# Higher-risk MDS and AML: How new guidelines are changing diagnosis, classification and management

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# Presenting symptoms and the diagnostic process for MDS and AML

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# Presenting symptoms of MDS and AML

## MDS[1]

- Easy bruising
- Pallor
- Pale conjunctiva
- Mucosal bleeding
- Hypotension
- Tachycardia
- Emphysema
- Heart failure
- Epistaxis[1,2]
- Petechiae[1,2]
- Fatigue[1,2]
- Headache[1,2]
- Angina pectoris[1,2]
- Frequent infections[1,2]
- Exercise intolerance[1,2]
- Major bleeding[1,2]

## AML[2]

- Gingival haemorrhage
- Fever
- Adenopathy
- Dyspnoea
- Confusion
- Palpitations
- Coma visual disturbances
- Hypoxia
- Organomegaly
- Respiratory failure
- Seizures
- Menorrhagia
- Claudication

AML, acute myeloid leukaemia; GI, gastrointestinal; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Barzi A, Sekeres MA. *Cleve Clin J Med*. 2010;77:37–44; 2. Smith M, et al. *Crit Rev Oncol Hemat*. 2004;50:197–222.

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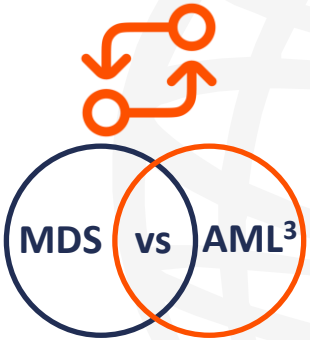
# Modes of presentation

**Incidental cytopenia[1]**

- ICUS[2]
- CCUS[2]

**Prior cytotoxic therapy[3]**




AML, acute myeloid leukaemia; CCUS, clonal cytopenia of undetermined significance; ICC, International Consensus Classification; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Samiev D, et al. *Korean J Fam Med*. 2014;35:111–8; 2. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 3. Khoury JD, et al. *Leukemia*. 2022;36:1703–19.

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# Diagnosing MDS or AML

## Laboratory parameters (MDS only)[1]

- Ferritin
- Transferrin
- Transferrin saturation
- Reticulocyte counts
- Vitamin B12
- Folate concentrations
- Haptoglobin
- Creatinine levels

## Blood counts (MDS only)[1]

**Blood counts**

- Evaluate cytopenia

**Cytomorphology**

- Dysplastic features

## Bone marrow aspiration[1,2]

**Cytomorphology**

- Dysplastic features
- Blast counts

**Cytogenetics**

**Molecular studies**

## Bone marrow biopsy[1,2]

**Cellularity and fibrosis**

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712.

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# Categorization of MDS by WHO and ICC

<table>
<tr><th>Blast burden</th><th>Genetic</th><th colspan="4">WHO 2022[1]</th><th>ICC 2022[2]</th></tr>
<tr><td rowspan="3">BM blasts <5%<br>PB blasts <2%</td><td>del(5q)</td><td colspan="3">MDS-5q</td><td rowspan="5">AML with defining genetic abnormalities*</td><td>MDS-del(5q)</td></tr>
<tr><td>SF3B1</td><td colspan="3">MDS-SF3B1</td><td>MDS-SF3B1</td></tr>
<tr><td>Other</td><td colspan="2">MDS-LB</td><td rowspan="3">MDS-biTP53</td><td>MDS, NOS<br>Without dysplasia<br>or with SL/ML dysplasia</td></tr>
<tr><td colspan="2">BM blasts 5–9%<br>PB blasts 2–4%</td><td>MDS-IB1</td><td rowspan="2">MDS-f</td><td>MDS-EB†</td></tr>
<tr><td colspan="2">BM blasts 10–19%<br>PB blasts 5–19%<br>Auer rods</td><td>MDS-IB2</td><td>MDS/AML‡<br>Unless AML-defining cytogenetic or molecular abnormality*</td></tr>
</table>

*AML except *BCR::ABL* and *CEBPA* mut (≥20% blasts required). †PB blasts 2–9%. ‡PB blasts 5–19% and no requirement for auer rods.
AML, acute myeloid leukaemia; BM, bone marrow; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, MDS with excess blasts; MDS-f, MDS with fibrosis; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-NOS, MDS not otherwise specified; ML, multilineage; PB, peripheral blood; SL, single lineage; WHO, World Health Organization.
1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

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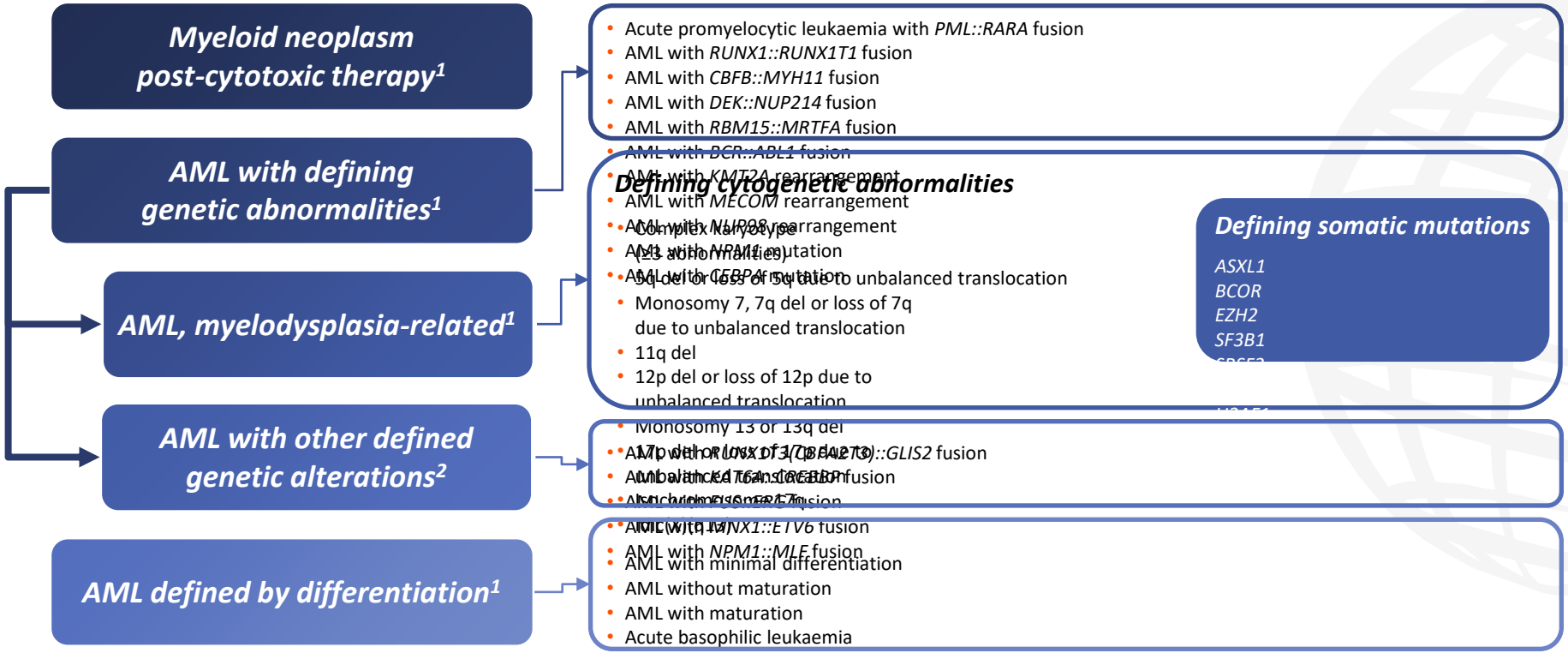
# WHO 2022 classification of AML[1]




*Previously pure erythroid leukaemia. AML, acute myeloid leukaemia; WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Li W. In: Li W (ed). *Leukemia: Diagnosis and Therapy*. Exon Publications, 2022;1–21.

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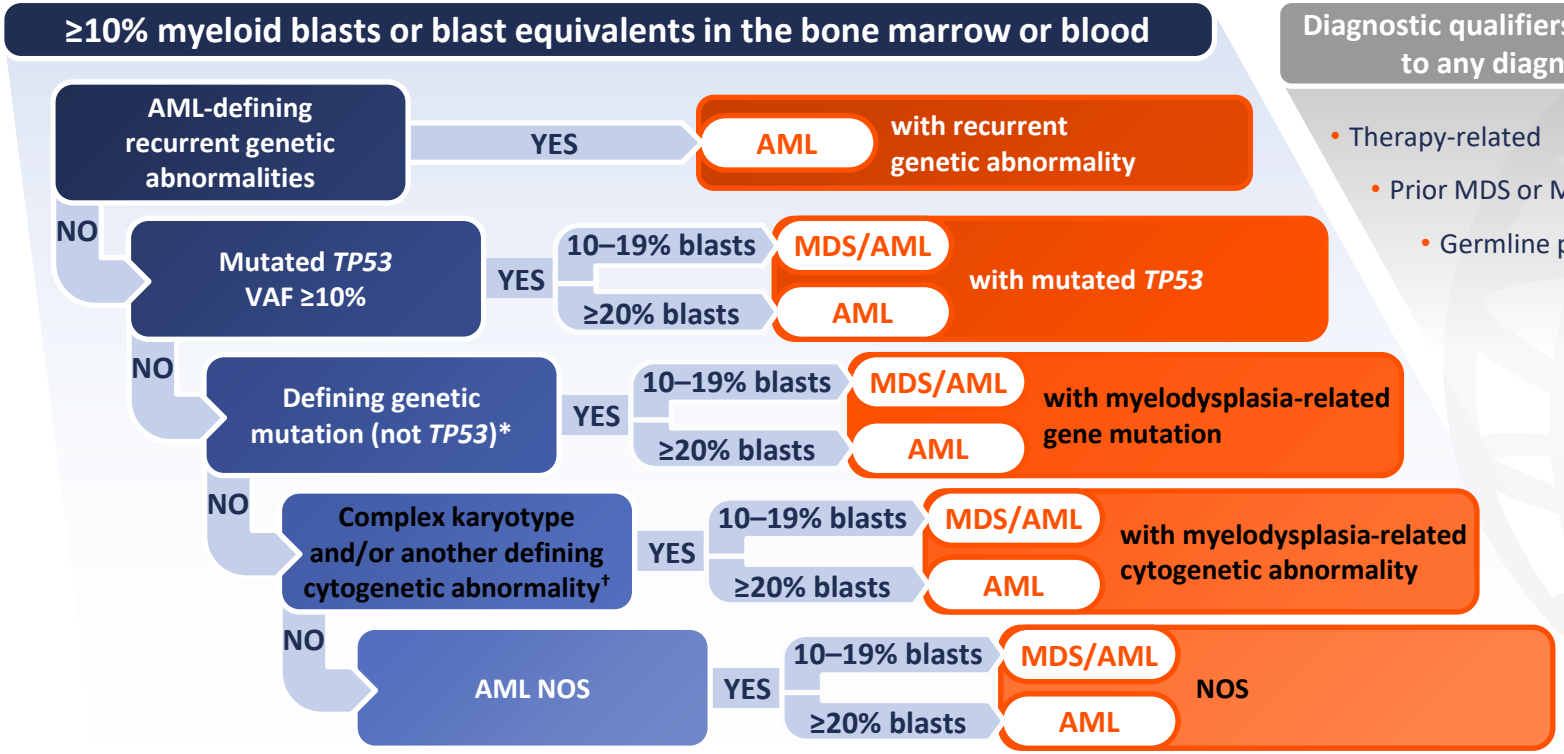
# Hierarchical classification of AML: ICC




**ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1* and/or *ZRSR2*. †del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/(add(12p), i(17q), -17/add(17p)/del(17p), del(20q) or idic(X)(q13). AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MPN, myeloproliferative neoplasms; NOS, not otherwise specified; VAF, variant allele frequency; WHO, World Health Organization.

Döhner H, et al. *Blood*. 2022;140:1345–77.

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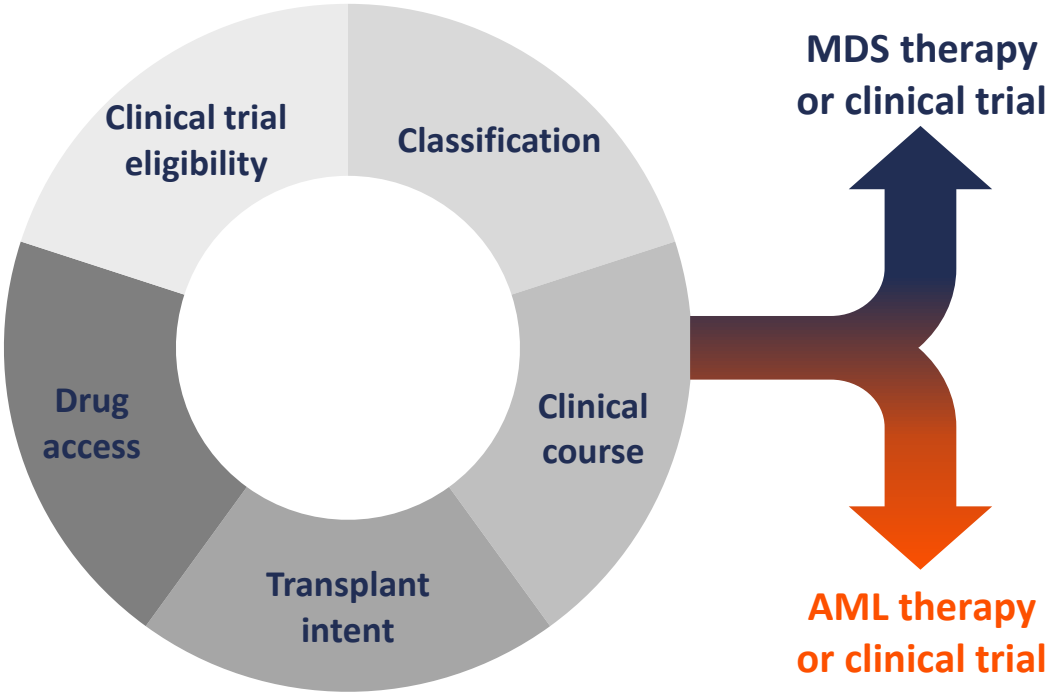
# MDS vs AML: Treatment considerations[1–3]




AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712; 3. Döhner H, et al. *Blood*. 2022;140:1345–77.

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# Pathophysiology of MDS and AML and how it relates to disease classification

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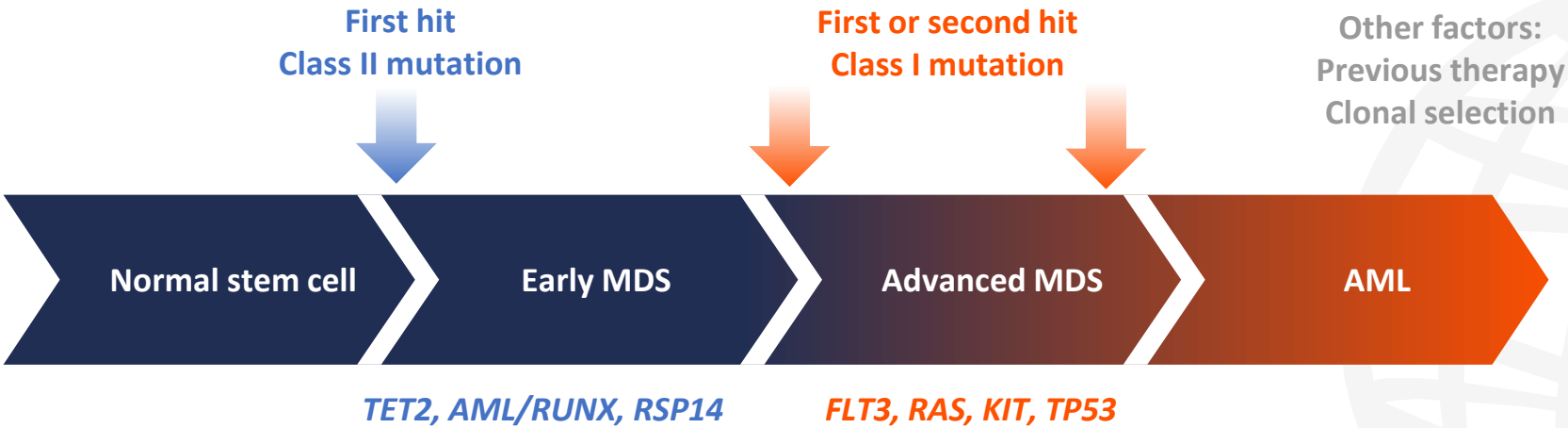
# Model of progression from MDS to AML[1]




**MDS[2]**

- Cytopenia
- Inefficient haematopoiesis
- Dysplasia in one or more myeloid cell lineages
- Increased risk of development of AML

**AML[3]**

- Clonal expansion of myeloid blasts in the bone marrow, peripheral blood or other tissues

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022).

1. Porwit A, Saft L. *J Hematop.* 2011;4:69–79; 2. Visconte V, et al. *Blood Res*. 2014;49:216–27; 3. He GL, et al. *Cancer Cell Int*. 2014;14:111.

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# WHO and ICC classification comparison

## WHO[1]

**MDS = myelodysplastic neoplasms**

**MDS with defining genetic abnormalities**

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

**MDS, morphologically defined**

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

## ICC[2]

**MDS = myelodysplastic syndromes**

- MDS with del(5q)
- MDS with mutated *SF3B1*
- MDS with mutated *TP53*
- MDS, not otherwise specified (MDS, NOS)
  - MDS, NOS without dysplasia
  - MDS, NOS with single lineage dysplasia
  - MDS, NOS with multilineage dysplasia
- MDS with excess blasts (MDS-EB)
- MDS/AML
  - MDS/AML with mutated *TP53*
  - MDS/AML with myelodysplasia-related gene mutations
  - MDS/AML with myelodysplasia-related cytogenetic abnormalities
  - MDS/AML, not otherwise specified

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

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# Validation of MDS guideline updates (1/3)

**Retrospective, single-centred cohort study of patients with MDS**

*Validation of WHO 2022 guidelines*

Jan 2018 – Dec 2021

N=118

| WHO 2022 classification | % lower-risk patients | Median OS |
|---|---|---|
| **Genetically defined** | | |
| • MDS-*SF3B1* | 91 (IPSS-R/IPSS-M) | 7.0 years |
| • MDS-bi*TP53* | 14 (IPSS-R/IPSS-M) | 0.8 years |
| **Morphologically defined** | | |
| • MDS-LB | 71 (IPSS-R/IPSS-M) | NR |
| • MDS-IB1 | 21 (IPSS-R); 16 (IPSS-M) | NR |
| • MDS-IB2 | 0 (IPSS-R); 7 (IPSS-M) | 1.5 years |

- Differing mutational features were prominently associated with both morphologically and genetically defined subgroups
- OS differed between the defined subgroups

IPSS-M, international prognostic scoring system – molecular; IPSS-R, IPSS – revised; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; NR, not reached; OS, overall survival; WHO, World Health Organization.

Khanna V, et al. *Blood*. 2022;140(Suppl. 1):6955–7.

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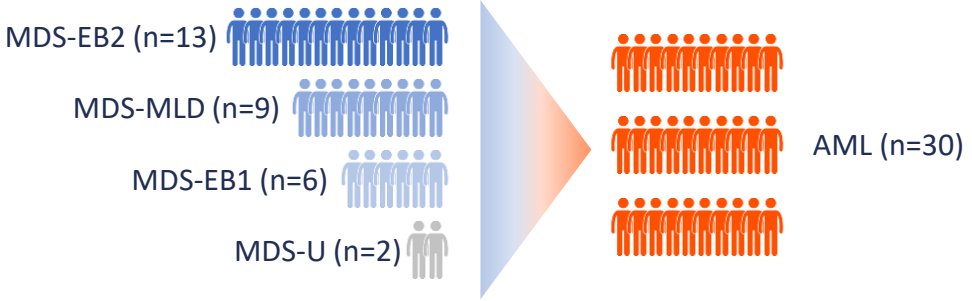
# Validation of MDS guideline updates (2/3)

**Patients with newly diagnosed MDS based on WHO 2016 criteria** → **Reclassified according to WHO 2022 guidelines**

N=852

Aug 2016 – Sep 2021

**30 subjects with *NPM1* mutation were reclassified as AML**




| WHO 2022 classification | Median OS |
|---|---|
| MDS-5q | 24 months |
| MDS-*SF3B1* | 58 months |
| MDS-bi*TP53* | 10 months |
| MDS-LB | Unreached |
| MDS-h | Unreached |
| MDS-IB1 | 24 months |
| MDS-IB2 | 26 months |
| MDS-f | 15 months |

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-EB, myelodysplastic syndromes with excess blasts; MDS-f, MDS with fibrosis; MDS-h, MDS, hypoplastic; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; MDS-U, myelodysplastic syndromes, unclassifiable; OS, overall survival; WHO, World Health Organization. Zhang Y, et al. *Blood*. 2022;140(Suppl. 1):1343–5.

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# Validation of MDS guideline updates (3/3)

**Retrospective, single-centred cohort study of patients with MDS**

N=2,231

**Reclassified by WHO 2022 and ICC 2022 proposed criteria**

## WHO 2022

- MDS-IB1 and MDS-IB2 had similar mOS (p=0.726)

## WHO 2022 and ICC 2022

- MDS with mutated *SF3B1* had best mOS across all subtypes
- Categories for MDS-m*TP53* had worst survival of all subtypes

## ICC 2022

- MDS-MLD had significantly worse mOS compared with MDS-SLD (49.6 months vs 79.4 months; p<0.001)

ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-IB, MDS with increased blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-m*TP53*, MDS with mutated *TP53*; MDS-SLD, MDS with single lineage dysplasia; mOS, median overall survival; WHO, World Health Organization.

Ball S, et al. *Blood*. 2022;140(Suppl. 1):1118–20.

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# Impact of WHO and ICC 2022 on AML diagnosis

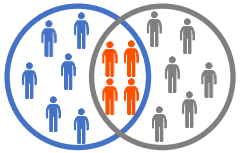
**1,451 non-therapy-related cases with MDS or AML according to 2017 revised 4th edition WHO guidelines**

## WHO 2022 guidelines

- 746 patients diagnosed with AML
- **<1%** of cases were **upgraded from MDS to AML** compared with the revised 4th edition WHO guidelines

## ICC 2022 guidelines

- 742 patients diagnosed with AML
- 137 patients diagnosed with MDS/AML
- **10%** of cases were **upgraded from MDS to AML** compared to the revised 4th edition WHO guidelines, **mainly due to the introduction of the MDS/AML class**



**4/16** patients with **MDS-EB2 according to the revised 4th edition WHO** guidelines were **upgraded to AML using both the WHO 2022 and ICC 2022 guidelines**

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, myelodysplastic syndrome with excess blasts; WHO, World Health Organization.

Huber S, et al. *Blood*. 2022;140(Suppl. 1):555–6.

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# Updated prognostic risk stratification and its impact on patient management

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# Comparison between IPSS-R and IPSS-M

## IPSS-R

Risk based on haematologic and cytogenetic features

- 5 cytogenetic risk categories
- Haemoglobin level
- Marrow blast percentage
- Platelet count

**Factors from IPSS-R conserved in IPSS-M**

## IPSS-M

Risk based on haematologic parameters, cytogenetic abnormalities and somatic mutations

**Additional factors in IPSS-M**

- 16 main effect genes
- 15 residual genes
- Mutations associated with worse outcome:
  - *TP53*$^{\text{multihit}}$
  - *FLT3*
  - *MLL*$^{\text{PTD}}$

IPSS, International Prognostic Scoring System; M, Molecular; R, Revised.

Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

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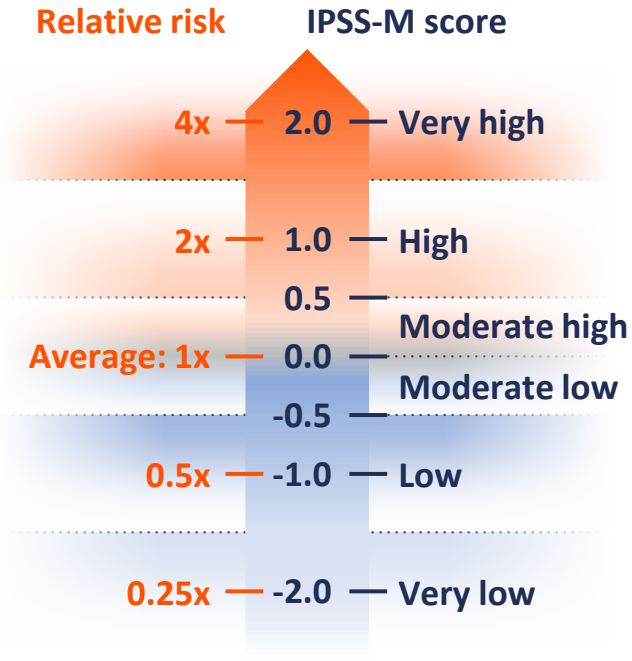
# IPSS-M risk categories

## The IPSS-M score corresponds to the relative risk compared with an ‘average’ patient




A patient’s IPSS-M score can be calculated using the IPSS-M web calculator*

*www.mds-risk-model.com
IPSS-M, Molecular International Prognostic Scoring System.
Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

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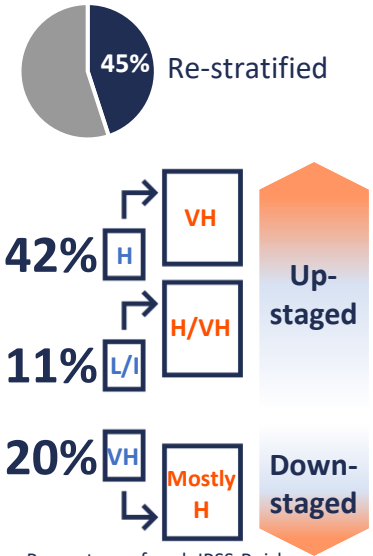
# Validation of the IPSS-M: Data from ASH 2022

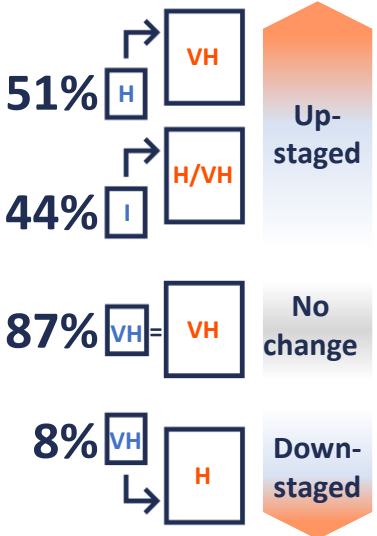
## Aguirre LEE, et al.[1]

N=2,333



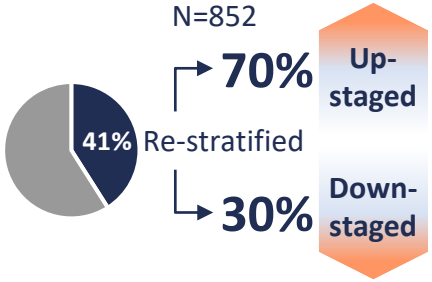

## Santini V, et al.[2]

N=512



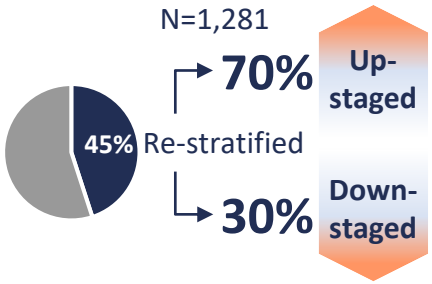

## Wu J, et al.[3]

N=852



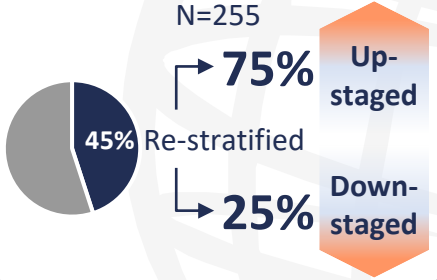

## Kewan T, et al.[4]

N=1,281




## Ma J, et al.[5]

N=255




ASH, American Society of Hematology; H, high risk; I, intermediate risk; IPSS, International Prognostic Scoring System; L, low risk; M, Molecular; R, Revised. sig, significant; VH, very high risk. 1. Aguirre LEE, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 465; 2. Santini V, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 559; 3. Wu J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 1780; 4. Kewan T, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3087; 5. Ma J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 4400.

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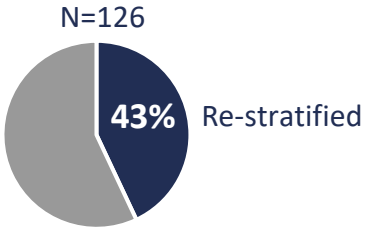
# Real-world use of IPSS-R vs IPSS-M: Data from ASH 2022

**Jáuregui SN, et al.**

**Patients with MDS from a single centre**




**17.4%** of re-stratifications of patients had a potential impact on therapeutic choices

- Of these, 11.9% of patients were up-staged, 5.6% were down-staged

**9.5%** would have actually been treated differently if IPSS-M was initially applied

- Some of the higher-risk patients were not candidates for intensive care due to age and comorbidities

ASH, American Society of Hematology; IPSS, International Prognostic Scoring System; M, Molecular; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); R, Revised; WHO, World Health Organization.

Jáuregui SN, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3096.

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# ELN 2022: Genetic risk classification changes

- ***FLT3*-ITD allelic ratio is no longer considered in the risk classification**
  - AML with *FLT3*-ITD (without adverse-risk genetic lesions) is categorized in the intermediate-risk group, irrespective of allelic ratio or concurrent presence of an *NPM1* mutation
- **AML with myelodysplasia-related gene mutations are now in the adverse-risk group**
  - Mutations include pathologic variants in at least one of the following:
    - *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **In-frame mutations in the leucine zipper region of *CEBPA* are now classified in the favourable-risk group**
  - Classification is irrespective of biallelic or monoallelic mutations
- **The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML are now classified as adverse risk**
- **Additional disease-defining, recurring cytogenetic abnormalities are now in the adverse-risk group**
  - Include mutations in t(3q26.2;v) involving the *MECOM* gene, or t(8;16)(p11.2;p13.3) associated with *KAT6A::CREBBP* gene fusion
- **Hyperdiploid karyotypes with multiple trisomies are no longer on the list of complex karyotypes or in the adverse risk group**

AML, acute myeloid leukaemia; ELN, European LeukemiaNet; ITD, internal tandem duplication.

Döhner H, et al. *Blood*. 2022;140:1345–77.

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