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# Diagnosis and classification of MDS

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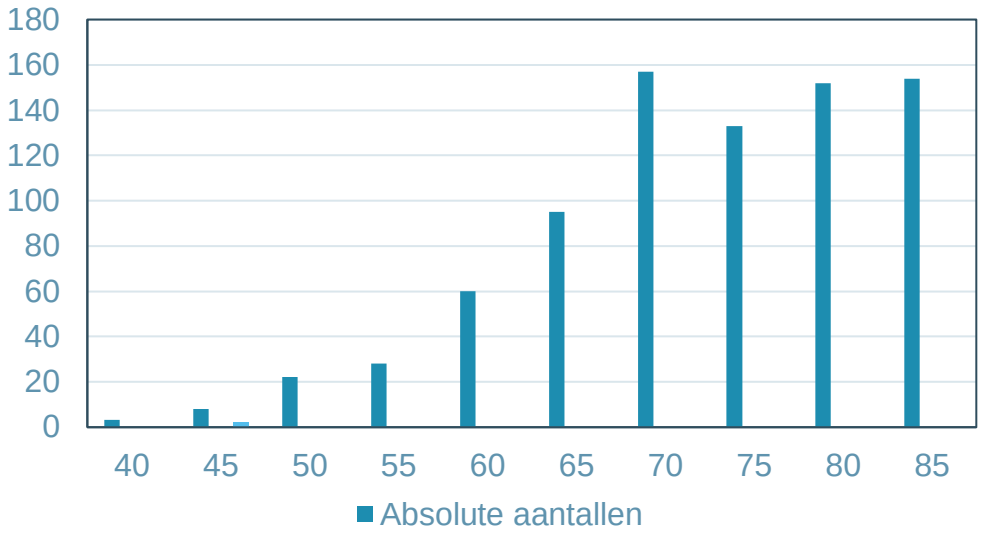
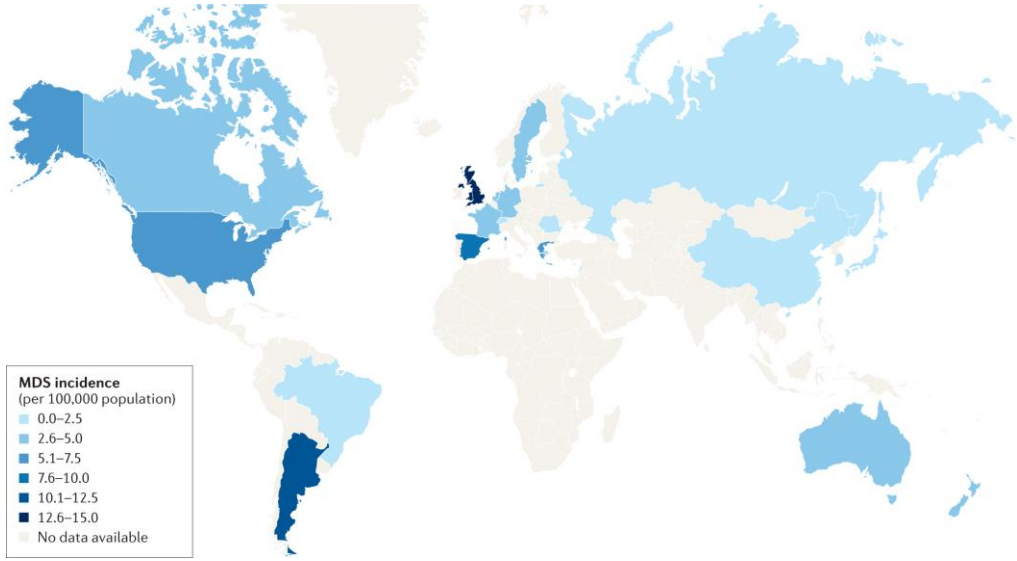
# Introduction

- Clonal hematological disorder
  - Ineffective hematopoeisis
  - Dysplasia in hematopoeitic lineages
  - Acquired cytogenetic abnormalities in 40-50% of cases
  - Clonal hematopoeisis in 90% of cases
- Progression to AML
- Bone marrow morphology
  - Bone marrow aspirate and bone marrow biopsy
  - Usually hypercellular for age
  - Hypocellular in ~10% of cases

# Epidemiology

- Overall incidence
- Median age 70 yrs, male predominance
- In Belgium in 2020: 826 new cases

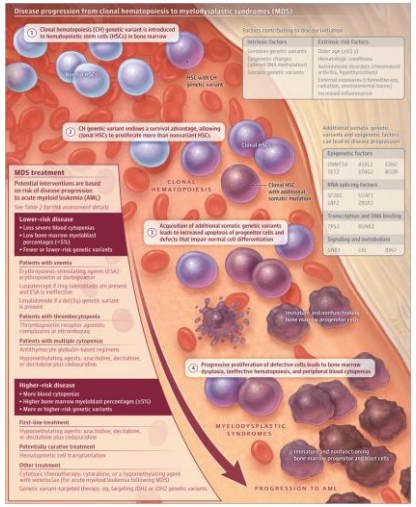


# Etiology of MDS

## De novo

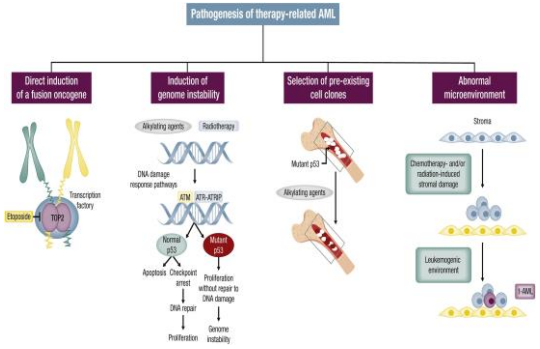
85%




Increased risk with aging
Median age 70 yrs

## Therapy related
(topoisomerase II inhibitors, radiation, alkylating agents, PPRAP)

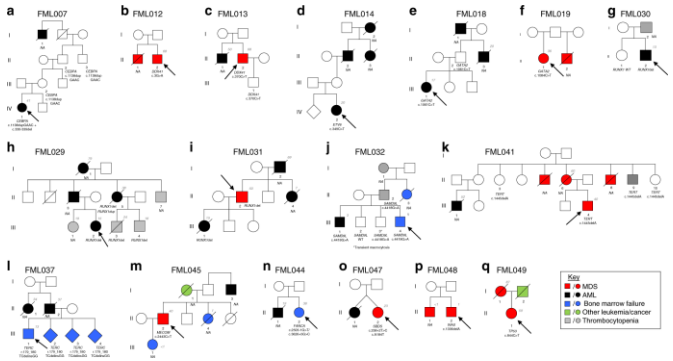
15%




Peaks 2-3 or 5-7 yrs after exposure

## Congenital or familial predisposition

< 2%




Usually at young age


Sekeres M, et al. JAMA 2022
Strickland S, Crit.reviews Oncol/Hematol 2022
Rio-Machin A, et al. Nat Commun 2020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# Minimal diagnostic criteria

- Persistent cytopenia(s) (> 4 months)
  - Hb < 10 g/dL
  - ANC < 1800/µL
  - Platelets < 100 x $10^9$/L
- Diagnosis per exclusionem
  - Vitamin B12/folate deficiency
  - Iron deficiency
  - Copper deficiency
  - Alcohol abuse
  - Medication (chemotherapy, MTX, tacrolimus, MMF, cotrimoxazole…)
  - Heavy metals (lead, zinc, arsenic,…)
  - Hereditary BMF syndromes
  - Other hematological disorders (PNH, LGL, HCL, AA,…)
  - Autoimmune disorders (SLE, PAN, JRA,…)
  - Hypothyroidism, infections (Parvo, HIV, Hepatitis C,…)

**Clinical history**

**Non-clonal disorders**

# MDS- defining criteria

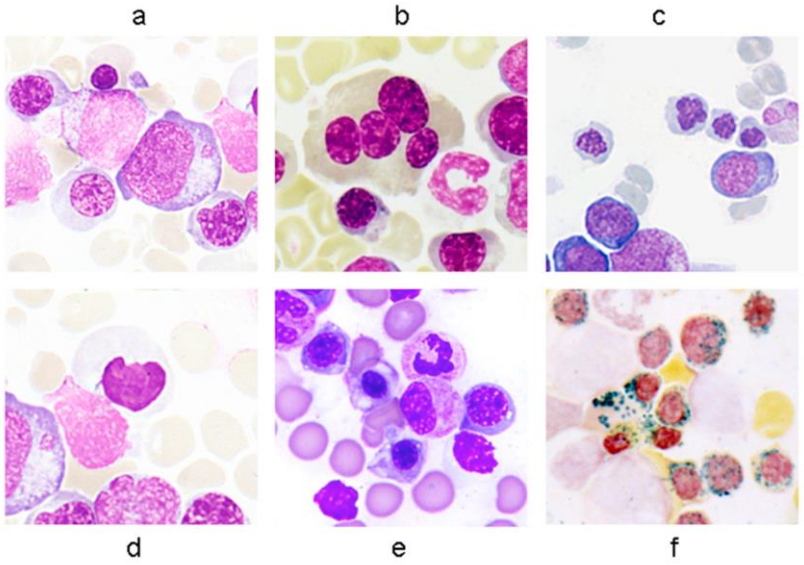
- Dysplasia in > 10% of cells in 1 or more hematopoietic lineage(s) and/or increase in RS ≥15% or ≥ 5% RS and SF3B1 mutation
- Myeloblast < 20 % in dysplastic BM or in peripheral blood smears
  - 5-19% in BM or 2-19% in PB
- MDS – associated clonal cytogenetic abnormalities or molecular markers
  - Complex karyotype, del(5q),…

- Unexplained cytopenia and no dysplasia
  - Monosomy 5, 7, or 13; 5q, 7q, and 13q deletions
  - (i(17p)) and t(17p)
  - 9q or 12p deletion; or t(12p), idic (X)(q13)

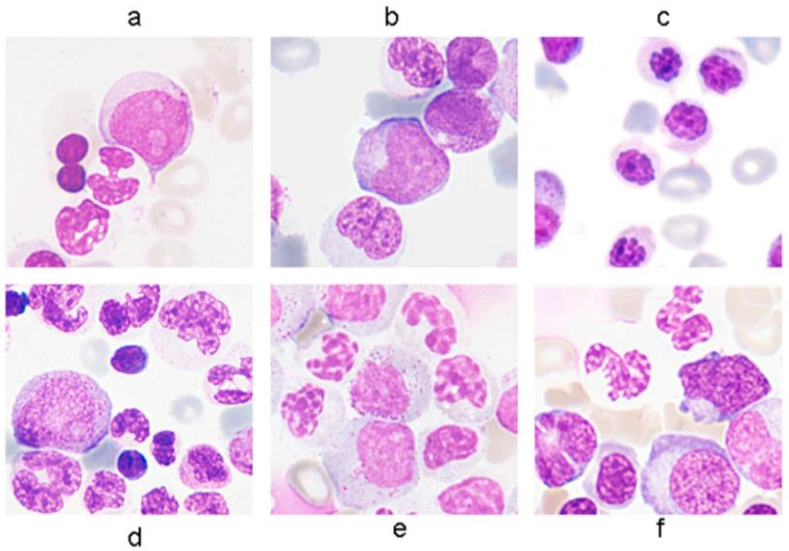
# Morphological manifestations of dysplasia

- Peripheral blood
  - Erythrocytes: anisocytosis
  - Neutrophils: Pseudo-Pelger-Huet, hypogranularity, Döhle bodies
  - Thrombocytes: anisocytosis, giant platelets
- Bone marrow
  - Dyserythropoiesis: nuclear budding, internuclear bridging, vacuolization, multinuclearity, ring sideroblast
  - Dysgranulopoiesis: small or unusually large size, nuclear hypo- or hypersegmentation, decreased granules/agranularity, Pseudo-Chédiak--Higashi granules, Döhle bodies, Auer rods
  - Dysmegakaryopoiesis: micromegakaryocytes, nuclear hypolobation, multinucleation

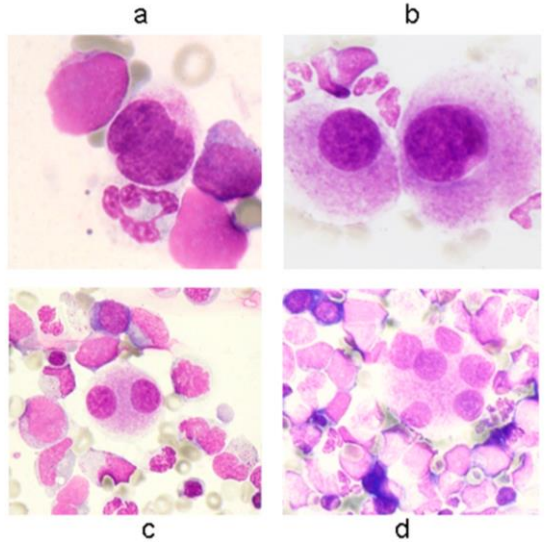
# Morphology




Erythroid dysplasia

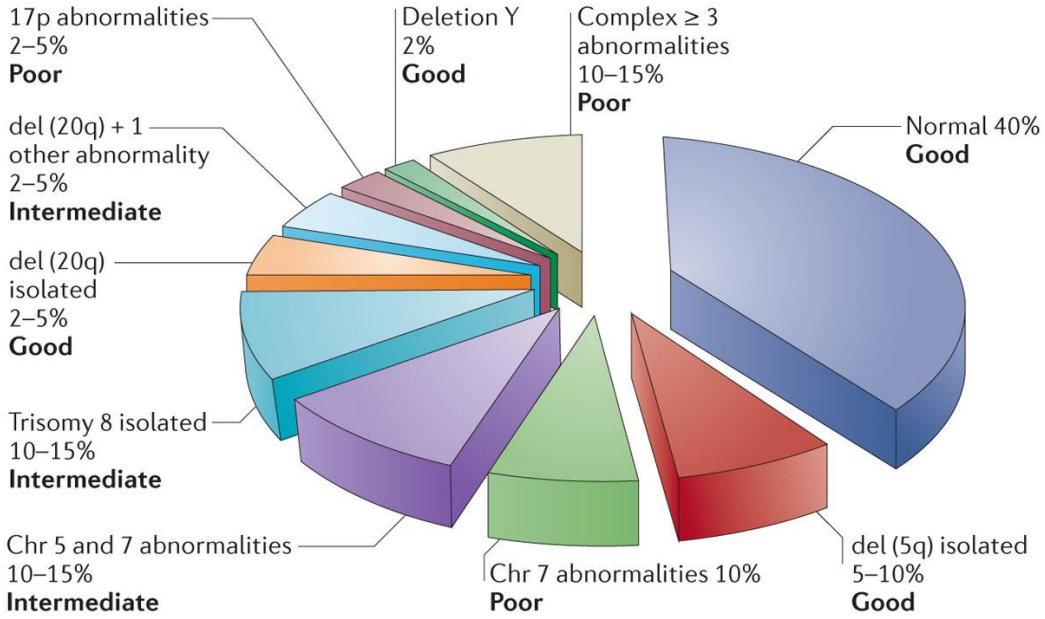


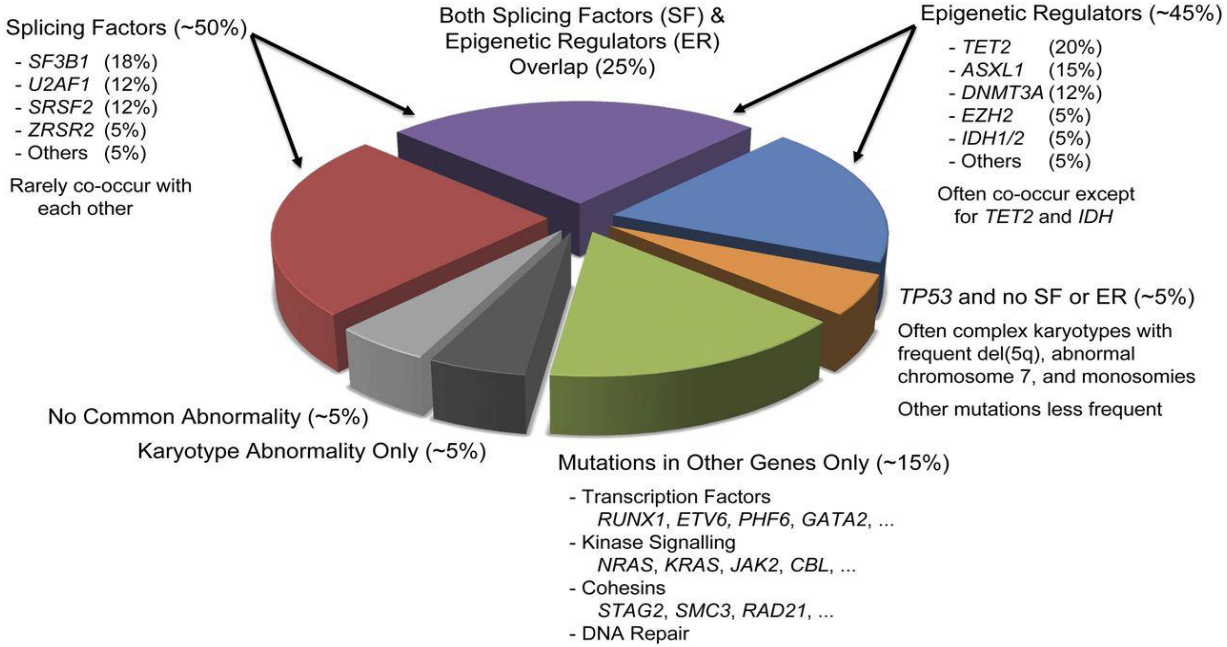

Granulocytic dysplasia




Megakaryocytic dysplasia

# Cytogenetics and somatic mutations




Raza A, et al. Nature Reviews Cancer. 2012
Bejar R, et al. blood 2014

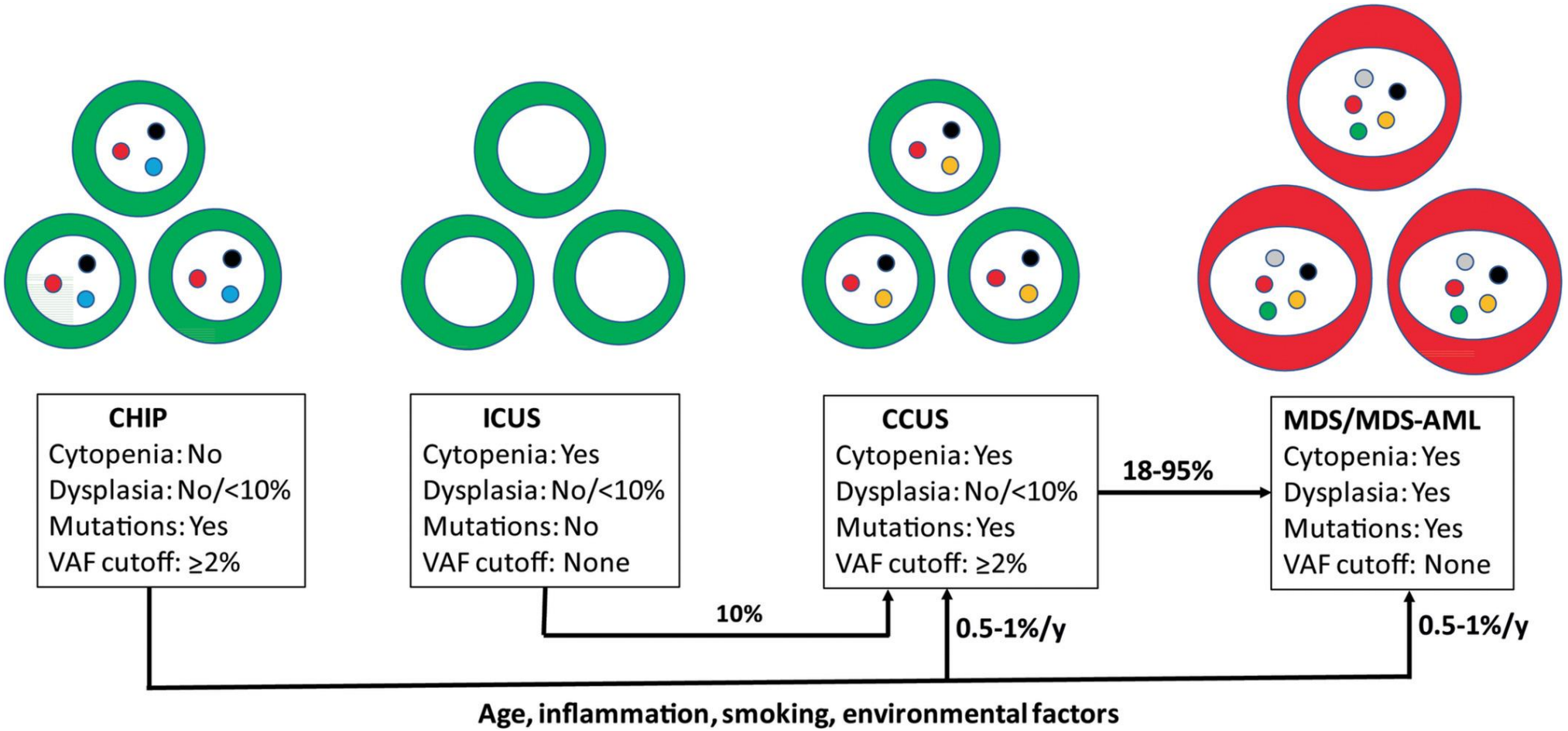
# Classification of MDS

- Replacement of the WHO 2016 classification of myeloid neoplasms
  - WHO 5th Edition
  - ICC
- Some differences between the WHO 2022 and ICC 2022 classification systems
  - Inclusion of MDS-RS in WHO but not in ICC
  - Nomenclature for categories of MDS with excess of blasts
  - Details of genetically defned subgroups of SF3B1 and TP53 mutation

# “Blue Book”: 5th Edition of WHO classification

- New Kids on the Block: CH, CHIP, CCUS definition
  - VAF of ≥ 2% (≥ 4% for X-linked gene mutations in males)
- Cytopenia definition for CCUS and MDS/MPN
  - Hb <13 g/dL (male) <12 g/dL (female), ANC <1.8 x $10^9$/L, Plt <150 x $10^9$/L

# Clonal cytopenias



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  - Hb <13 g/dL (male) <12 g/dL (female), ANC <1.8 x $10^9$/L, Plt <150 x $10^9$/L
- Myelodysplastic **neoplasms**
  - Genetically defined
  - Morphologically defined
- Biallelic TP53 mutations supersedes del(5q) and SF3B1
- Hypocellular MDS a distinct subtype
- Childhood MDS is updated

# WHO classification updates

## WHO 2008[1]

**Refractory cytopenia with unilineage dysplasia (RCUD)**

- Refractory anemia (RA)
- Refractory neutropenia (RN)
- Refractory thrombocytopenia (RT)

**Refractory anemia with ring sideroblasts (RARS)**

**Refractory cytopenia with multilineage dysplasia**

**Refractory anemia with excess blasts (RAEB)**

- *RAEB-1, RAEB-2*

**MDS with isolated del(5q)**

**MDS, unclassifiable (MDS-U)**

**Refractory cytopenia of childhood (provisional)**

## WHO 2016[2]

**MDS with single lineage dysplasia (MDS-SLD)**

**MDS with ring sideroblasts (MDS-RS)**

- MDS-RS-SLD, MDS-RS-MLD

**MDS with multilineage dysplasia (MDS-MLD)**

**MDS with excess blasts (MDS-EB)**

- *MDS-EB-1, MDS-EB-2*

**MDS with isolated del(5q)**

**MDS, unclassifiable (MDS-U)**

**Refractory cytopenia of childhood (provisional)**

## WHO 2022[3]

**MDS with defining genetic abnormalities**

- MDS with low blasts and isolated 5q deletion (MDS-5q)
- MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*)
- MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)

**MDS, morphologically defined**

- MDS with low blasts (MDS-LB)
- MDS with increased blasts (MDS-IB)
  - *MDS-IB1, MDS-IB2*
  - MDS with fibrosis (MDS-f)
- Hypoplastic MDS (MDS-h)

**Childhood MDS (<18 yr)**

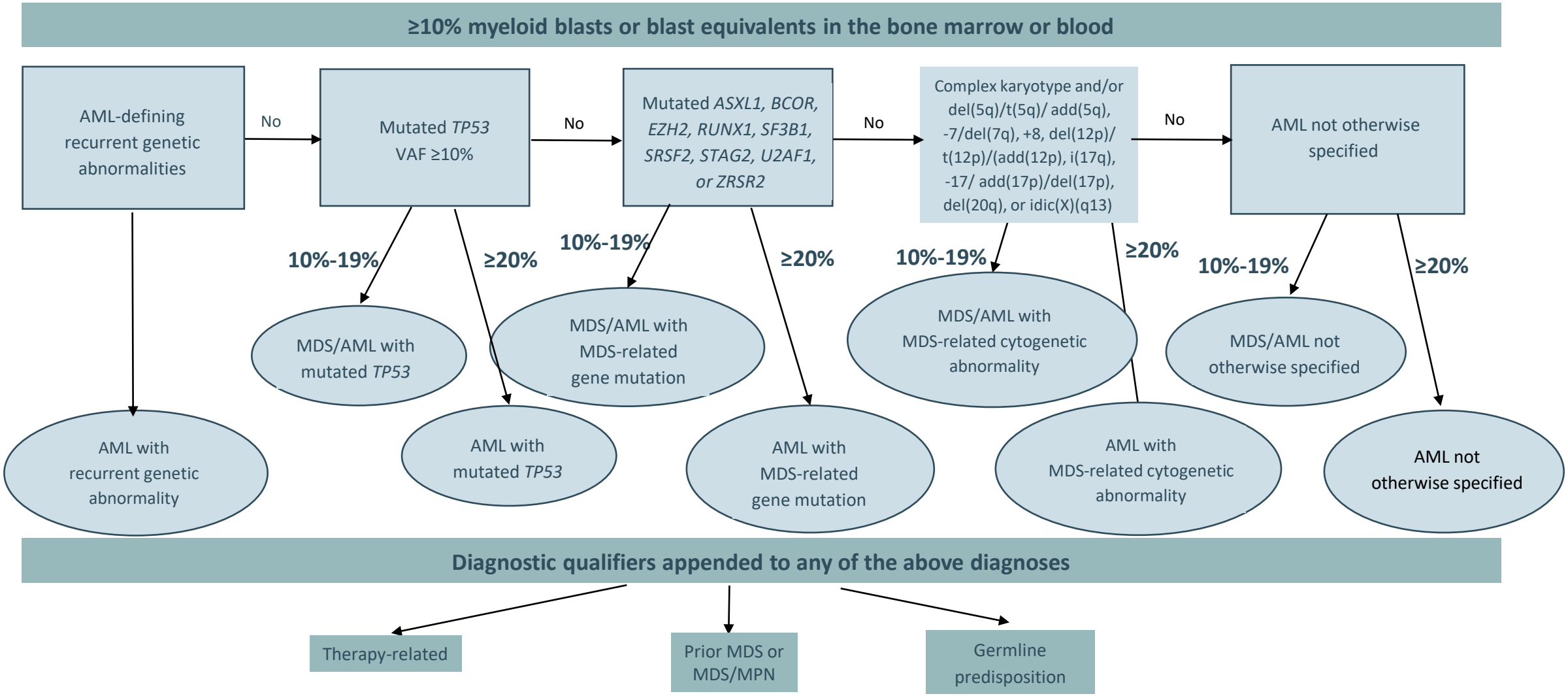
[1]Vardiman. Blood. 2009, [2]Arber DA, et al. Blood. 2016, [3]Khoury J, et al. Leukemia. 2022

# Features of MDS and MDS/AML in ICC

| | Dysplastic lineages | Cytopenias | BM/PB Blasts | Cytogenetics † | Mutations |
|---|---|---|---|---|---|
| MDS with mutated *SF3B1* | ≥ 1** | ≥ 1 | <5% BM<br>< 2% PB | Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex | *SF3B1* (≥ 10% VAF), without multi-hit *TP53* or *RUNX1* |
| MDS with del(5q) | ≥ 1** | ≥ 1* | <5% BM<br><2% PB | del(5q), with up to 1 additional, except<br>– 7/ del (7q) | Any, except multi-hit *TP53* |
| MDS, NOS without dysplasia | None | ≥ 1 | <5% BM<br><2% PB^ | - 7/del (7q) or complex | Any, except multi-hit *TP53* or *SF3B1* (≥10%VAF) |
| MDS, NOS with single lineage dysplasia | 1 | ≥ 1 | <5% BM<br><2% PB^ | Any, except not meeting criteria for MDS with del(5q) | Any, except multi-hit *TP53*; not meeting criteria for MDS-*SF3B1* |
| MDS, NOS with multilineage dysplasia | ≥2 | ≥1 | <5% BM<br><2% PB | Any, except not meeting criteria for MDS with del(5q) | Any, except multi-hit *TP53*; not meeting criteria for MDS-*SF3B1* |
| MDS with excess blasts | ≥ 1** | ≥1 | 5-9%BM,<br>2-9%PB | Any | Any, except multi-hit *TP53* |
| MDS/AML | ≥1cell lineage** | ≥1 | 10-19%BM or PB^ | Any, except AML-defining | Any, except *NPM1*, bZIP *CEBPA* or *TP53* |

* Trombocytosis is allowed in MDS with del(5q); ** Although dysplasia is usually observed, this is not required for diagnosis. ^ The entity MDS/AML does not apply to pediatric patients (<18 years)

# International Consensus Classification of AML




Döhner, et al. Blood 2022

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# Comparison WHO 2022 and ICC 2022

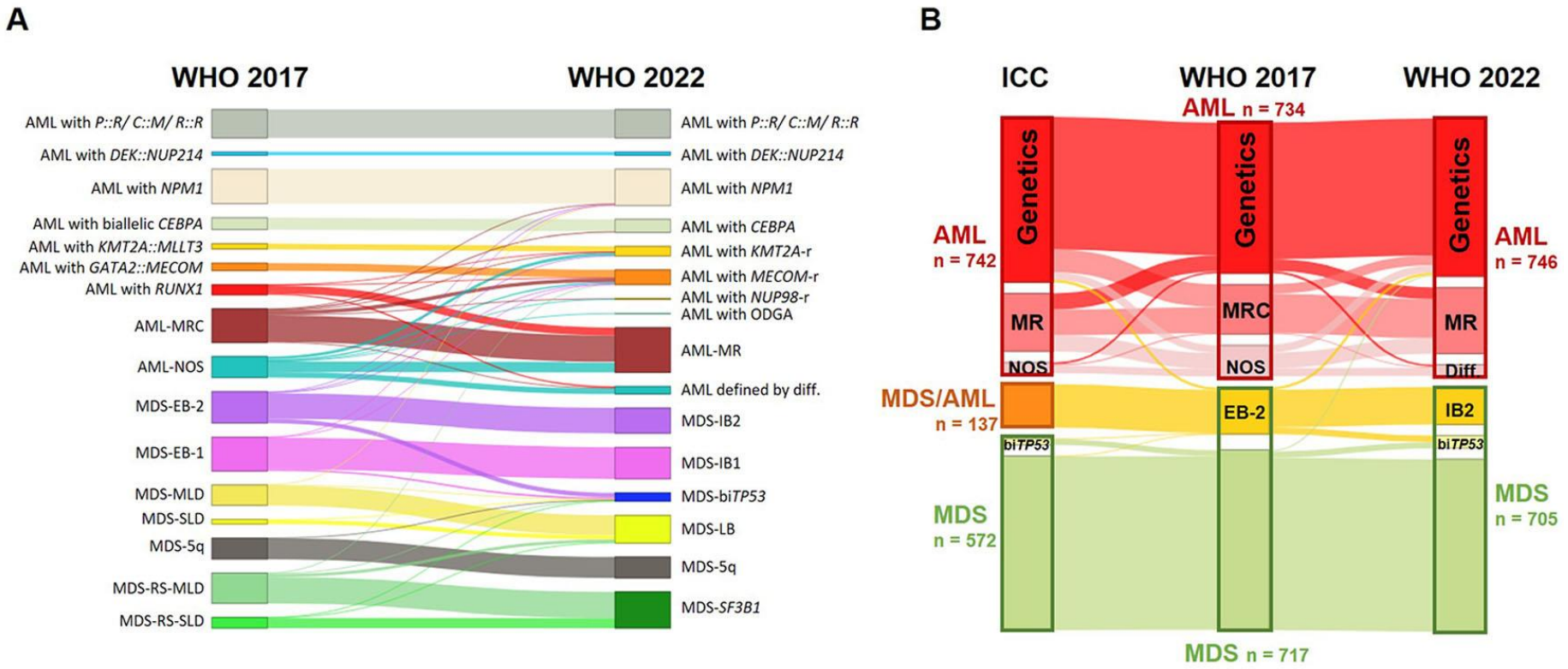


**Figure 1: (A) Changes in specific MDS and AML diagnoses according to WHO 2022. (B) Changes in MDS and AML diagnoses according to WHO 2022 and ICC.** *P::R = PML::RARA; C::M = CBFB::MYH11; R::R = RUNX1::RUNX1T1;* MRC: myelodysplasia-related changes; NOS: not otherwise specified; EB: excess blasts; SLD: single lineage dysplasia; MLD: multilineage dysplasia; 5q: isolated 5q deletion; RS: ring sideroblasts; -r: rearrangement; ODGA: other defined genetic alterations; MR: myelodysplasia-related; IB: increased blasts; bi*TP53*: biallelic *TP53* inactivation; LB: low blasts; Diff.: differentiation.

# MDS classification in 2023….

| WHO 2022[2] | ICC[3] | Dysplastic lineages | Cytopenias | Cytoses[4] | Blasts | Cytogenetics | Mutations | | Diagnostic Qualifiers[5] |
|---|---|---|---|---|---|---|---|---|---|
| MDS with defining genetic abnormality | | | | | | | | | Therapy-related or Germline Predipsosition |
| MDS-5q (low blasts and isolated 5q deletion (MDS-5q)) | MDS with del (5q) [MDSdel (5q)] | Typically >1[6] | ≥1 | Thromobcytosis allowed | <5% BM, <2% PB | 5q deletion alone, or with 1 other abnormality other than del 7 or del 7q | Any, except multi-hit TP53 | | |
| MDS with low blasts and SF3B1 mutation (MDS-SF3B1) | | | | | <5% BM, <2% PB | Absence of 5q deletion, del 7, deletion abn3q26.2 or complex karyotype | SF3B1 | ( ≥15% ring sideroblasts (RS) may substitute for SF3B1 mutation) | |
| | MDS with mutated SF3B1 (MDS-SF3B1) | Typically >1[6] | ≥1 | 0 | | | | *(≥10% VAF), without multi-hit TP53, or RUNX1* | |
| MDS with biallelic TP53 inactivation (MDS-bi*TP53)* | MDS with mutated TP53 | – | Any | – | <20% BM, PB | 0-9% BM or PB | Usually complex | 2 or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH at the 17p TP53 locus | Multi-hit TP53 mutation[7], or TP53 mutation (VAF >10%) and complex karyotype often with loss of 17p[8] |
| | MDS/AML with mutated TP53 | – | Any | – | 10-19% BM or PB | | | Any somatic TP53 mutation (VAF >10%) | |
| MDS, morphologically defined | | | | | | | | | |
| MDS with low blasts (MDS-LB) | MDS, NOS - without dysplasia | 0 | ≥1 | 0 | <5% BM, 2-4% PB | | Any, except multi-hit TP53 or SF3B1 (≥ 10% VAF) | | |
| | MDS, NOS - with single lineage dysplasia | 1 | ≥1 | 0 | | | Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1 | | |
| | MDS, NOS - with multilineage dysplasia | ≥2 | ≥1 | 0 | | | Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1 | | |
| MDS, hypoplastic (MDS-h)[9] | – | | | | <5% BM, 2-4% PB | | | | |
| MDS with increased blasts (MDS-IB) | | | | | | | | | |
| MDS-IB1 | MDS with excess blasts (MDS-EB) | Typically >1[6] | ≥1 | 0 | 5-9% BM or 2-4% PB | | Any, except multi-hit TP53 | | |
| MDS-IB2[10] | MDS/AML | Typically >1[6] | ≥1 | 0 | 10-19% BM or 5-19% PB, Auer rods (Age ≥ 18, not pediatric) | Any, except AML-defining | Any, except NPM1, bZIP CEBPA or TP53 | | |
| MDS with fibrosis (MDS-f) | – | | | | 5-19% BM, 2-19% PB | | | | |

[1] Defined by cytopenias and dysplasia (≥10% for all lineages). In general, there should be clinical evidence that the blood count abnormality is chronic in duration (typically 2-4 months or longer), and is not explained by a drug, toxin, or comorbid condition.
[2] Khoury J, et al, 5th Edition WHO Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022.
[3] Arber D, et al, The International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data. Blood 6/14/2022.
[4] Cytoses: Sustained white blood count ≥13x109/L, monocytosis (≥5x109/L and ≥% of leukocytes), or platelets ≥450x109/L; thrombocytosis is allowed in MDS-del(5q) or in any MDScase with inv(3) or t(3;3) cytogenetic abnormality.
[5] Therapy-relatedness and underlying germline predisposition conditions are applied as qualifiers to the diagnosis.
[6] Although dysplasia is typically present in these entities, it is not required.
[7] Defined as two distinct TP53 mutations (each VAF>10%) OR a single TP53 mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p TP53 locus.
[8] If TP53 locus LOH information is not available.
[9] ≤25% bone marrow cellularity, age adjusted.
[10] MDS-IB2 (MDS/AML) may be regarded as AML-equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate.

Ambinder A, et al. Front Oncol. 2022

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# Validation of MDS classification systems

- Single center study
- MDS patients according to WHO 2016 classification with available NGS data were reclassified by WHO 2022 and ICC 2022 criteria
  - N = 2231; median follow-up: 60.2 mo
- “Multihit TP53” state: TP53-VAF ≥50% or ≥2 TP53 mutations (VAF ≥10% each) or TP53 mutation + del17p (by karyotype or FISH)

Ball. ASH 2022. Abstr 463

# LFS and OS Comparisons Between MDS Subgroups

| Subgroup Comparison | n | LFS | | OS | |
|---|---|---|---|---|---|
| | | Median, Mo | *P* | Median, Mo | *P* |
| WHO 2022<br>▪ MDS-LB vs MDS-RS | 595 vs 82 | 47.8 vs 50.5 | .838 | 56.8 vs 54.3 | .876 |
| ▪ IB1 vs LB | 193 vs 775 | 21 vs 49 | <.001 | 25.9 vs 56 | <.001 |
| ▪ IB1 vs IB2 | 193 vs 224 | 21 vs 10 | <.001 | 25.9 vs 22.9 | .726 |
| ▪ MDS-f vs MDS-IB | 118 vs 417 | 13.7 vs 14.7 | .128 | 18.9 vs 24.3 | .003 |
| ▪ Multi-hit *TP53**:<br>Blast <5% vs 5%-9% vs ≥10% | 75 vs 70 vs 65 | 14.6 vs 7.5 vs 7.6 | <.001 | 18 vs 11.9 vs 11.4 | .009 |
| ICC 2022 | | | | | |
| ▪ SLD vs MLD | 248 vs 606 | 74.2 vs 41.5 | <.001 | 79.4 vs 49.6 | <.001 |
| ▪ MDS/AML cyto abn vs NOS | 55 vs 83 | 11.2 vs 14.0 | .039 | 16.3 vs 38.4 | <.001 |
| ▪ MDS/AML-MDSm vs NOS | 163 vs 83 | 11.5 vs 14.0 | .216 | 24.7 vs 38.4 | .015 |
| ▪ *mTP53*: MDS/AML vs MDS | 191 vs 115 | 6.4 vs 11.5 | <.001 | 11.0 vs 14.5 | .001 |

*TP53-VAF ≥50% or ≥2 TP53 mutations (VAF >10% each) or 1 TP53 mutation plus del(17p) by karyotype or FISH.

# Independent Predictors of Survival in Multivariate Analysis

| Variables | LFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| No. of dysplastic lineages | 1.73 (1.35-2.21) | <.001 | 1.68 (1.31-2.16) | <.001 |
| Blast count category* | 1.46 (0.53-3.99) | .453 | 1.39 (0.51-3.80) | .514 |
| BM fibrosis grade | 1.11 (0.98-1.26) | .086 | 1.14 (1.00-1.30) | .038 |
| *SF3B1* mutation | 0.57 (0.44-0.74) | <.001 | 0.59 (0.46-0.77) | <.001 |
| Multihit *TP53*† | 3.09 (2.06-4.61) | <.001 | 3.39 (2.25-5.12) | <.001 |

*<5% vs 5%-9% vs ≥10%.
†*TP53*-VAF ≥50% or ≥2 *TP53* mutations (VAF ≥10% each) or *TP53* mutation + del17p (by karyotype or FISH).

# Validation of MDS Classification Systems: conclusions

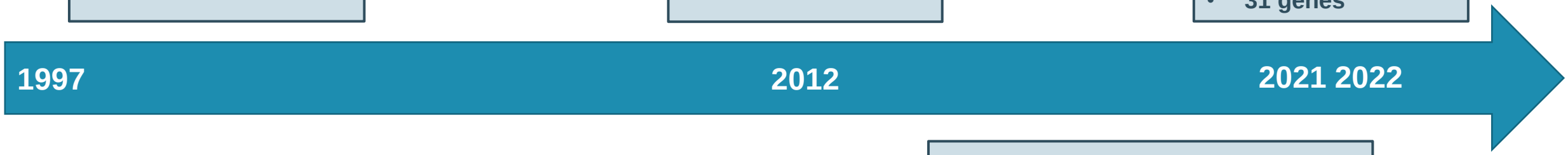
- Molecularly defined subtypes (SF3B1, del5q, and multihit TP53) are unique
- TP53 mutation predicted poor survival, and multihit TP53 independently predicted survival
- MDS-RS (SF3B1 wild-type) and MDS-LB subtypes showed similar survival
- Outcomes were worse for MDS-MLD vs MDS-SLD
- Blast percentage correlated with OS, but precise cutoffs should be examined further
- Grade 2/3 fibrosis was associated with decreased OS and was independent predictor of OS within MDS-IB

# Risk stratification

**IPSS[1]**
- Bone marrow blasts
- Number of cytopenias
- Cytogenetics

**IPSS-R[2]**
- Bone marrow blasts
- Hb/platelets/ANC
- Cytogenetics

**IPSS-M[3]**
- Bone marrow blasts
- Hb/platelets/ANC
- Cytogenetics
- **31 genes**



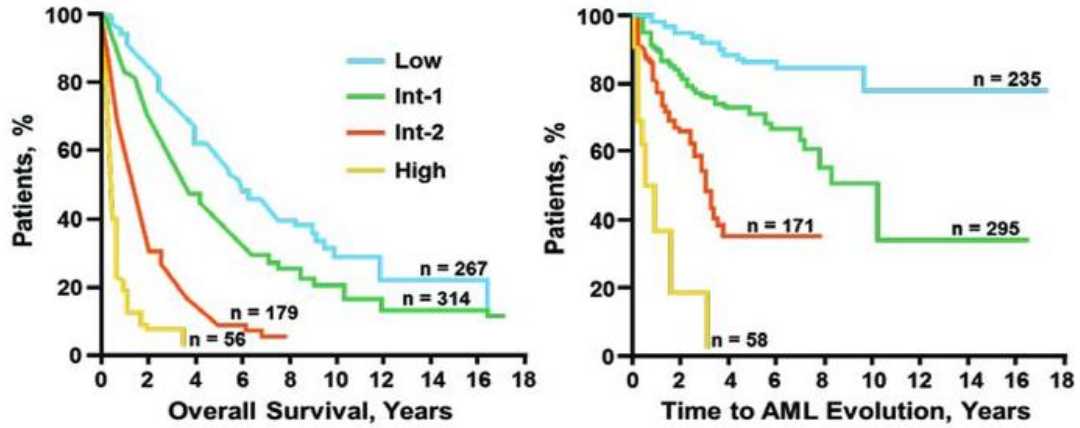

**Personalized prediction models**
- Molecular genetics
- ASXL1, DNMT3A, SF3B1,TP53, etc

Greenberg P, et al. Blood 1997, Greenberg P, et al. Blood 2012, Bernard E et al. NEJM Evidence 2022,
Nazha A et al. JCO 2021, Bersanelli, et al. JCO 2021

# IPSS score…important for reimbursement of AZA

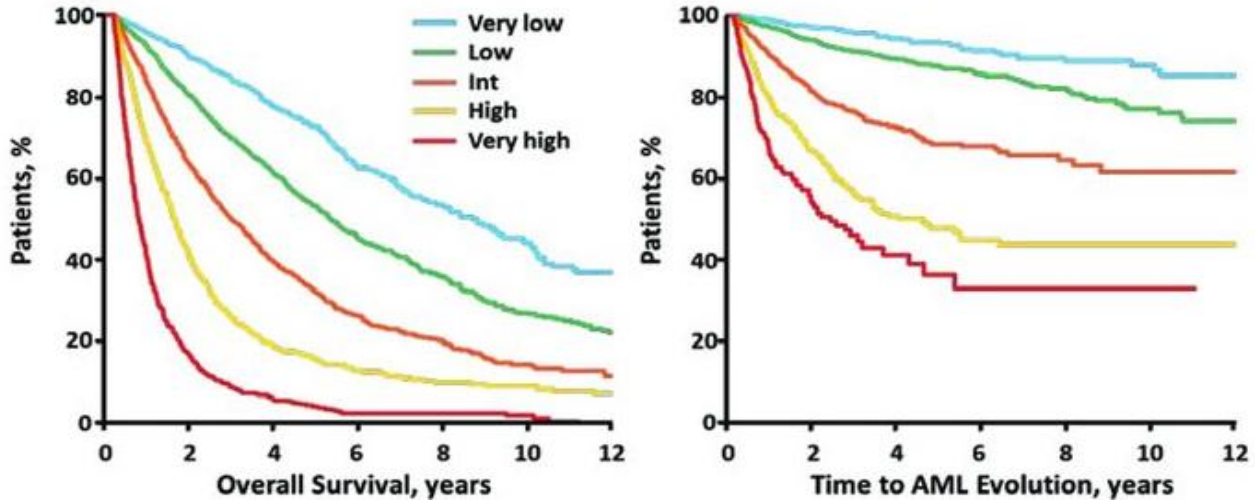
| Prognostic Factors Scored | Risk Groups Based on Total Risk Score |
|---|---|
| **Percent of blast cells in bone marrow**<br>○ Less than 5 = 0 points<br>○ 5 to 10 = 0.5 points<br>○ 11 to 20 = 1.5 points<br>○ 21 to 30 = 2 points | ○ 0 points = Low<br>○ 0.5 to 1 point = Intermediate-1<br>○ 1.5 to 2 points = Intermediate-2<br>○ 2.5 or more points = High |
| **Cytogenetics (chromosome changes)**<br>○ None, del(5q), del(20q) = 0 points<br>○ 3 or more abnormalities, abnormal chromosome 7 = 1 point<br>○ Other abnormalities = 0.5 points | |
| **Number of cytopenias (anemia, neutropenia or thrombocytopenia)**<br>○ None or 1 = 0 points<br>○ 2 or 3 = 0.5 points | |

**Key.** IPSS, International Prognostic Scoring System; del, deletion.



# IPSS-R score

| Prognostic Factors Scored | Risk Groups Based on Total Risk Score |
|---|---|
| **Percent of blast cells in bone marrow**<br>○ Less than or equal to 2 = 0 points<br>○ Greater than 2 to less than 5 = 1 point<br>○ 5 to 10 = 2 points<br>○ Greater than 10 = 3 points | ○ 1.5 or less points = Very Low<br>○ 2 to 3 points = Low<br>○ 3.5 to 4.5 points = Intermediate<br>○ 5 to 6 points = High<br>○ 6.5 or more points = Very High |
| **Cytogenetics (chromosome changes)**<br>○ –Y, del(11q) = 0 points<br>○ Normal, del(5q), del(12p), del(20q), double including del(5q)* = 1 point<br>○ del(7q), +8, +19, i(17q), any other single or double independent clone** = 2 points<br>○ –7, inv(3), +(3q), del(3q), double including –7/del(7q), complex: 3 abnormalities = 3 points<br>○ More than 3 abnormalities = 4 points | |
| **Hemoglobin concentration (g/dL)**<br>○ Equal to or greater than 10 = 0 points<br>○ 8 to less than 10 = 1 point<br>○ Less than 8 = 1.5 points | |
| **Platelet count (x $10^9$/L of blood)**<br>○ Equal to or greater than 100 = 0 points<br>○ 50 to less than 100 = 0.5 points<br>○ Less than 50 = 1 point | |
| **Absolute neutrophil count ([ANC] x $10^9$/L of blood)**<br>○ Equal to or greater than 0.8 = 0 points<br>○ Less than 0.8 = 0.5 points | |



# IPSS-M

- Discovery cohort: diagnostic MDS samples (N = 2957) with <20% blasts and WBC <13 x $10^9$/L were profiled for mutations in 156 driver genes
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders

# IPSS-M: development

| Step | Development |
|---|---|
| Encoding for clinical and molecular variables | ▪ Continuous encoding of clinical variables; linear function for BM blasts, Hg<br>▪ Platelet values capped at 250 x $10^9$/L; ANC not included<br>▪ Maintained 5 IPSS-R cytogenetic categories<br>▪ Gene mutations incorporated as binary variables aside from *TP53* allelic state and *SF3B1* subsets accounting for comutations |
| Determination of independent IPSS-M prognostic variables | ▪ Model fit with a Cox multivariable regression adjusted for confounder variables (age, sex, primary vs therapy-related MDS)<br>▪ Continuous clinical parameters<br>▪ IPSS-R cytogenetic categories<br>▪ 17 genetic variables from 16 main effect genes<br>▪ 1 genetic variable from 15 residual genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*) |

**Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.***

| Category and Variable | Adjusted Hazard Ratio (95% CI)† | Model Weight‡ |
|---|---|---|
| Clinical | | |
| Bone marrow blasts — % | 1.07 (1.05–1.09) | 0.0704 |
| min(Platelets,250) — $x10^9$/l | 0.998 (0.997–0.999) | –0.00222 |
| Hemoglobin — g/dl | 0.84 (0.81–0.88) | –0.171 |
| Cytogenetic | | |
| IPSS-R cytogenetic category§ | 1.33 (1.21–1.47) | 0.287 |
| Gene main effects (17 variables, 16 genes)¶ | | |
| *TP53*$^{multihit}$ | 3.27 (2.38–4.48) | 1.18 |
| *MLL*$^{PTD}$ | 2.22 (1.49–3.32) | 0.798 |
| *FLT3*$^{ITD+TKD}$ | 2.22 (1.11–4.45) | 0.798 |
| *SF3B1*$^{5q}$ | 1.66 (1.03–2.66) | 0.504 |
| *NPM1* | 1.54 (0.78–3.02) | 0.430 |
| *RUNX1* | 1.53 (1.23–1.89) | 0.423 |
| *NRAS* | 1.52 (1.05–2.20) | 0.417 |
| *ETV6* | 1.48 (0.98–2.23) | 0.391 |
| *IDH2* | 1.46 (1.05–2.02) | 0.379 |
| *CBL* | 1.34 (0.99–1.82) | 0.295 |
| *EZH2* | 1.31 (0.98–1.75) | 0.270 |
| *U2AF1* | 1.28 (1.01–1.61) | 0.247 |
| *SRSF2* | 1.27 (1.03–1.56) | 0.239 |
| *DNMT3A* | 1.25 (1.02–1.53) | 0.221 |
| *ASXL1* | 1.24 (1.02–1.51) | 0.213 |
| *KRAS* | 1.22 (0.84–1.77) | 0.202 |
| *SF3B1*$^{\alpha}$ | 0.92 (0.74 1.16) | –0.0794 |
| Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖ | | |
| min(Nres,2) | 1.26 (1.12–1.42) | 0.231 |

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariables and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = $1.15467 + (\sum_{\text{variables } j} w_j x_j)/\log(2)$, where $w_j$ denotes the weight of variable $j$, and $x_j$ the value of the variable $j$ observed in a given patient.

§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ *SF3B1*$^{5q}$ is the *SF3B1* mutation in the presence of isolated del(5q) —that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*$^{\alpha}$ is the *SF3B1* mutation without comutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, and del(5q).

‖ Nres is defined as the number of mutated genes within the following list: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.

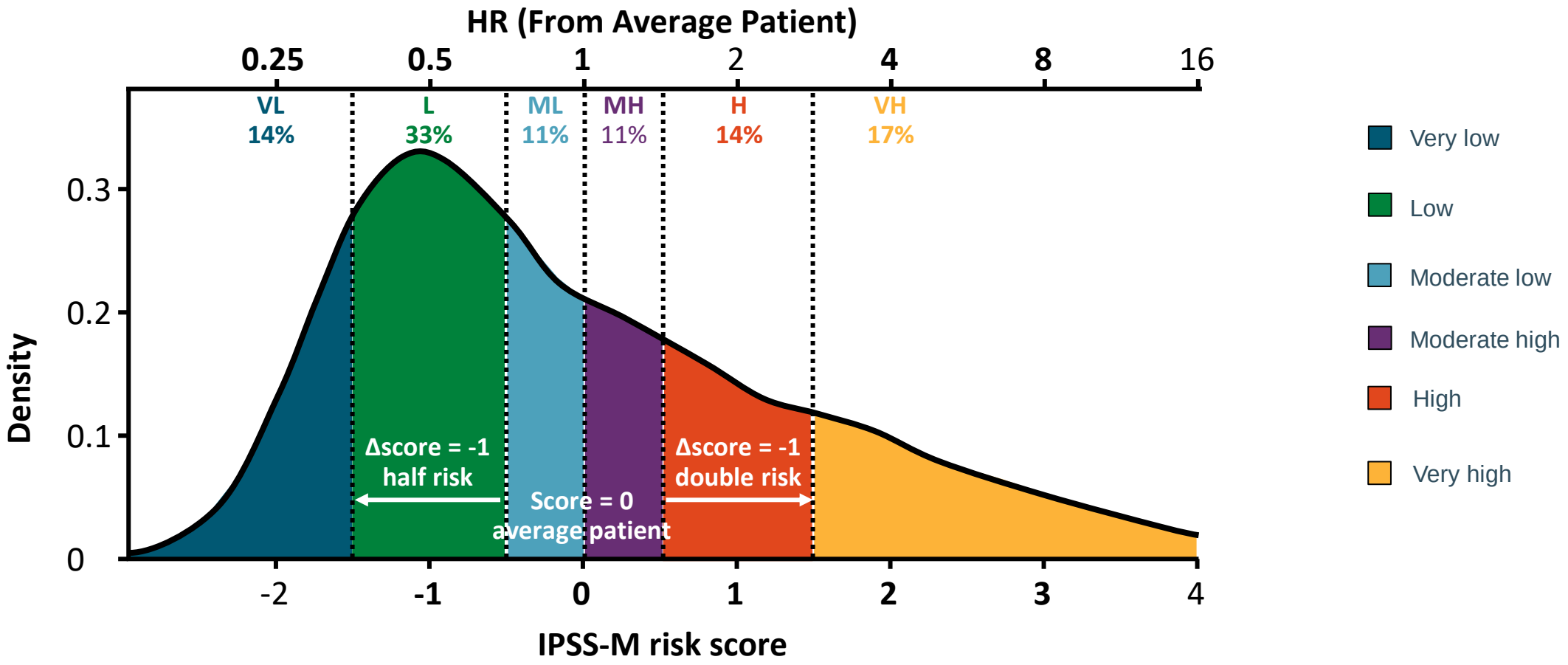
# IPSS-M: association between gene mutations and clinical endpoints

- After adjusting for age, sex, MDS type (primary vs therapy related), and IPSS-R raw score, multiple genes were associated with adverse outcomes including LFS (14 genes), OS (16 genes), and AML transformation (15 genes)
- Strongest associations found with:
  - TP53 multi-hit (multiple mutations, mutation with deletion or copy-neutral LoH)2 (7% of patients)
  - MLL partial tandem duplication (2.5% of patients)
  - FLT3 mutations (1.1% of patients)

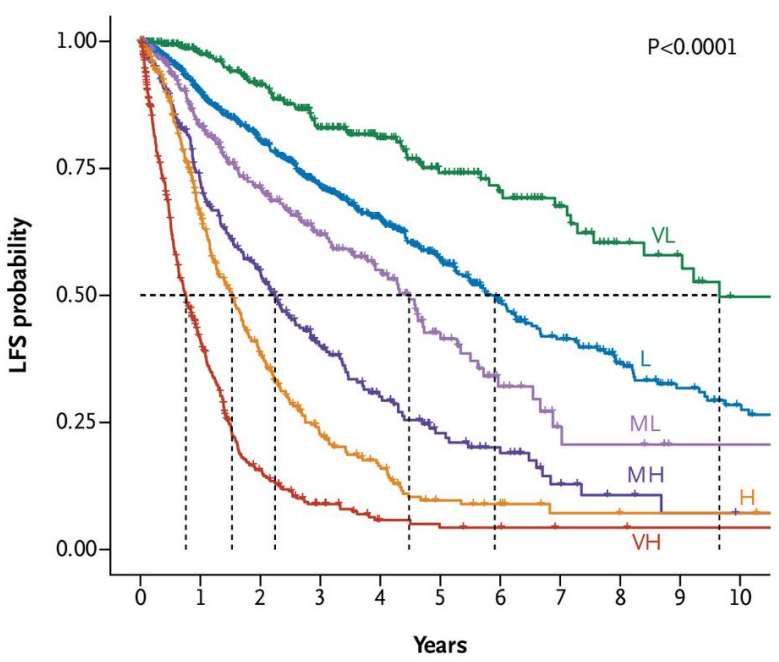
# IPSS-M: association between gene mutations and clinical endpoints

- *SF3B1* mutations were associated with favorable outcomes, modulated by pattern of comutations
  - *SF3B1*$^{5q}$: concomitant isolated del(5q) (7%)
  - *SF3B1*$^{\beta}$: co-occurrence of mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2* (15%)
  - *SF3B1*$^{\alpha}$: any other *SF3B1* mutations

# IPSS-M risk categories

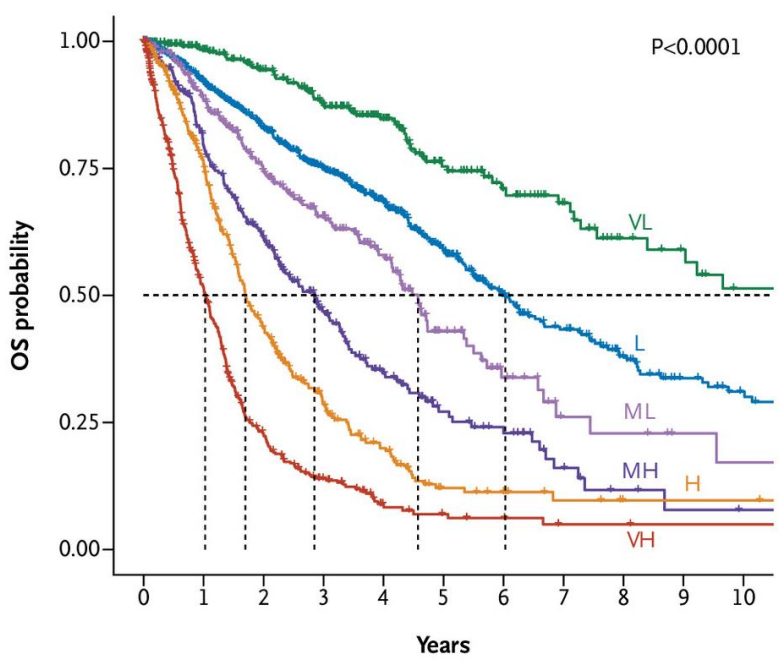


# IPSS-M: LFS and OS




**No. at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VL | 315 | 243 | 199 | 153 | 110 | 75 | 55 | 40 | 26 | 22 | 16 |
| L | 788 | 584 | 442 | 331 | 240 | 162 | 107 | 80 | 56 | 40 | 30 |
| ML | 274 | 188 | 135 | 92 | 62 | 34 | 16 | 7 | 6 | 3 | 3 |
| MH | 258 | 166 | 114 | 65 | 41 | 25 | 18 | 8 | 4 | 2 | 1 |
| H | 353 | 194 | 101 | 48 | 29 | 13 | 10 | 4 | 3 | 3 | 3 |
| VH | 440 | 152 | 50 | 21 | 8 | 6 | 5 | 3 | 3 | 2 | 2 |

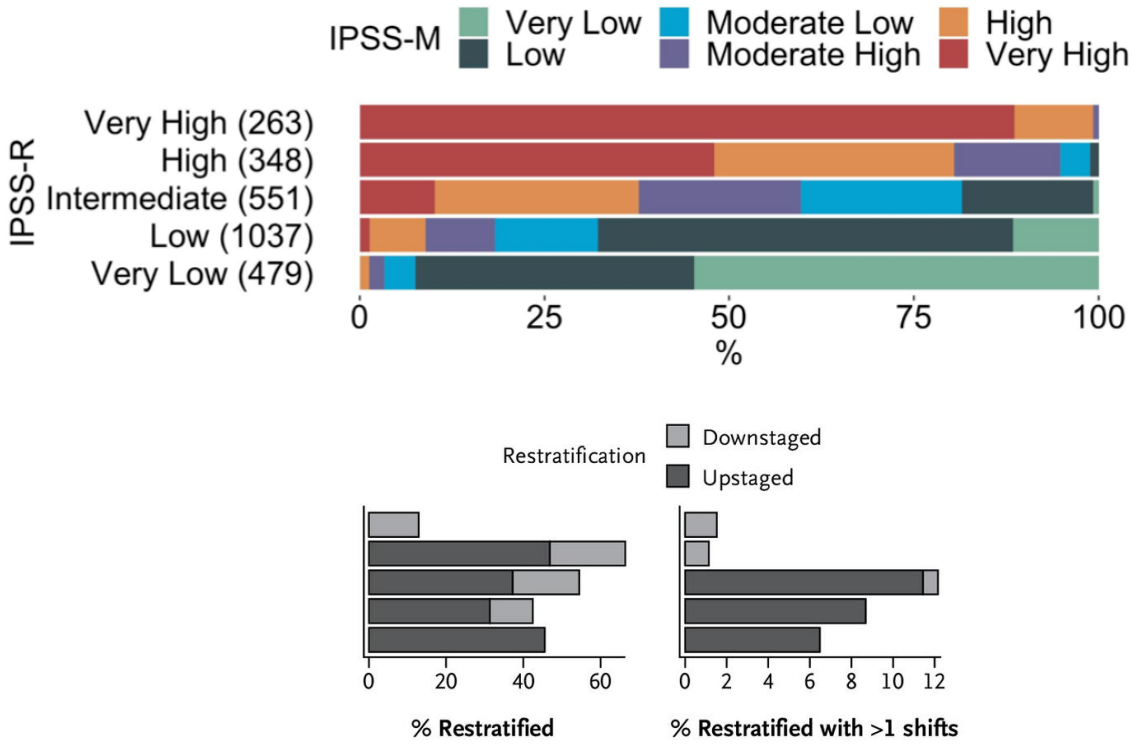



**No. at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VL | 344 | 267 | 224 | 180 | 126 | 82 | 57 | 42 | 28 | 24 | 18 |
| L | 852 | 640 | 496 | 382 | 270 | 176 | 112 | 83 | 57 | 40 | 31 |
| ML | 295 | 214 | 152 | 111 | 72 | 35 | 18 | 8 | 7 | 4 | 3 |
| MH | 278 | 191 | 134 | 80 | 48 | 27 | 20 | 9 | 4 | 2 | 1 |
| H | 367 | 235 | 121 | 65 | 37 | 15 | 12 | 6 | 3 | 3 | 3 |
| VH | 460 | 200 | 77 | 37 | 14 | 9 | 6 | 3 | 3 | 2 | 2 |

# IPSS-M

- Improvement of prognostic discrimination of IPSS-M vs IPSS-R
- 46% of patients restratified from IPSS-R to IPSS-M with 7% restratified by >1 strata



# IPSS-M

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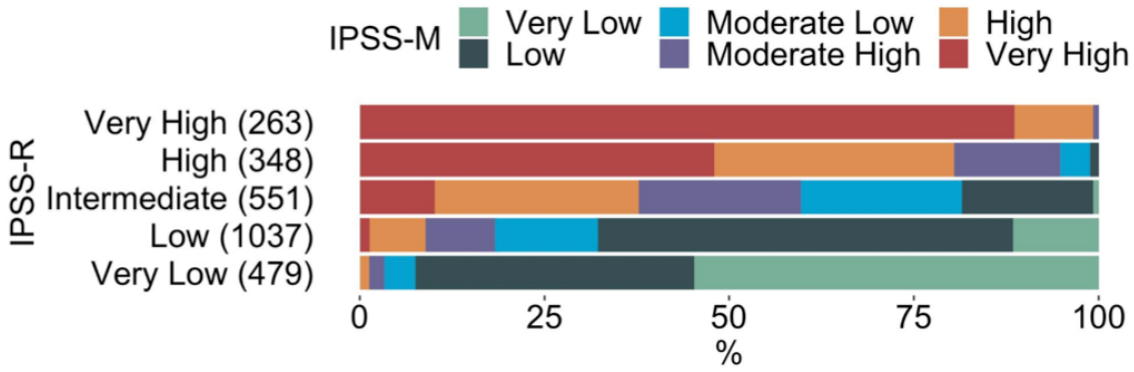
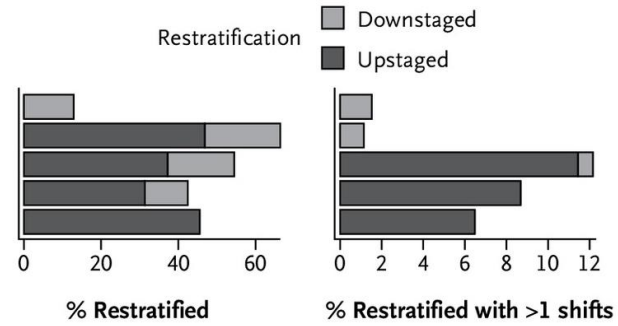


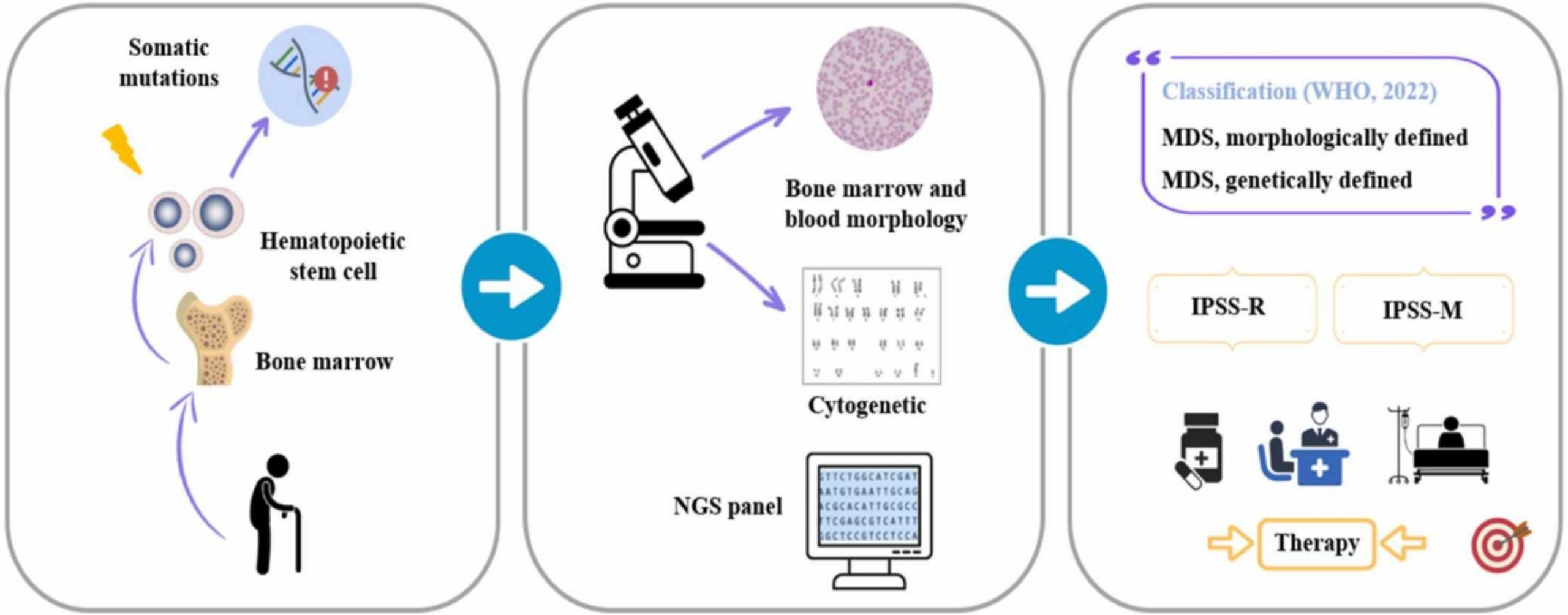

- IPSS-M web calculator; strategy of missing variables (calculation for best, average and worse scenarios)
- https://mds-risk-model.com/

Bernard E et al. NEJM Evidence 2022

KU LEUVEN

# Take home messages…

- Heterogeneous disease
- Morphology is still important
- Classification of MDS
  - WHO 2022
  - ICC 2022
- IPSS score for reimbursement of Azacitidine
- Riisk stratification includes clinical, molecular and patient-related variables


Somatic mutations
Hematopoietic stem cell
Bone marrow
Bone marrow and blood morphology
Cytogenetic
NGS panel
Classification (WHO, 2022)
MDS, morphologically defined
MDS, genetically defined
IPSS-R
IPSS-M
Therapy