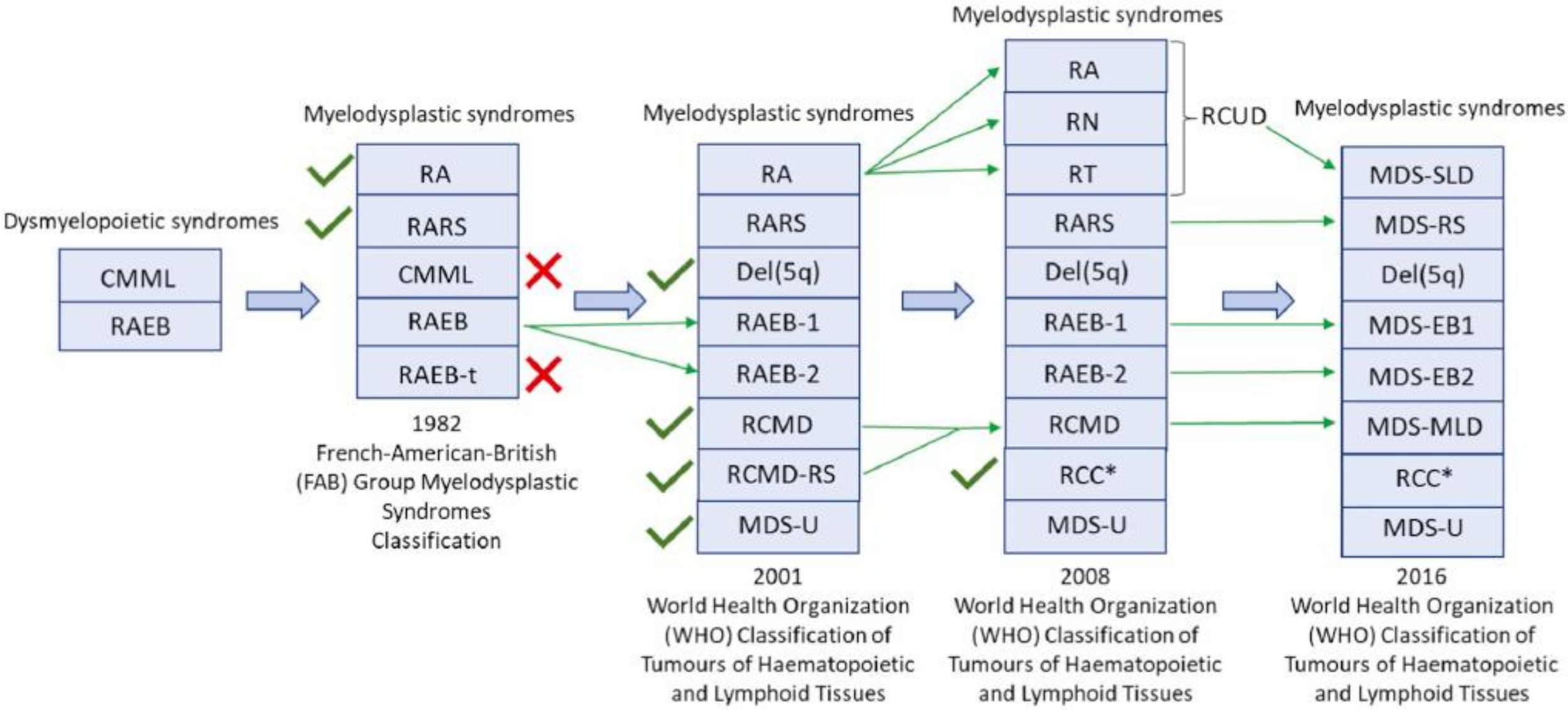
†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

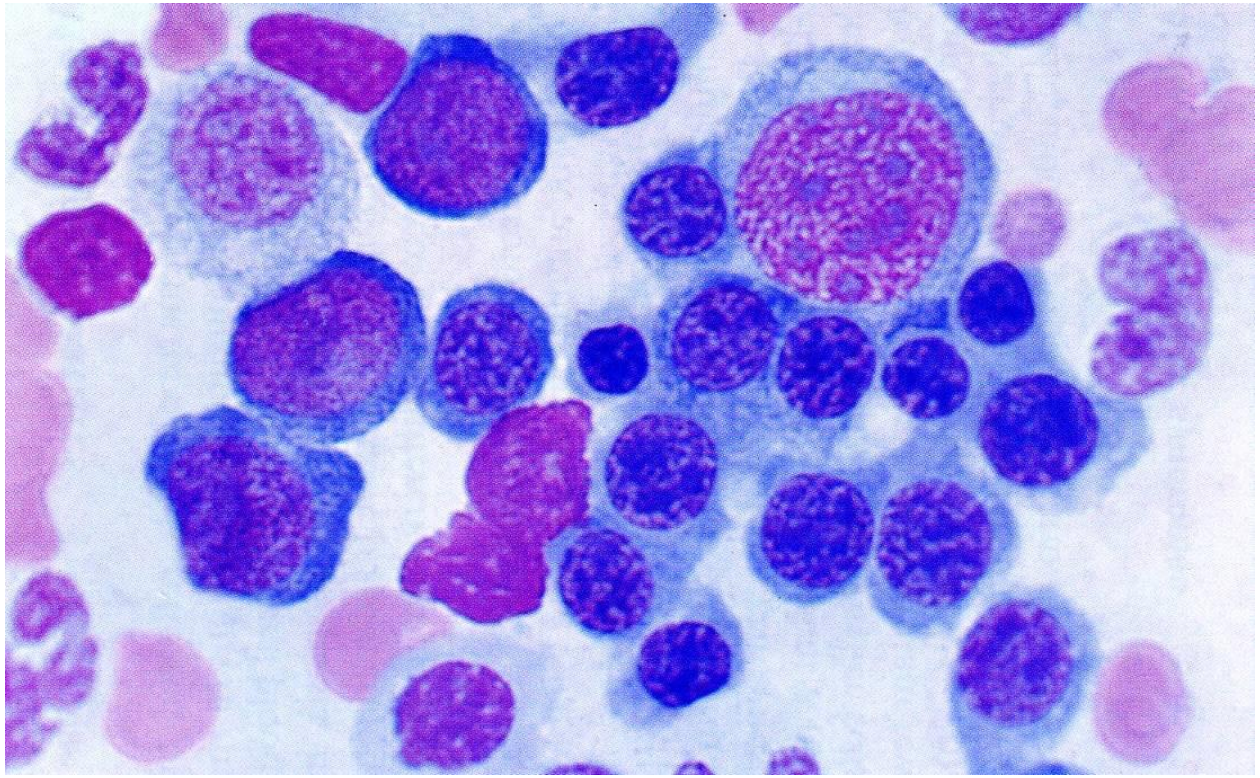
**Blood. 2016;127(20):2391-2405**

# Evolution of MDS classification systems



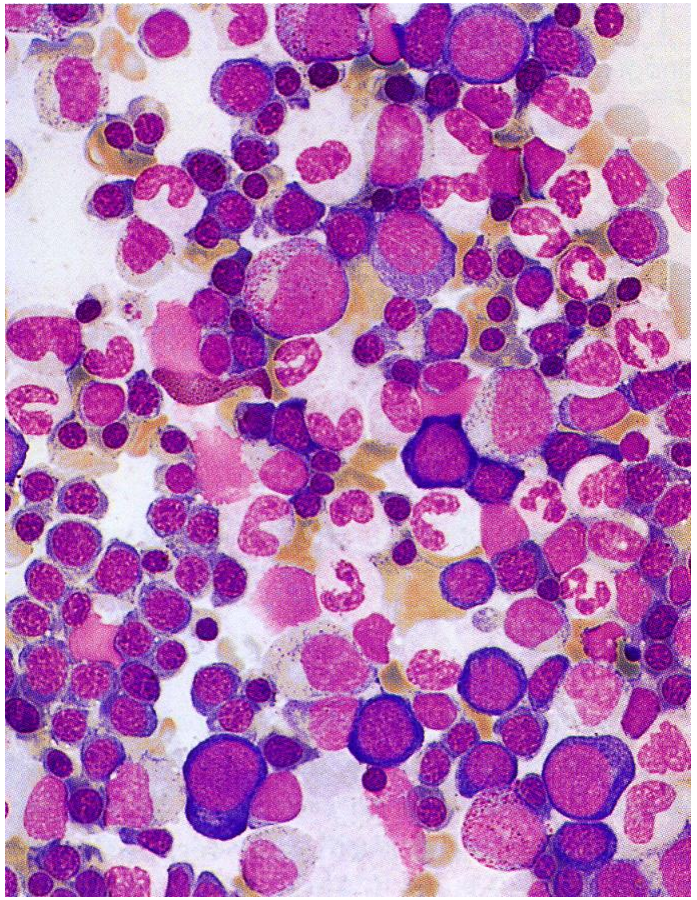

Zeidan et al. Blood Reviews 2018

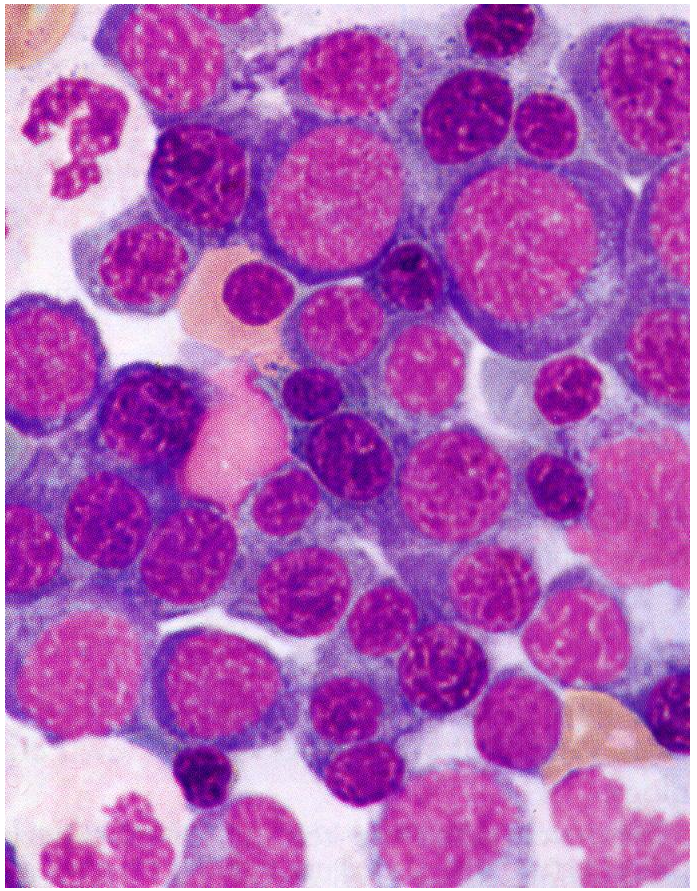
# RA

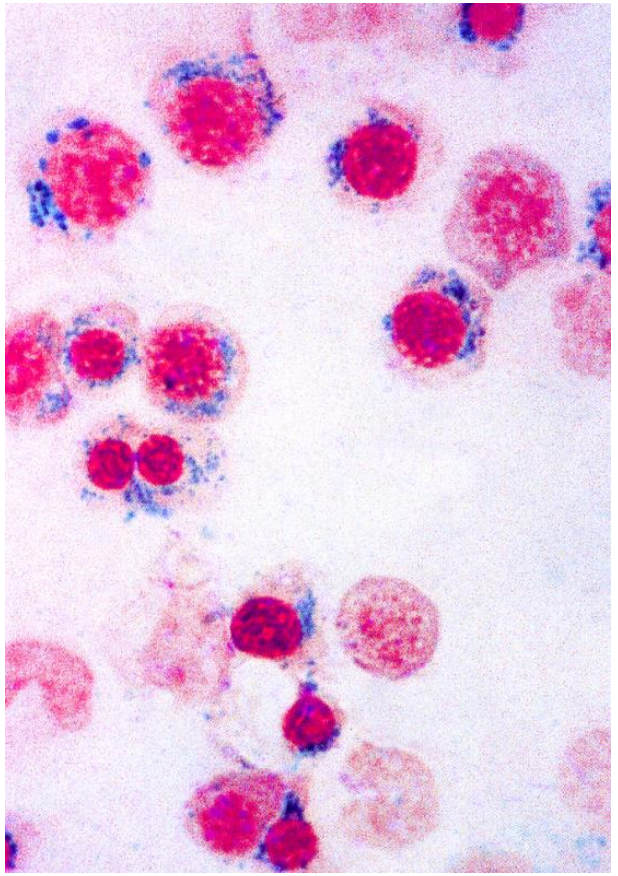


**Castoldi G. Atlas of blood cells. 2003; p 285-98.**

# RARS

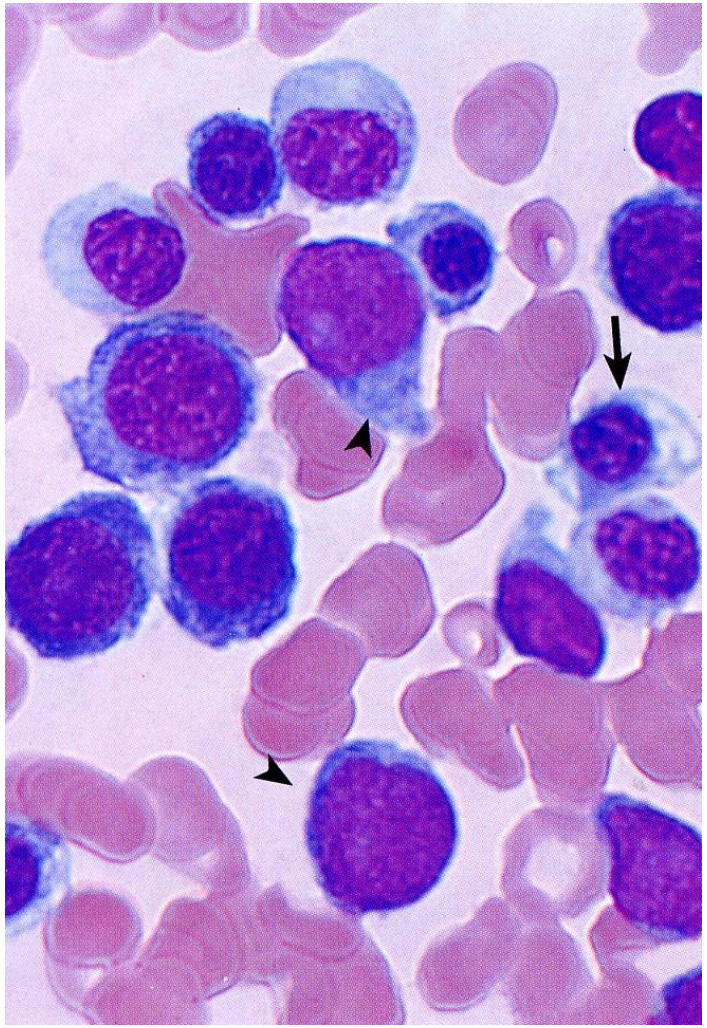


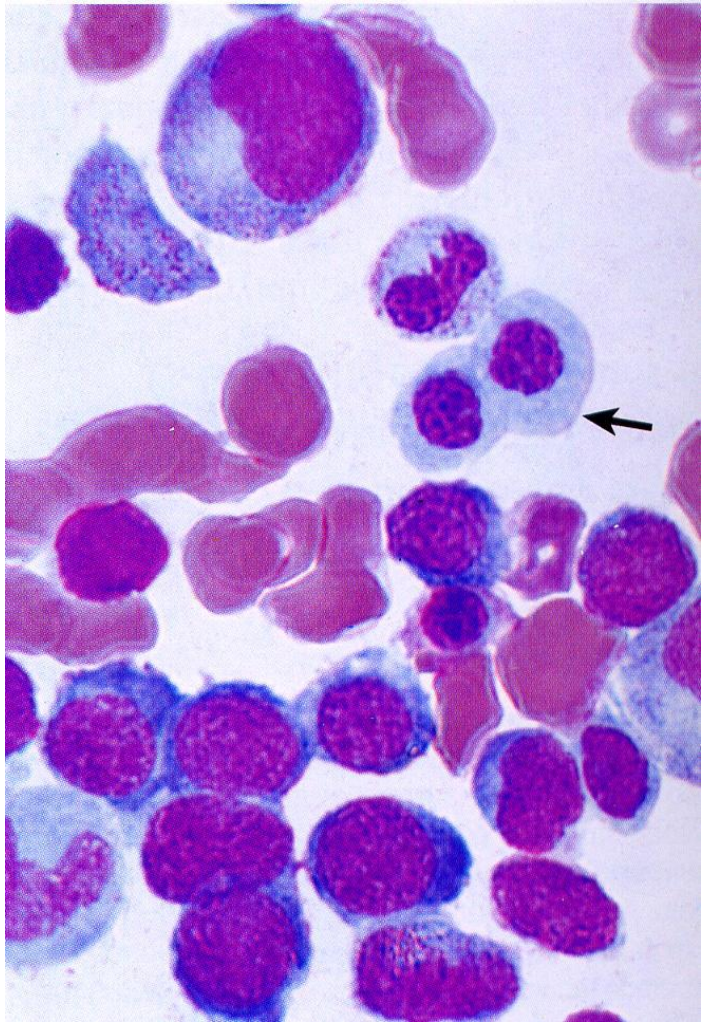




**Castoldi G. Atlas of blood cells. 2003; p 285-98.**

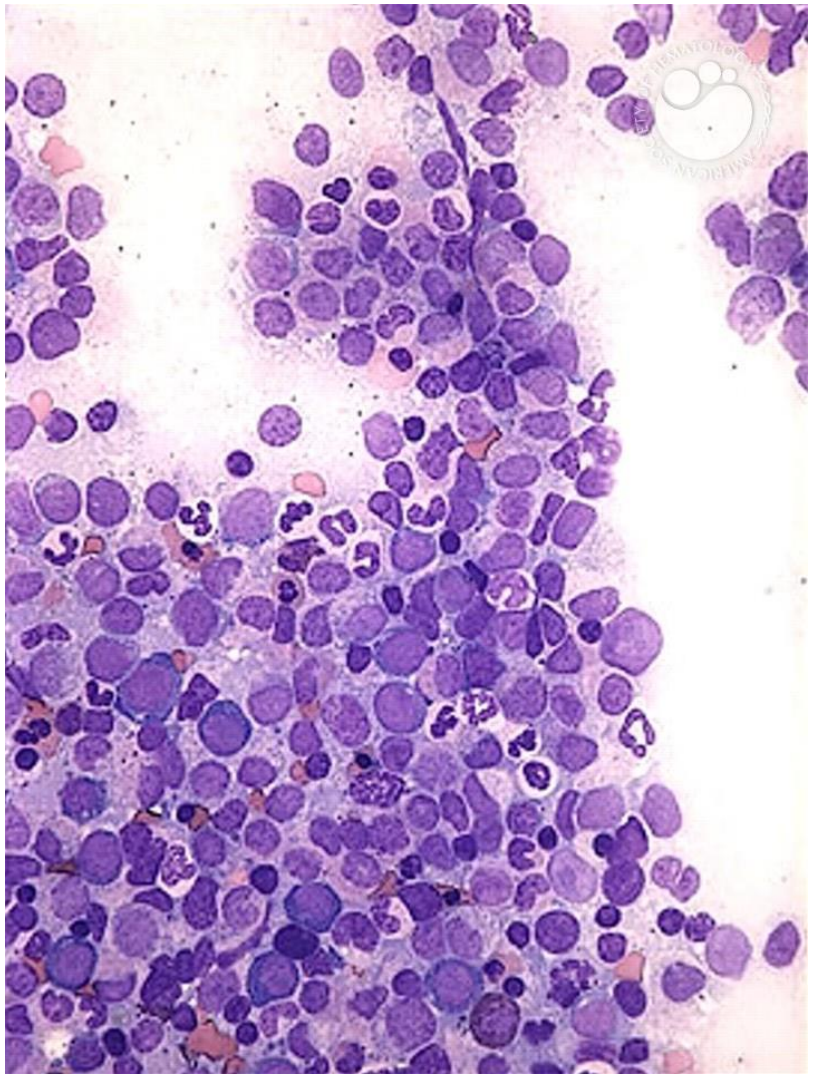
# RAEB-1

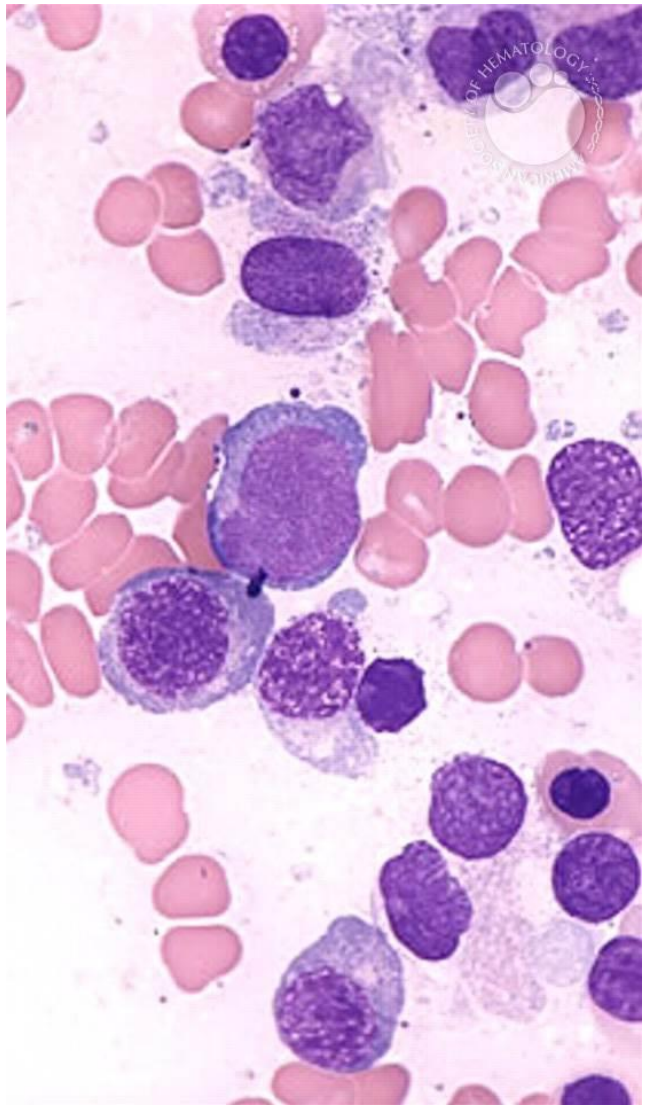




**Castoldi G. Atlas of blood cells. 2003; p 285-98.**

# RAEB 2



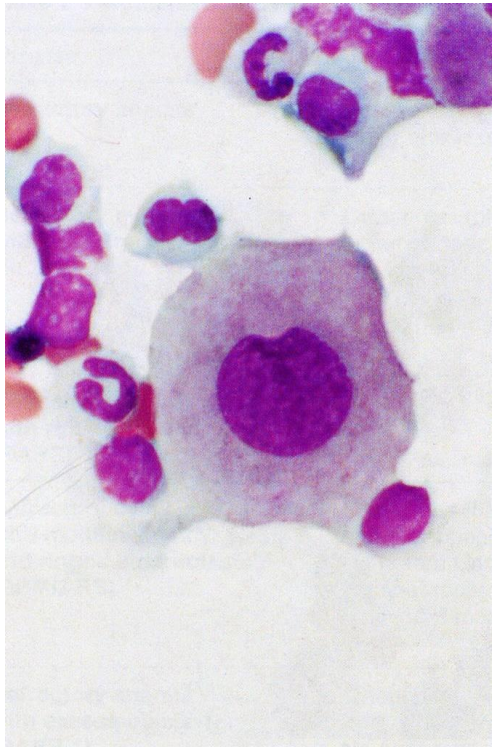


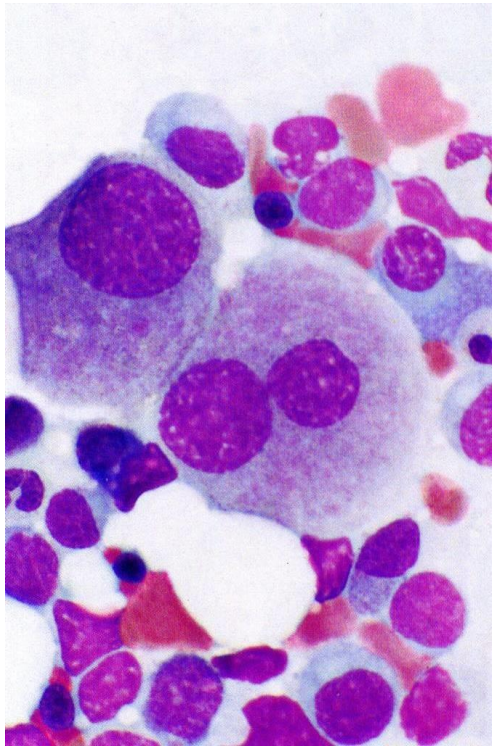
**ASH image bank**

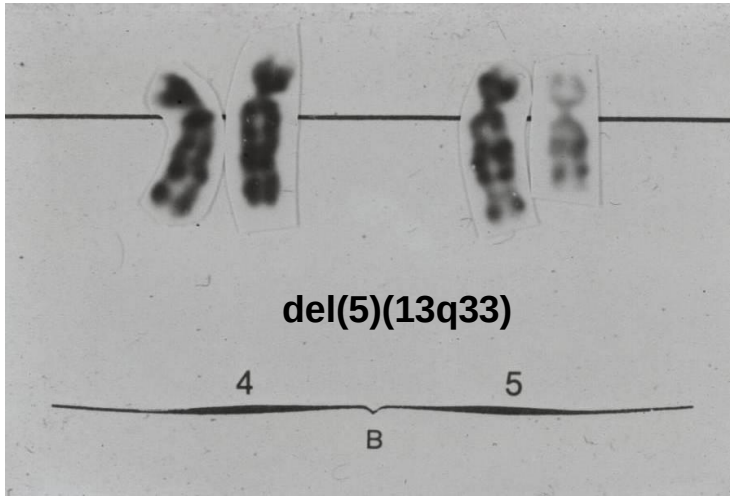
# Sindrome da 5q-

- Presentazione clinica
  - Età avanzata
  - Sesso femminile (F:M 7:3)
  - Basso rischio di progressione in LAM
  - Buona prognosi

- Quadro ematologico
  - Anemia macrocitica
  - Modesta leucopenia
  - Normale/elevato numero di piastrine
  - ipoplasia eritroide midollare
  - Megacariociti monolobati
  - Delezione intestiziale braccio lungo del cromosoma 5 come singola anomalia
  - Blasti < 5%







# MDS: clinical findings

- Clinical features are non-specific and mainly result from cytopenias.
- **Anaemia**, is symptomatic in many pts, leading to fatigue, poor quality of life, and destabilisation of underlying cardiovascular disease.

- **Thrombocytopenia** is commonly associated with platelet dysfunction, potentially leading to bleeding symptoms even in moderate thrombocytopenia.

- **Infections** (especially with gram-neg bacilli, gram-pos cocci, and fungi) can occur with only moderate neutropenia due to neutrophil function defects.

- Many patients have **immune disorders**, including relapsing polychondritis, vasculitis, and seronegative polyarthritis.
  - The two disorders tend to be diagnosed almost simultaneously, which suggests a pathophysiological relation.

**Ades et al. Lancet 2014; 383: 2239–52**

# MDS: Differential diagnosis

- All other causes of cytopenias must be carefully excluded;
  - vitamin deficiencies
  - autoimmune disease,
  - Liver disease,
  - hypersplenism,
  - viral infections,
  - drug intake,
  - exposure to environmental toxins,
  - aplastic anaemia,
  - Acute leukemias
  - Large granular lymphocytic leukemia
  - Hairy cell leukemia
  - Myelofibrosis
  - Paroxysmal nocturnal haemoglobinuria,
  - bone-marrow infiltration by malignancy,
  - rare forms of hereditary anaemias (such as congenital dyserythropoetic anaemias).

# therapy related MDS

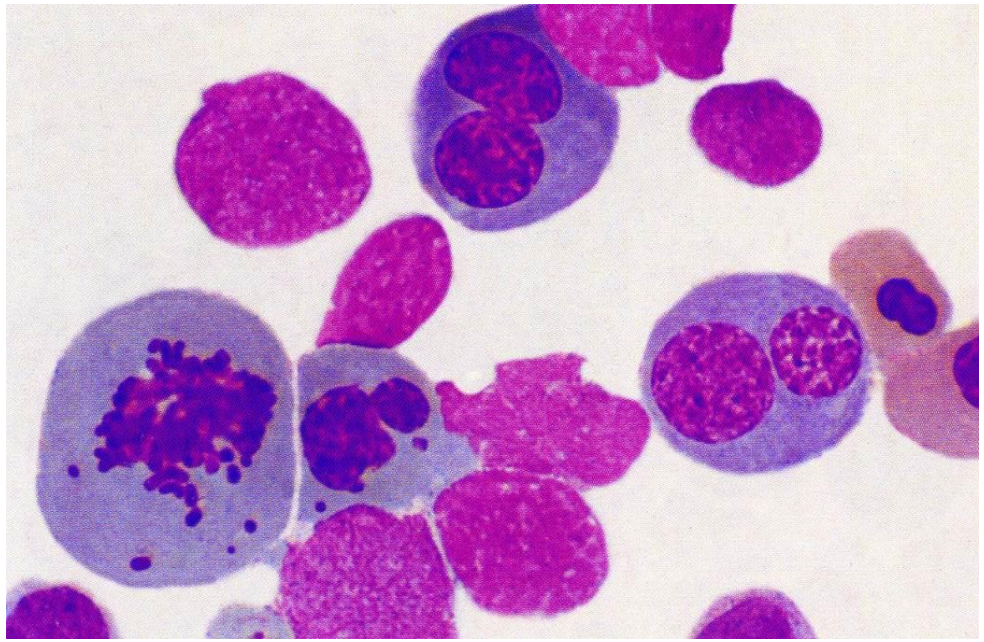
- **Rischio attuariale 0.25-1% per anno da 2 a 5-7 anni dalla fine della chemioterapia**

- **Rischio dose dipendente e aumenta esponenzialmente dopo i 40 anni**

Genomic differences between t-MDS/AML and de novo (d)-MDS/AML.

| Mutation [70] | t-MN (%) | d-MN (%) |
|---|---|---|
| *tP53* | 39 in t-MDS | 17 in d-MDS, p0.04 |
| | 35.7 in t-AML | 12.8 in d-AML, p0.002 |
| *PTPN11* | 11.9 in t-AML | 2.1 in d-AML, p0.0075 |
| *FLT3* | 7.1 in t-AML | 21.7 in d-AML, p0.03 |
| *NPM1* | 2.5 in t-AML | 16.4 in d-AML, p0.01 |
| Cytogenetic differences | | |
| -5/del5q [68] | 40 in t-MDS/AML | 10-20 in d-MDS/AML |
| −7/del(7q) [69] | 55 in t-MDS | 5 in d MDS (as sole abnormality) |
| Translocations of 11q23 [122] | 25 in t-MDS | 5.1 in d-MDS |
| T (11,16) [123] | 2 in t-MDS | 0 |
| Complex karyotype [68,69,123] | 39-90 in t-MDS | 20 in d-MDS |

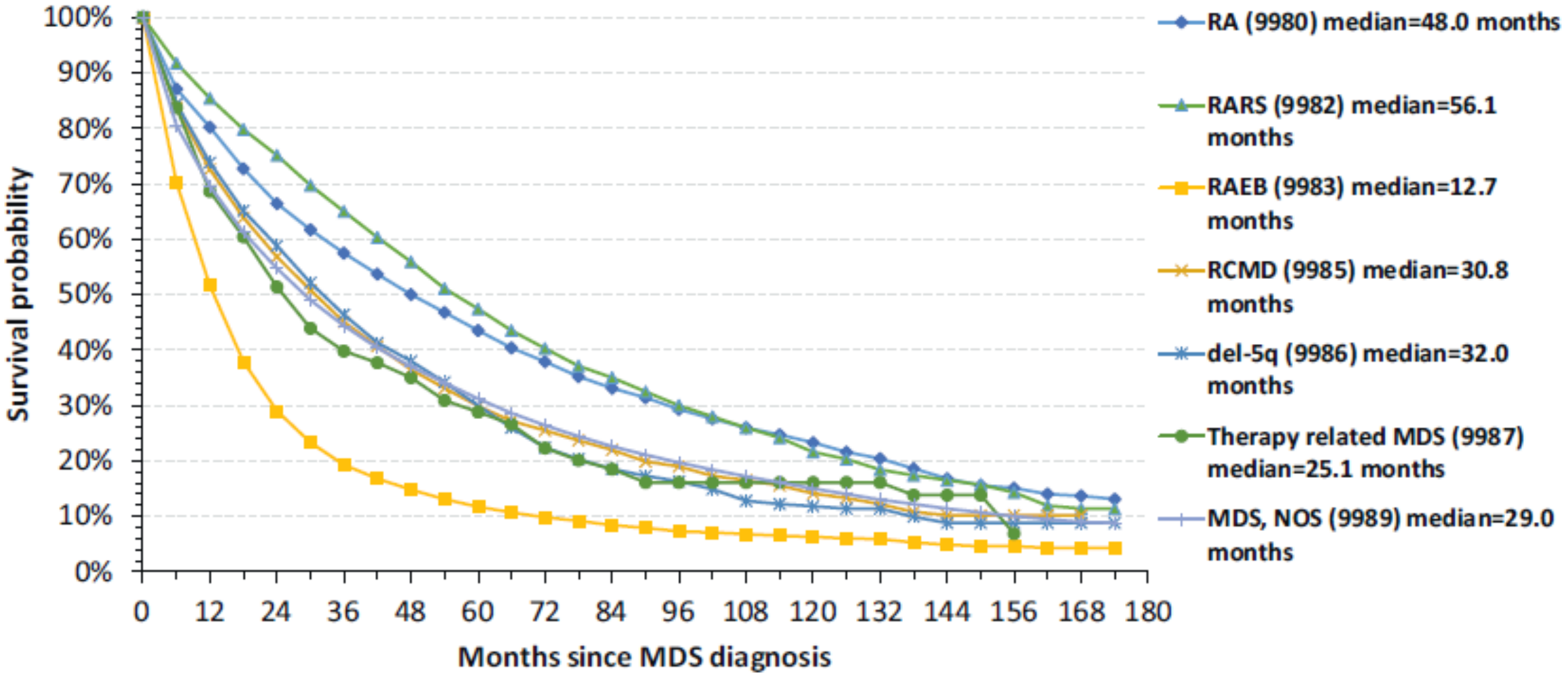
A. Abou Zahr et al. / Blood Reviews 31 (2017) 119–128



Castoldi G. Atlas of blood cells. 2003; p 285-98.

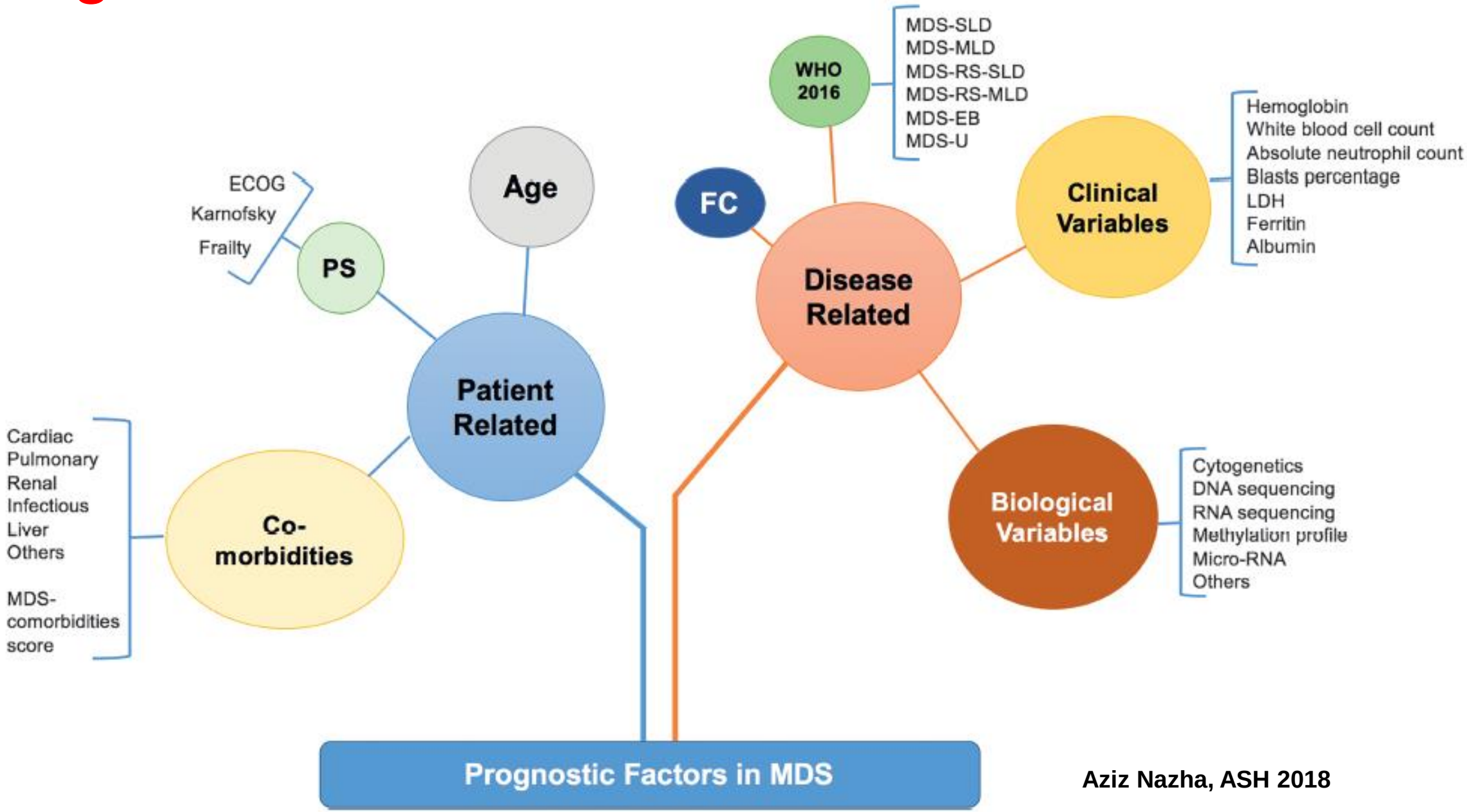
# Survival MDS by subtype in the USA

(Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).




Zeidan et al Blood Reviews 2018

# Prognostic factors in MDS




Aziz Nazha, ASH 2018

# International prognostic Scoring System

| | 0 points | 0·5 points | 1·0 point | 1·5 points | 2·0 points |
|---|---|---|---|---|---|
| Bone-marrow blasts (%) | <5% | 5–10% | .. | 11–20% | 21–30% |
| Number of cytopenias* | 0–1 | 2–3 | .. | .. | .. |
| Cytogenetics | Good: normal, Y, del(5q), del(20q) | Intermediate: other abnormalities | Poor: complex ≥3 abnormalities, chromosome 7 abnormalities | .. | .. |

*Platelet count <100 × $10^9$/L; haemoglobin <100 g/L; absolute neutrophil count <1·8 × $10^9$/L.

*Table 4:* The international pronostic scoring sytem (IPSS)[7] score values

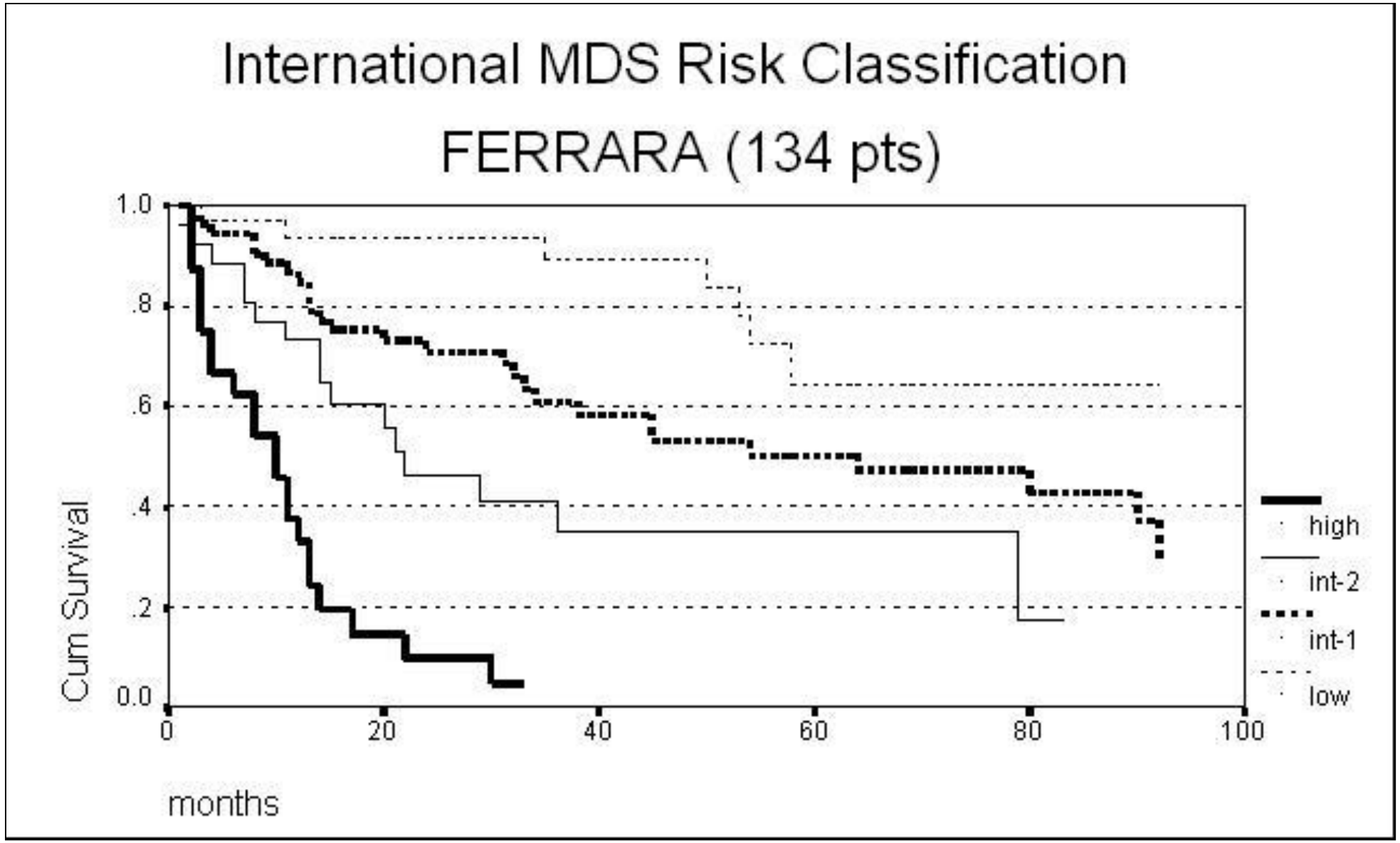
| | Low | Intermediate 1 | Intermediate 2 | High |
|---|---|---|---|---|
| Risk score | 0 | 0·5–1·0 | 1·5–2·0 | ≥2·5 |
| Proportion of patients (%) | 33% | 38% | 22% | 7% |
| Median survival (years) | 5·7 | 3·5 | 1·2 | 0·4 |
| Time to 25% AML evolution (years) | 9·4 | 3·3 | 1·1 | 0·2 |

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia.

*Table 5:* IPSS prognostic risk category clinical outcomes

Greenberg et al, Blood, 1997;89:2079

# IPSS e sopravvivenza



# Revised International Prognostic Scoring System for Myelodysplastic Syndromes

| | 0 points | 0·5 points | 1·0 point | 1·5 points | 2·0 points | 3·0 points | 4·0 points |
|---|---|---|---|---|---|---|---|
| Cytogenetics* | Very good | -- | Good | -- | Intermediate | Poor | Very poor |
| Bone-marrow blasts (%) | ≤2% | -- | >2 to <5% | -- | 5–10% | >10% | -- |
| Haemoglobin (g/L) | ≥100 | -- | 80 to <100 | <80 | -- | -- | -- |
| Platelet count (x10⁹/L) | ≥100 | 50 to <100 | <50 | -- | -- | -- | -- |
| Absolute neutrophil count (x10⁹/L) | ≥0·8 | <0·8 | -- | -- | -- | -- | -- |

*As in table 2.

*Table 6*: Revised international prognostic scoring system prognostic score values

Greenberg PL et al. Blood. 2012;120(12): 454-2465

| | Very low | Low | Intermediate | High | Very high |
|---|---|---|---|---|---|
| Risk score | ≤1·5 | >1·5–3·0 | >3·0–4·5 | >4·5–6·0 | >6·0 |
| Proportion of patients (%) | 19% | 38% | 20% | 13% | 10% |
| Median survival (years) | 8·8 | 5·3 | 3·0 | 1·6 | 0·8 |
| Time to 25% evolution to AML (years) | NR | 10·8 | 3·2 | 1·4 | 0·73 |

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia. NR=not reached.

*Table 7*: Revised IPSS prognostic risk category clinical outcomes

## IPSS

### BM Blast %

| Parameter | Score |
|---|---|
| < 5 | 0 |
| 5 - 10 | 0.5 |
| 15 - 20 | 1.5 |
| 21 - 30 | 2 |

### Cytogenetics

| Parameter | Score |
|---|---|
| Good | 0 |
| Intermediate | 0.5 |
| Poor | 1 |

### Cytopenias

| Parameter | Score |
|---|---|
| 2 / 3 | 0.5 |

### Others

None

## IPSS-R

### BM Blast %

| Parameter | Score |
|---|---|
| ≤ 2 | 0 |
| > 2 - < 5 | 1 |
| 5 – 10 | 2 |
| > 10 | 3 |

### Cytogenetics

| Parameter | Score |
|---|---|
| Very Good | 0 |
| Good | 1 |
| Intermediate | 2 |
| Poor | 3 |
| Very Poor | 4 |

### Cytopenias

| Parameter | Score |
|---|---|
| **Hb** 8 - < 10 | 1 |
| < 8 | 1.5 |
| **ANC** < 0.8 | 0.5 |
| **Plts** 50 - <100 | 0.5 |
| < 50 | 1 |

### Others

None

## WPSS

### BM Blast %

None

### Cytogenetics

| Parameter | Score |
|---|---|
| Good | 0 |
| Intermediate | 1 |
| Poor | 2 |

### Cytopenias

None

### Others

| Parameter | Score |
|---|---|
| **WHO 2008** | |
| RA, RARS, 5q- | 0 |
| RCMD/ RCMD-RS | 1 |
| RAEB-1 | 2 |
| RAEB-2 | 3 |
| **RBC transfusion** | 1 |

## MDAPSS

### BM Blast %

| Parameter | Score |
|---|---|
| 5 – 10 | 1 |
| 11 – 29 | 2 |

### Cytogenetics

| Parameter | Score |
|---|---|
| Chromosome 7 Abn | 3 |
| Complex ≥ 3 | 3 |

### Cytopenias

| Parameter | Score |
|---|---|
| **Hb** < 12 | 2 |
| **WBC** > 20 | 1.5 |
| **Plts** 50 - 199 | 1 |
| 30 - 49 | 2 |
| < 30 | 3 |

### Others

| Parameter | Score |
|---|---|
| **Age** 60 - 64 | 1 |
| ≥ 65 | 2 |
| **PS** ≥ 2 | 2 |
| **RBC transfusion** | 1 |

## LRPSS

### BM Blast %

| Parameter | Score |
|---|---|
| > 4 | 1 |

### Cytogenetics

| Parameter | Score |
|---|---|
| Unfavorable | 1 |

### Cytopenias

| Parameter | Score |
|---|---|
| **Hb** < 10 | 1 |
| **Plts** 50 - 200 | 1 |
| < 50 | 2 |

### Others

| Parameter | Score |
|---|---|
| **Age** ≥ 60 | 2 |

**Aziz Nazha, ASH 2018**

# Risk stratification, scores, and median OS by each model.

## IPSS

| Risk Group | score | OS (Y) |
|---|---|---|
| Low | 0 | 5.7 |
| Inter-1 | 0.5 - 1 | 3.5 |
| Inter-2 | 1.5 - 2.0 | 1.1 |
| High | ≥ 2.5 | 0.4 |

## IPSS-R

| Risk Group | score | OS (Y) |
|---|---|---|
| Very Low | ≤ 1.5 | 8.8 |
| Low | > 1.5 - 3 | 5.3 |
| Inter | > 3 – 4.5 | 3.0 |
| High | > 4.5 - 6 | 1.6 |
| Very High | > 6 | 0.8 |

## WPSS

| Risk Group | score | OS (M) |
|---|---|---|
| Very Low | 0 | 141 |
| Low | 1 | 66 |
| Inter | 2 | 48 |
| High | 3 - 4 | 26 |
| Very High | 5 - 6 | 9 |

## MDAPSS

| Risk Group | score | OS (M) |
|---|---|---|
| Low | 0 - 4 | 54 |
| Inter-1 | 5 - 6 | 25 |
| Inter-2 | 7 - 8 | 14 |
| High | ≥ 9 | 6 |

## LRPSS

| Risk Group | score | OS (M) |
|---|---|---|
| Cat-1 | 0 - 2 | 80 |
| Cat-2 | 3 - 4 | 27 |
| Cat-3 | ≥ 5 | 14 |

- **Current models can overestimate or underestimate the OS for some MDS pts.**
- 
- **Recognizing this limitation of current models is very important as the choice of therapy and disease expectations are highly dependent on prognosis, and identifying the actual risk in these patients could alter their treatment recommendations**

**Aziz Nazha, ASH 2018**

# Comorbidities in MDS

| Comorbidity | Definition | Prevalence | |
|---|---|---|---|
| Cardiac | Arrhythmia* | 7% | 25% |
| | Heart valve disease** | 2% | |
| | Coronary artery disease *** or myocardial infarction | 8% | |
| | Congestive heart failure or ejection fraction ≤50% | 19% | |
| Cerebrovascular | Transient ischemic attack and/or ischemic or hemorrhagic cerebrovascular accident | 5% | |
| Mild to moderate pulmonary | DLCO and/or FEV1 66%-80% or dyspnea on moderate or slight activity | 3% | |
| Severe pulmonary | DLCO and/or FEV1 ≤65% or dyspnea at rest or requires oxygen | 2% | |
| Mild hepatic **** | Chronic hepatitis, persistent bilirubin > ULN to 1.5 x ULN or AST/ALT > ULN to 2.5 x ULN | 14% | |
| Moderate to severe hepatic **** | Cirrhosis, fibrosis, persistent bilirubin > 1.5 x ULN or AST/ALT > 2.5 x ULN | 3% | |
| Renal | Persistent creatinine > 2 mg/dL, renal dialysis, or renal transplant | 4% | |
| Solid tumor | Malignancy at any time point in the patient's history, excluding non-melanoma skin cancer | 10% | |
| Rheumatological | One or more of the following conditions: systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, polymyalgia rheumatica | 2% | |
| Gastrointestinal | One or more of the following conditions: Crohn's disease, ulcerative colitis, or peptic ulcer requiring treatment | 6% | |
| Diabetes | Diabetes requiring treatment with insulin or oral hypoglycemics | 11% | |
| Endocrine | One or more of the following conditions: thyroid disorders, adrenal disorders, parathyroid gland disorders, pituitary gland disorders, or hypogonadism | 5% | |
| Obesity | Body mass index >35 kg/m$^2$ | 2% | |
| Psychiatric | Depression or anxiety requiring psychiatric counseling or treatment | 2% | |

*DLCO indicates diffusion capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in one second; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase. *Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias; **Except mitral valve prolapse; ***One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft; ****HCV infection was documented in 7% of patients.*

**Della Porta Haematologica 2011;96:441**

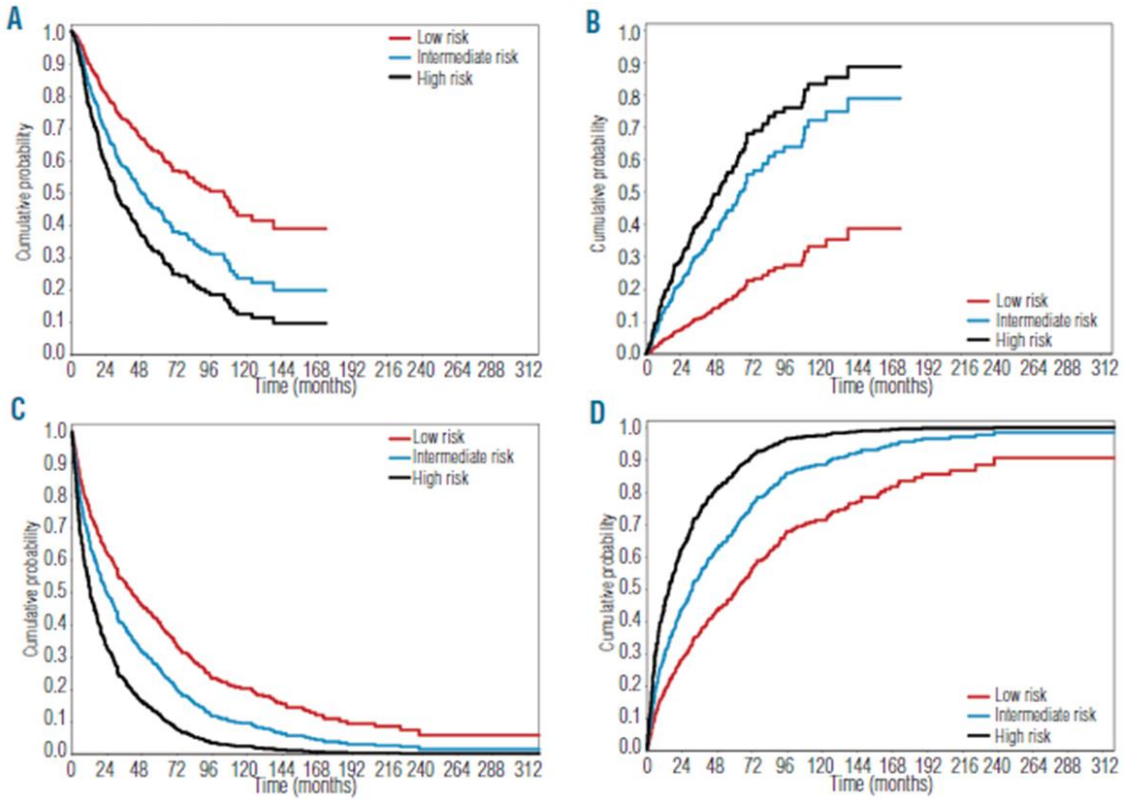



Figure 1. Relationship between MDS-CI category, risk of non-leukemic death and overall survival in the learning and validation cohorts of MDS patients. (A-B) Italian learning cohort; (A) Probability of overall survival according to time-dependent MDS-CI risk. (B) Probability of non-leukemic death according to time-dependent MDS-CI risk. (C-D); German validation cohort. (C) Probability of overall survival according to time-dependent MDS-CI risk. (D) Probability of non-leukemic death according to time-dependent MDS-CI risk.

# MDS comorbidity score

**Della Porta Haematologica 2011;96:441**

| Comorbidity | HR obtained through a multivariable Cox's survival analysis with NLD as an outcome | Variable weighted score (to be taken into account if the specific comorbidity is present) |
|---|---|---|
| Cardiac disease | 3.57 ($P<0.001$) | 2 |
| Moderate-to-severe hepatic disease | 2.55 ($P=0.01$) | 1 |
| Severe pulmonary disease | 2.44 ($P=0.005$) | 1 |
| Renal disease | 1.97 ($P=0.04$) | 1 |
| Solid tumor | 2.61 ($P<0.001$) | 1 |

| MDS-CI risk | Sum of individual variable scores | Proportion of patients in the learning cohort belonging to the risk group (%) |
|---|---|---|
| Low risk | 0 | 546/840 (65%) |
| Intermediate risk | 1-2 | 244/840 (29%) |
| High risk | >2 | 50/840 (6%) |

*NLD: non-leukemic death.*

**Table 1. Commonly mutated genes in MDS**

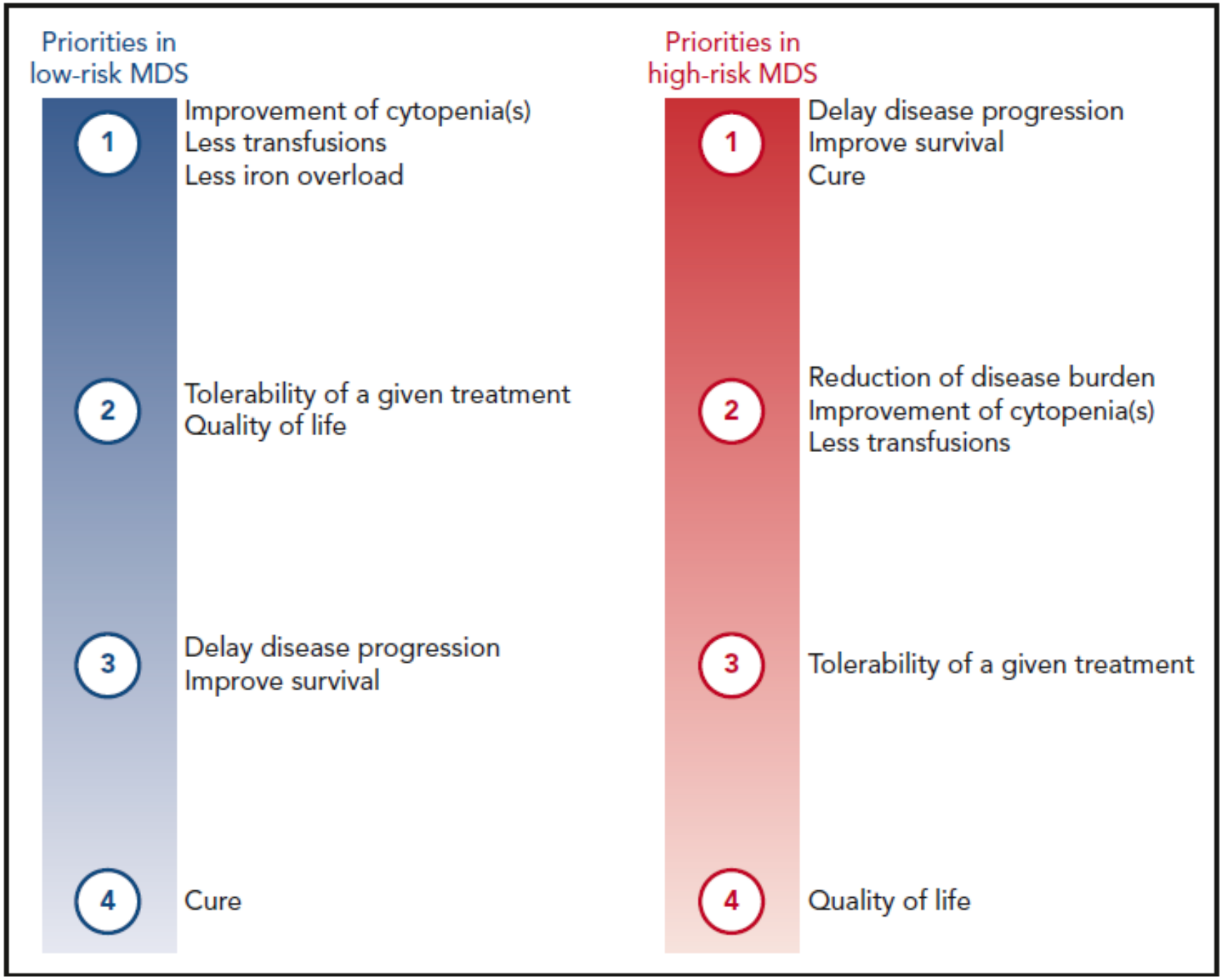
| Mutated gene | Frequency, % | Blasts <5% | Blasts 5%-30% | Notes | Reference |
|---|---|---|---|---|---|
| *TET2* | 20-30 | Neutral | Neutral | Commonly associated with normal karyotype | 12, 13, 27, 28, 30 |
| *SF3B1* | 20-25 | Favorable | Neutral | Associated with ring sideroblasts | 12, 13, 27, 28 |
| *ASXL1* | 15-20 | Adverse | Neutral | Adverse in CMML | 12, 13, 27 |
| *SRSF2* | 10-20 | Adverse | Neutral | Commonly comutated with TET2 in CMML | 12, 13, 27 |
| *DNMT3A* | 10-15 | Neutral | Neutral | Associated with MDS-MLD and MDS-EB | 12, 13, 27, 28, 30 |
| *RUNX1* | ~10 | Adverse | Adverse | Associated with MDS-MLD and MDS-EB | 12, 13, 27, 28 |
| *U2AF1* | <10 | Adverse | Neutral | Associated with MDS-MLD and MDS-EB | 12, 13, 27 |
| *EZH2* | 5 | Adverse | Adverse | Higher frequency in CMML | 12, 13, 27, 28 |
| *TP53* | 5-10 | Adverse | Adverse | Commonly associated with therapy-related MDS and CK | 12, 13, 27-32 |
| *IDH1/IDH2* | <10 | Neutral | Neutral | Associated with MDS-MLD and MDS-EB | 12, 13, 27, 28 |

Adapted from Nazha et al[34] with permission.
CMML, chronic myelomonocytic leukemia; MDS-EB, myelodysplastic syndromes with excess blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia.

**Aziz Nazha, ASH 2018**

# terapia

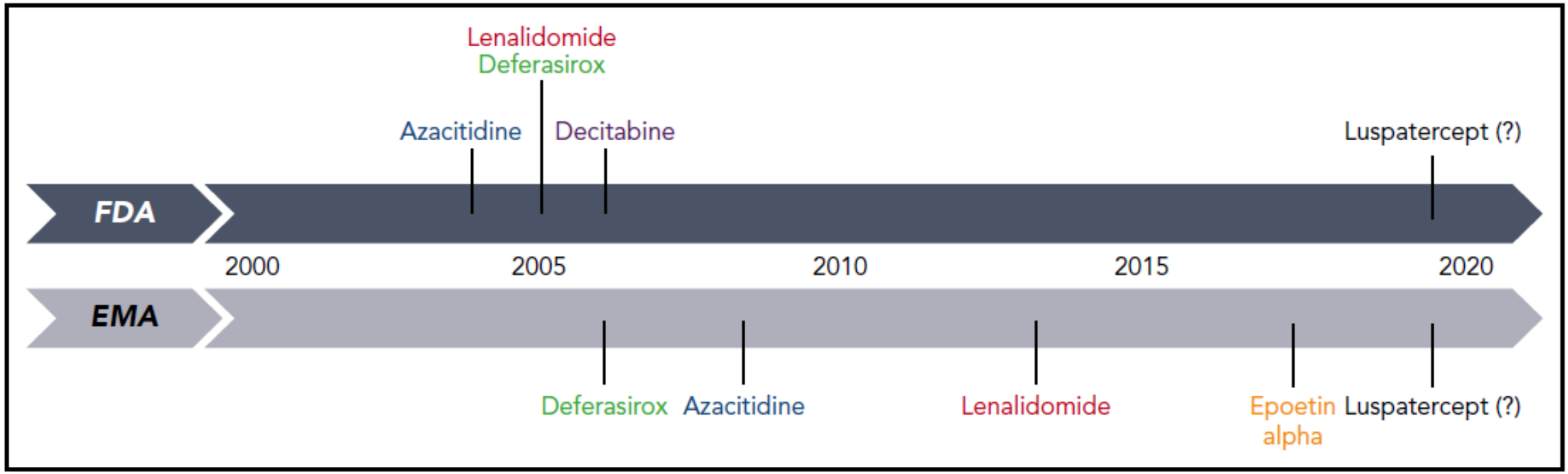
- Trapianto di cellule staminali (nei pazienti fit e “giovani”)
  - Allogenico
- Terapia di supporto
  - Trasfusioni,
  - Fattori di crescita: Epo, G-CSF
  - antibiotici,
  - etc
- Chemioterapia
- Terapia immunosoppressiva: ciclosporina, globulina antilinfocitaria (cariotipo normale / trisoma 8)
- Farmaci immunomodulanti: lenalidomide (del5q)
- Agenti ipometilanti: 5 azacitidina, decitabina
- Terapie target




# Priorities of interventions in MDS according to stage

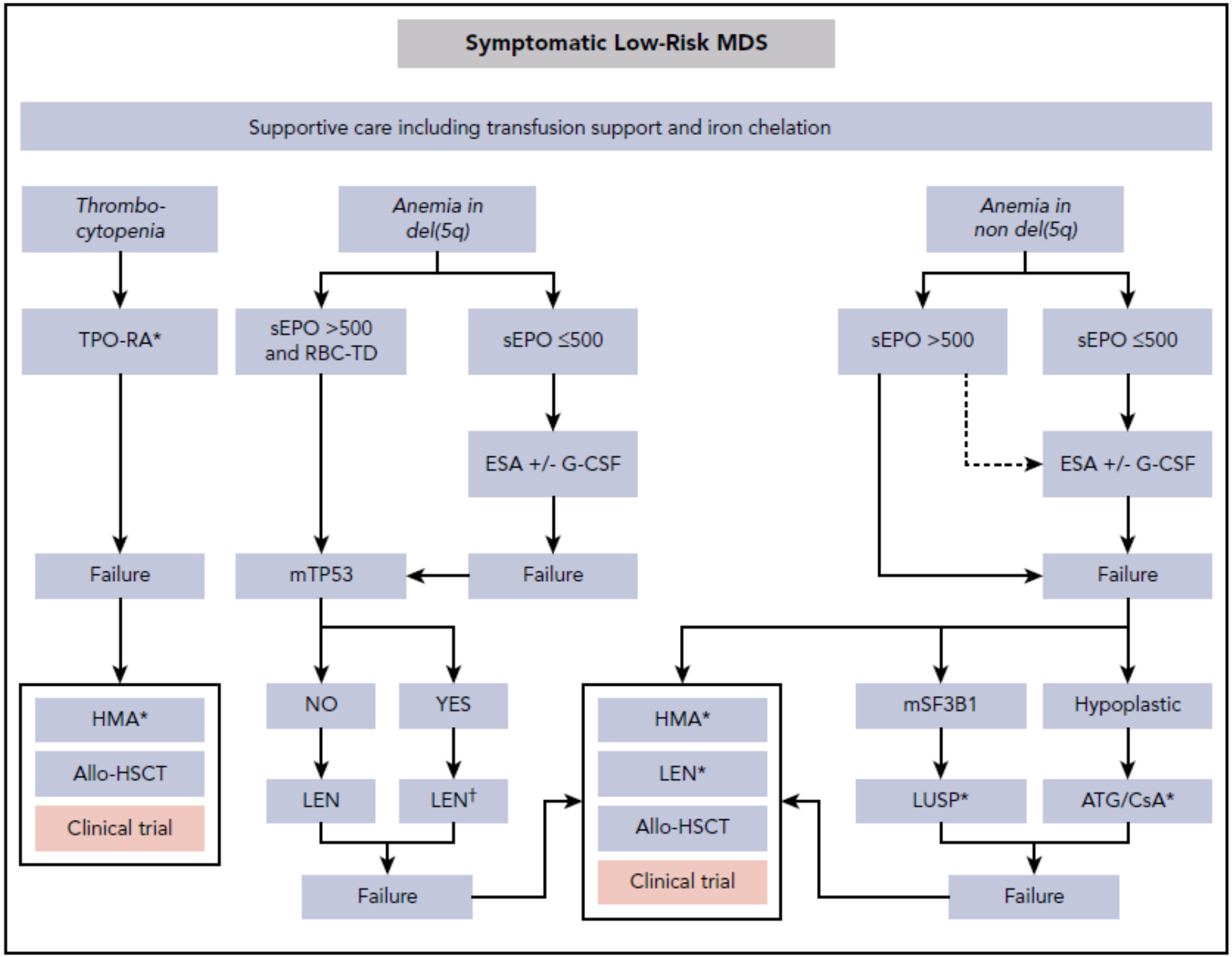
Platzbecker U. Blood. 2019;133(10):1096-1107)

# Historical time scale of registration of therapeutic agents forMDS in the EU and United States.




Platzbecker U. Blood. 2019;133(10):1096-1107)

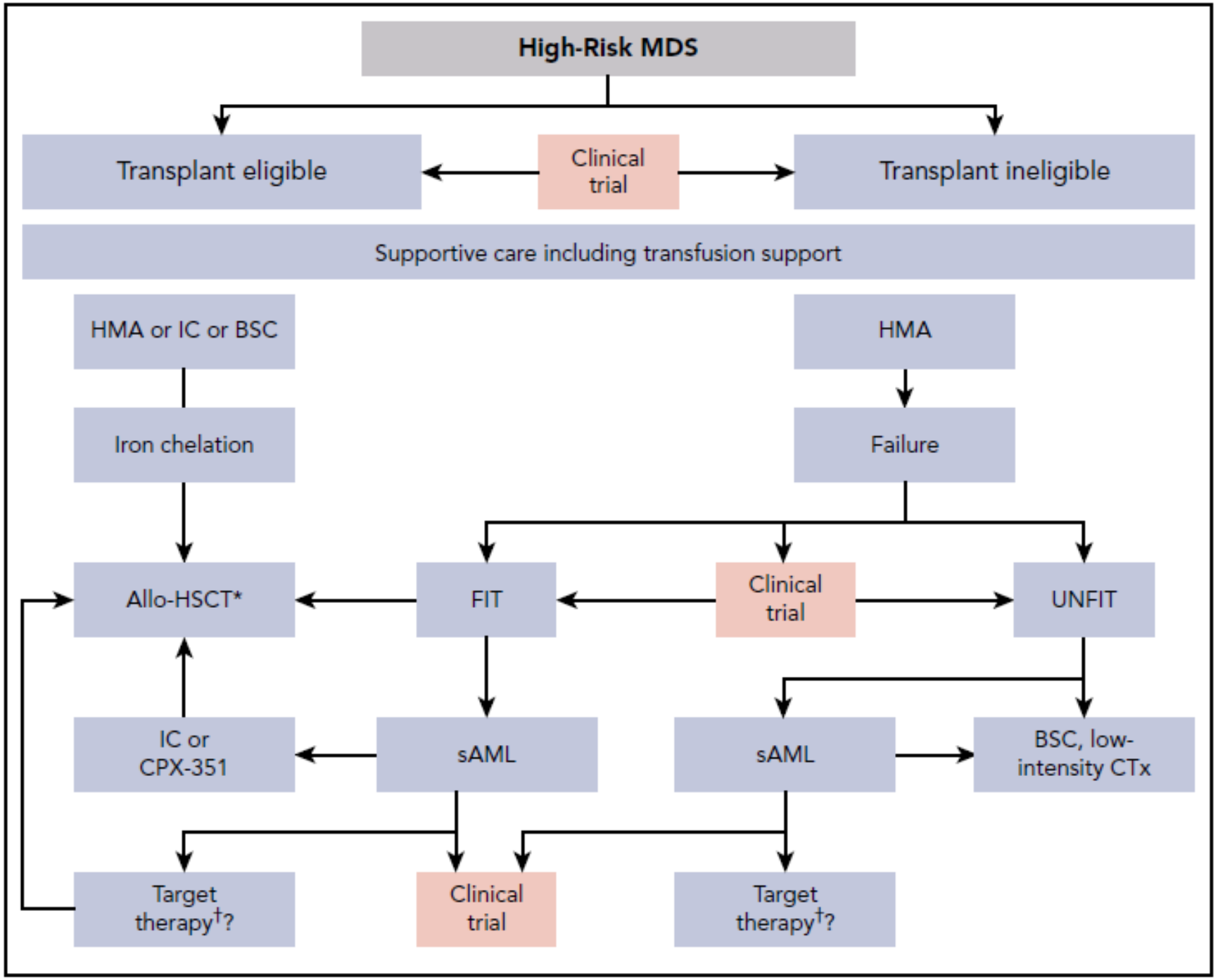
# Therapeutic algorithm in LR-MDS.




**G-CSF, granulocyte colony-stimulating factor;**
**ATG, antithymocyte globulin;**
**CSA, cyclosporine;**
**HMA, hypomethylating agent; LEN, lenalidomide;**
**LUSP, luspatercept;**
**sEPO, serum EPO;**
**TPO-RA, thrombopoietin receptor agonist.**
***Not presently approved.**
**†Intensified disease surveillance.**

**Platzbecker U. Blood. 2019;133(10):1096-1107)**

# Therapeutic algorithm in HR-MDS.

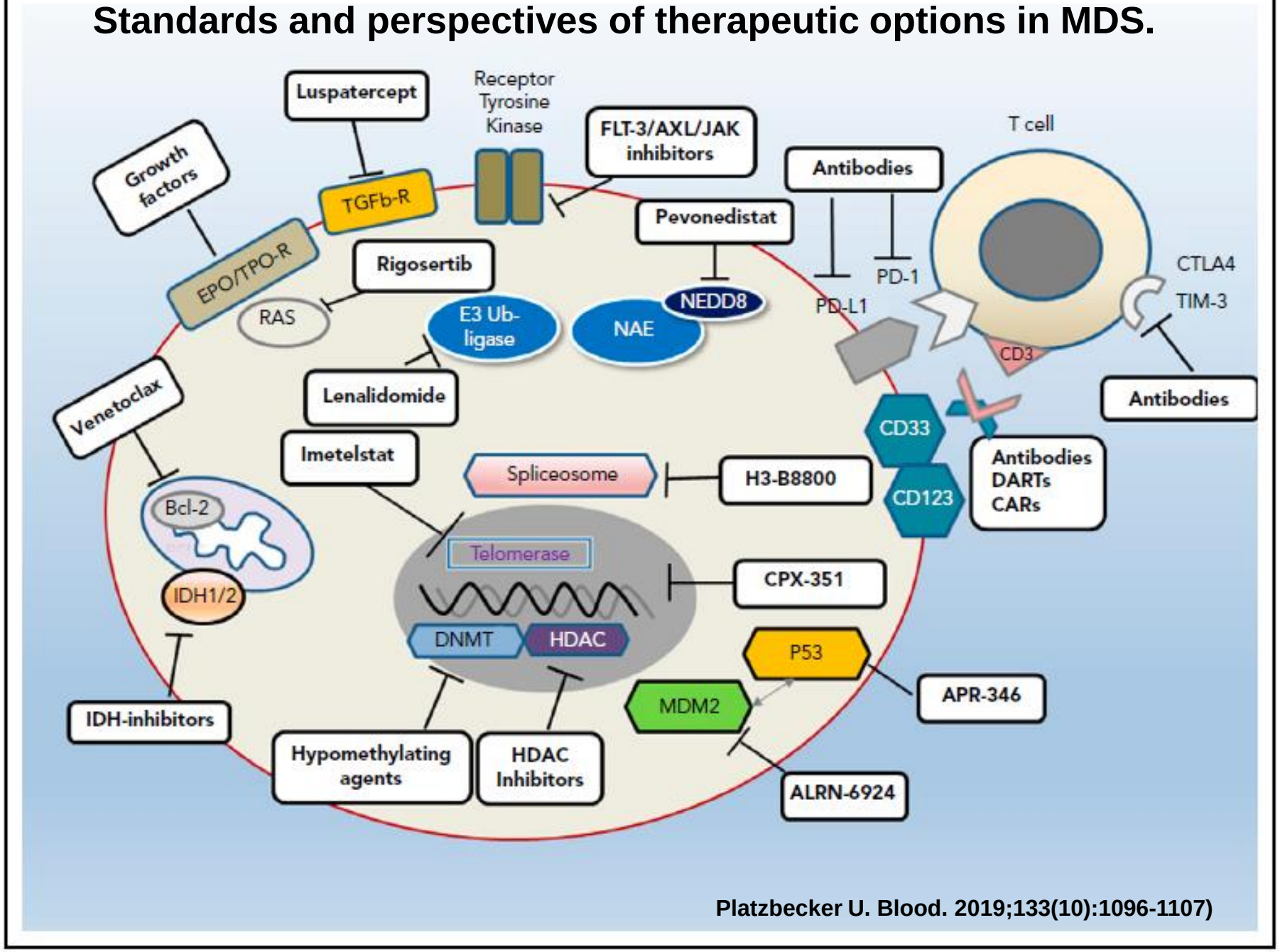



**CTx, chemotherapy;**
**IC, induction chemotherapy;**
**BSC, best supportive care;**
**TKI; tyrosine kinase inhibitor.**

***These could be IDH or FLT3-inhibitors (not presently approved).**
**†Consider posttransplant disease surveillance strategies**

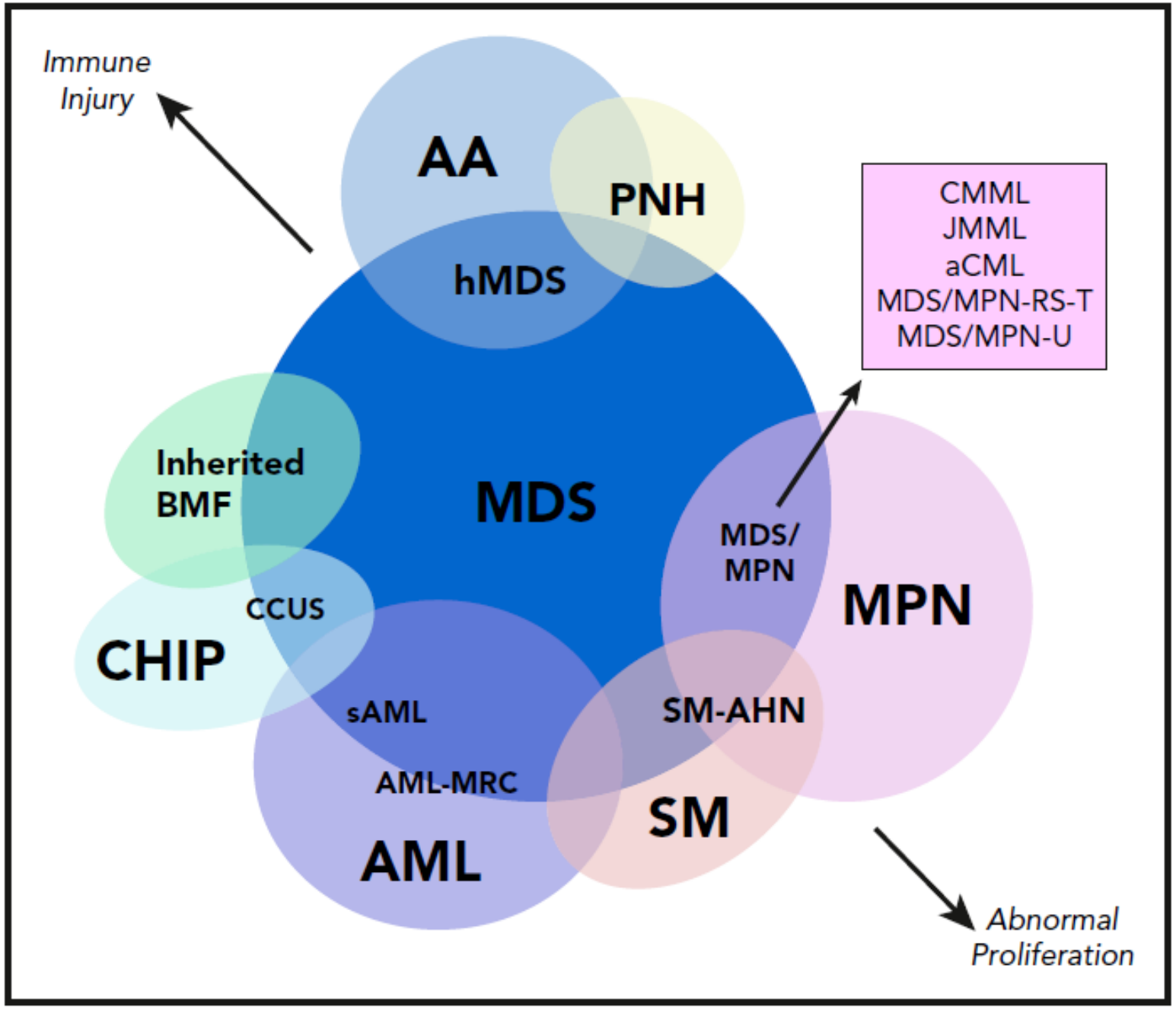
**Platzbecker U. Blood. 2019;133(10):1096-1107)**

# Standards and perspectives of therapeutic options in MDS.




Platzbecker U. Blood. 2019;133(10):1096-1107)

**Diagram depicting myeloid disorders with clinical and genetic features shared with MDS and the degree to which they are driven by proliferative and immunologic mechanisms.**




Tanaka TN, Blood. 2019;133(10):1086-1095

# WHO 2016: MDS/MPN

| **Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)** |
| --- |
| Chronic myelomonocytic leukemia (CMML) |
| Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$ |
| Juvenile myelomonocytic leukemia (JMML) |
| MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) |
| MDS/MPN, unclassifiable |

Arber DA et al. Blood. 2016; 127(20):2391-2405

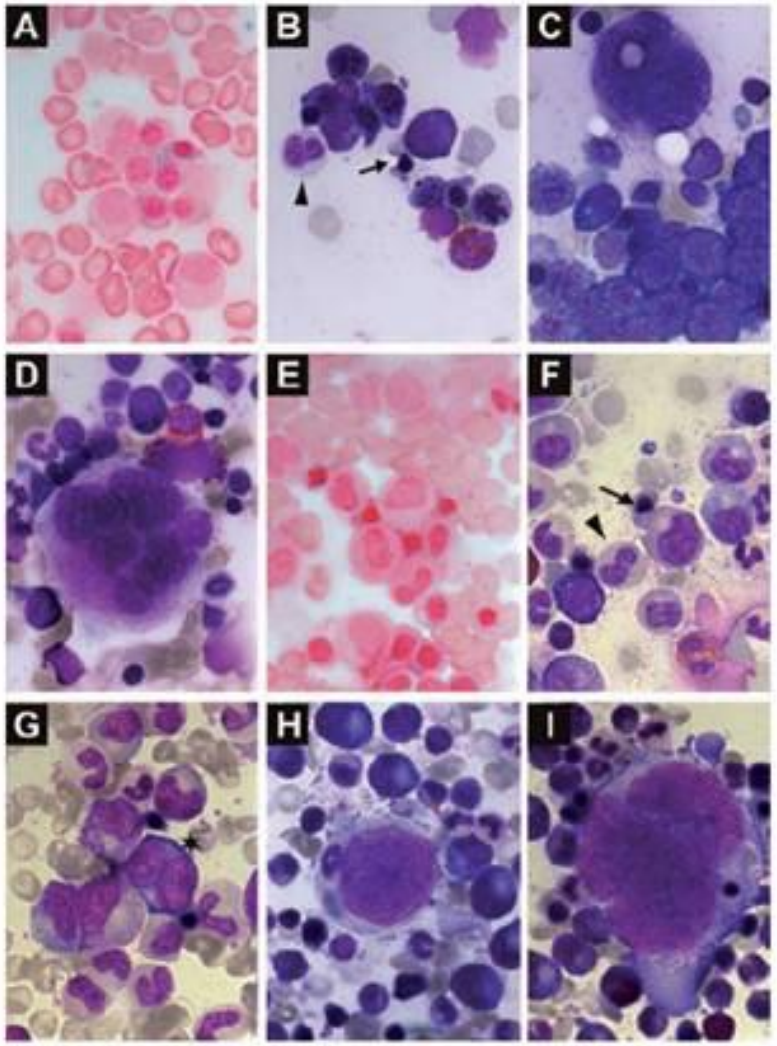



Figure 2. Bone marrow morphology demonstrating both dysplastic and proliferative features in a *JAK* V617F negative patient (n. 511; A-D) and a patient with the mutation (n. 510; E-I). Ringed sideroblastosis (A,E) associated with immaturity, megaloblastoid changes and abnormal nuclear budding (arrows) and binuclearity (asterix) of erythroblasts (B,C,F,G). Dysgranulopoiesis with numerous hypogranular (arrowheads) myeloid cells (B,F,G; Pappenheim's stain). Evidence of both small megakaryocytes with round nuclei and mature cytoplasm (C,H) and large multinucleated forms (D, I). A, E, Perls' stain; B-D, F-I, Pappenheim's stain; ×1000.

Schmitt-Graeff AH, Haematologica. 2008; 93:34

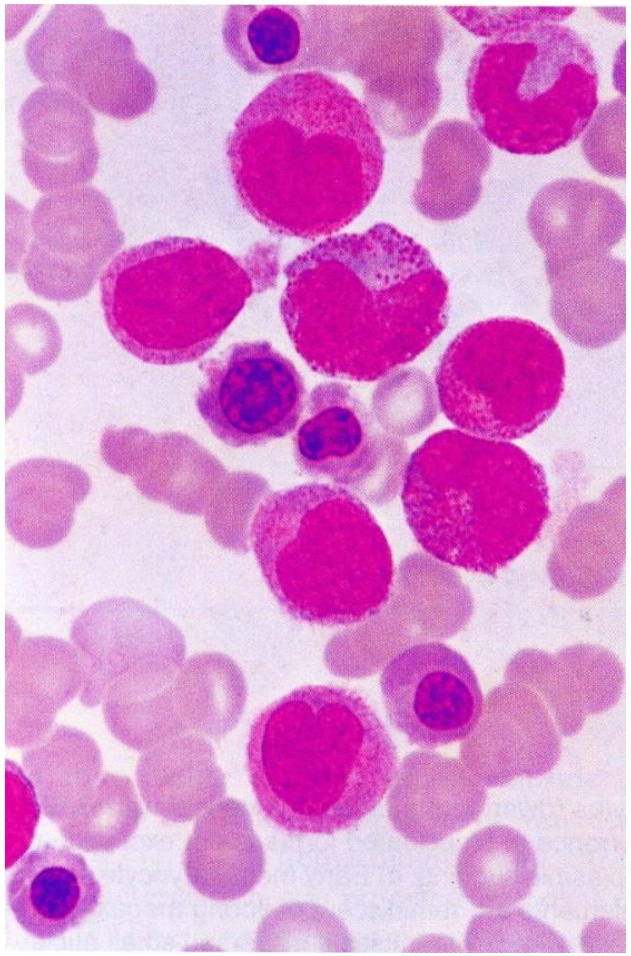
# Diagnostic criteria for MDS/MPN with ring sideroblasts and thrombocytosis

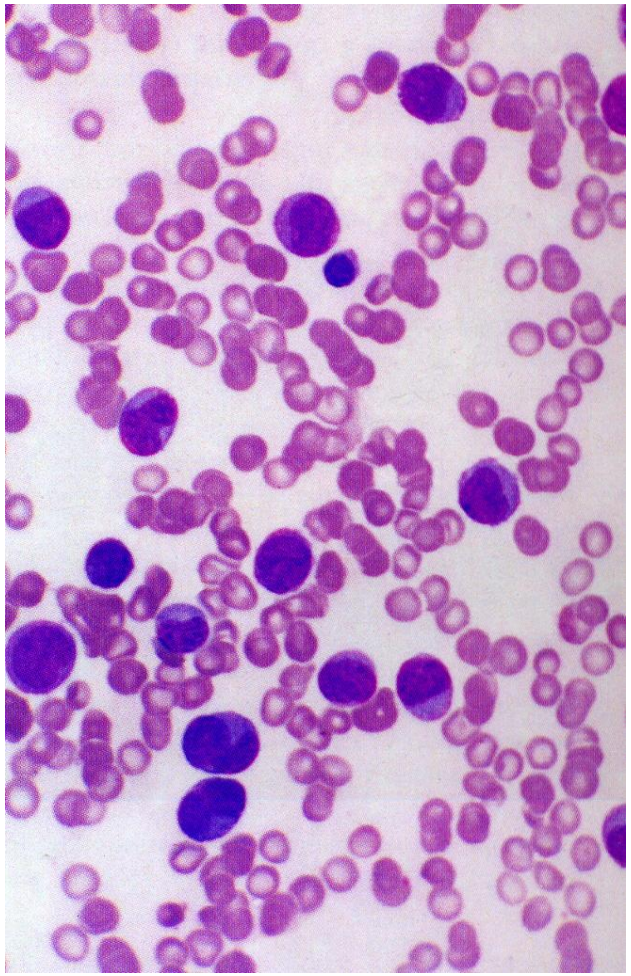
- Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia≥15% ring sideroblasts*, <1% blasts in PB and <5% blasts in the BM
- Persistent thrombocytosis with platelets ≥450 x $10^9$/L
- Presence of a SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†
- No BCR-ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB, or FGFR1; or PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
- No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN

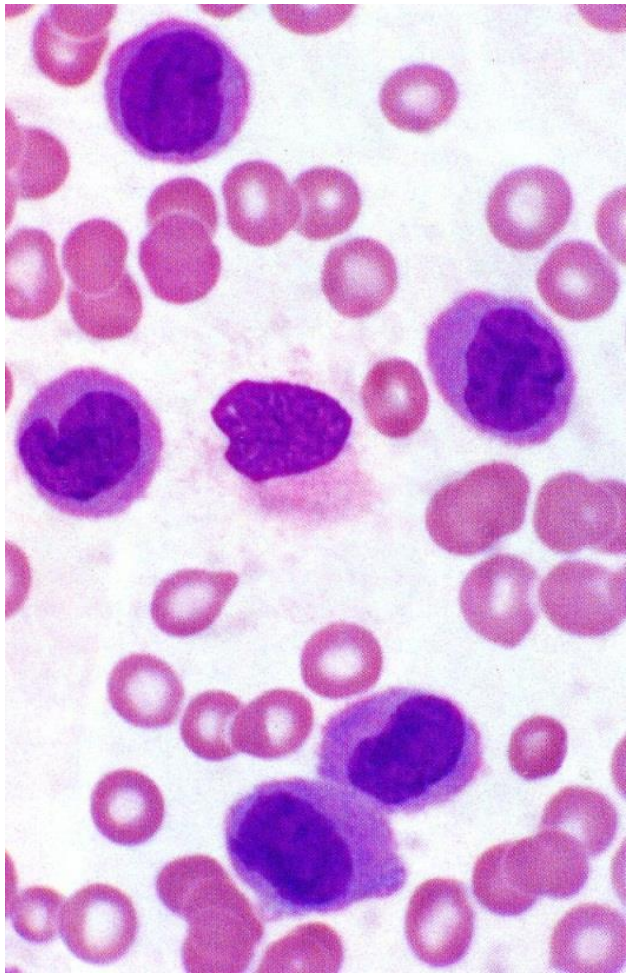
*At least 15% ring sideroblasts required even if SF3B1 mutation is detected.
†A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of SF3B1 mutation together with a mutation in JAK2 V617F, CALR, or MPL genes.
‡In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del (5q)- no or minimal absolute basophilia; basophils usually ,2% of leukocytes.

Blood. 2016;127(20):2391-2405

# CMML







**Castoldi G. Atlas of blood cells. 2003; p 285-98.**

# WHO 2016: Diagnostic criteria for CMML (1/2)

| CMML diagnostic criteria |
| --- |
| • Persistent PB monocytosis ≥1 × $10^9$/L, with monocytes accounting for ≥10% of the WBC count |
| • Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET* |
| • No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia) |
| • <20% blasts in the blood and BM† |
| • Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and |
| • An acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells‡ |
| or |
| • The monocytosis (as previously defined) has persisted for at least 3 mo and |
| • All other causes of monocytosis have been excluded |

Arber DA et al. Blood. 2016; 127(20):2391-2405

# WHO 2016: Diagnostic criteria for CMML (2/2)

*Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

†Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes. Promonocytes are monocytic precursors with abundant light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count.

‡The presence of mutations in genes often associated with CMML (eg, *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in subclones. Therefore, caution would have to be used in the interpretation of these genetic results.

Arber DA et al. Blood. 2016; 127(20):2391-2405

**Table 1. Clinical features associated with different MDS/MPN overlap conditions and disorders at the diagnostic boundary with MDS**

| | Median age (y) | Female/ male ratio | Laboratory features | Physical features | Bone marrow features | | |
|---|---|---|---|---|---|---|---|
| | | | | | Dysplasia | Cellularity | Other |
| MDS | 70-71 | 1:1.5 | Anemia is the most common cytopenia seen, 25-40% have thrombocytopenia | Hepatosplenomegaly or extramedullary involvement not seen | Present | Hypercellular (10-20% hypocellular) | Dysplasia in ≥1 cell lineage; <20% blasts; 10% may have fibrosis |
| CMML | 65-75 | 1:1.5-3 | Absolute monocyte count ≥1.0 × $10^9$/L, accounting for ≥10% of total WBCs for ≥3 mo | Splenomegaly present in up to half of patients; hepatomegaly and extramedullary involvement (skin, LNs) may be seen | Typically present but not required for diagnosis | Hypercellular | Dysplasia typical in ≥1 cell lineage, but may be absent; <20% blasts |
| MDS/MPN-RS-T | 72-73 | 1:1 | Anemia and platelet count ≥450 × $10^9$/L | Thromboembolism may occur | Present | Hypercellular | ≥15% erythroid precursors with ring sideroblasts; megakaryocytic atypia; <5% blasts |
| aCML | 69-72 | 1:1.5 | WBCs >13 × $10^9$/L, increased dysplastic neutrophils, no or minimal monocytosis and basophilia | Splenomegaly may be present | Present | Hypercellular | Dysplasia in ≥1 cell lineage; <20% blasts |
| JMML | 1-2 | 1:2-3 | Absolute monocyte count ≥1.0 × $10^9$/L accounting for ≥10% of total WBCs for ≥3 mo | Splenomegaly common; monocytic and granulocytic infiltration of LNs, liver, skin, GI tract, and lungs also seen | Present | Hypercellular | <20% blasts |
| sAML | 70-73 | 1:1.5 | Variety of peripheral blood cytopenias may be seen, with or without leukocytosis | Hepatosplenomegaly may be present; infiltration of skin, gingiva, and CNS common in monocytic subtypes | Present | Hypercellular | ≥20% blasts; Auer rods |
| SAA | 50% <50 y old | 1:1 | Pancytopenia | Hepatosplenomegaly is not common; congenital anomalies may suggest an inherited marrow failure syndrome | Absent | Hypocellular | Profoundly hypocellular with all myeloid cell lineages diminished; marrow primarily composed of fat/stroma |
| CCUS | 65-75 | 1:1.5 | Anemia most common; other cytopenias can occur, often isolated | Hepatosplenomegaly or extramedullary involvement not seen | Absent or minimal | Normocellular or hypercellular | Does not meet MDS diagnostic criteria; fewer mutations in MDS genes but with comparable VAF |

Tanaka TN, Blood. 2019;133(10):1086-1095