2022 ICC AND 5TH WHO CLASSIFICATION OF HEMATOPOIETIC NEOPLASMS GUIDELINES: AN OVERVIEW

The 2022 WHO / ICC new classifications: what has changed in the diagnostic approach to non-lymphoid hematological malignancies?

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LABORATORY MEDICINE

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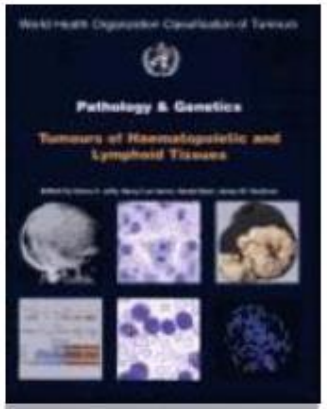
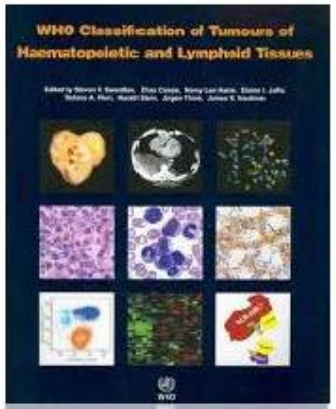
CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

FAB 1976

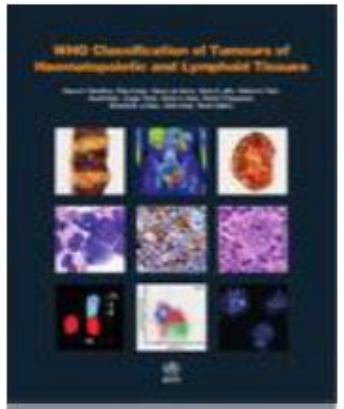
WHO 2001
HAEM3



WHO 2008
HAEM4



WHO 2016
HAEM4R



WHO 2022
HAEM5

ICC 2022

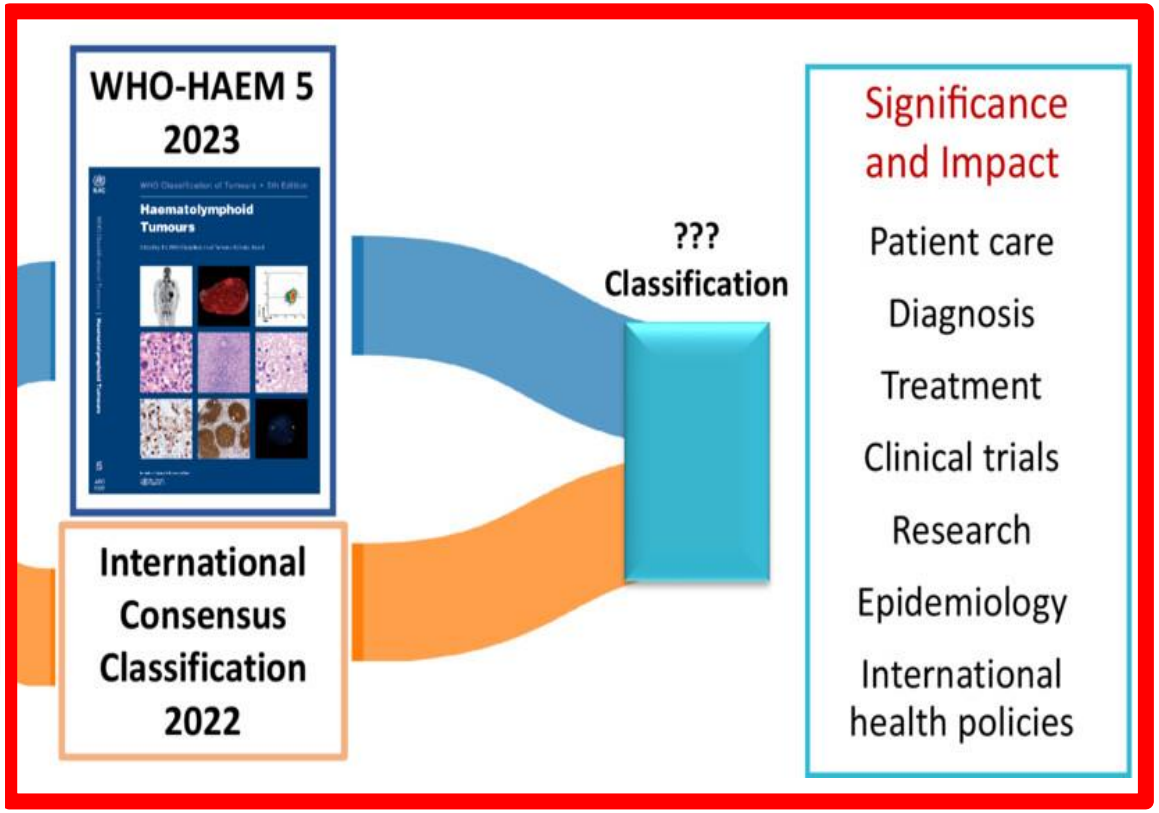
FUTURE?

FAB
1976

WHO-HAEM 3
2001

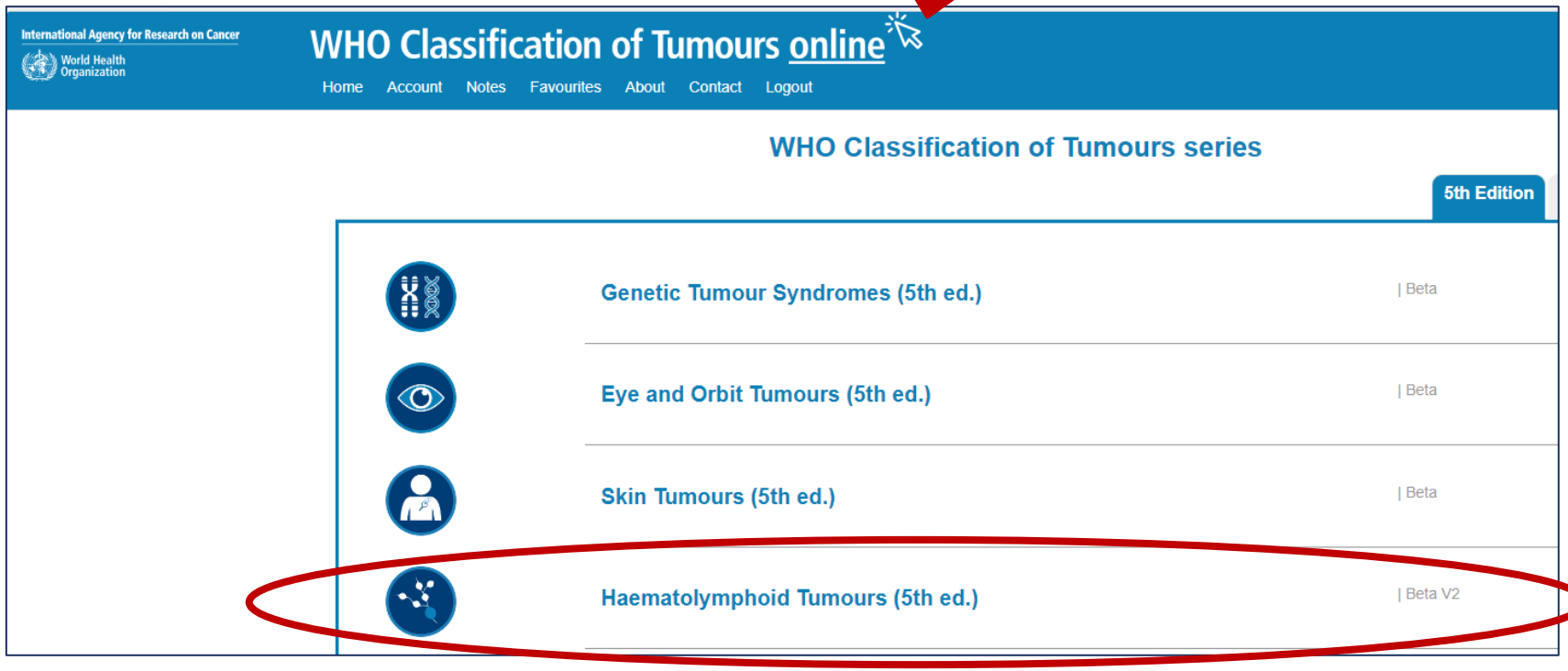
WHO-HAEM 4
2008

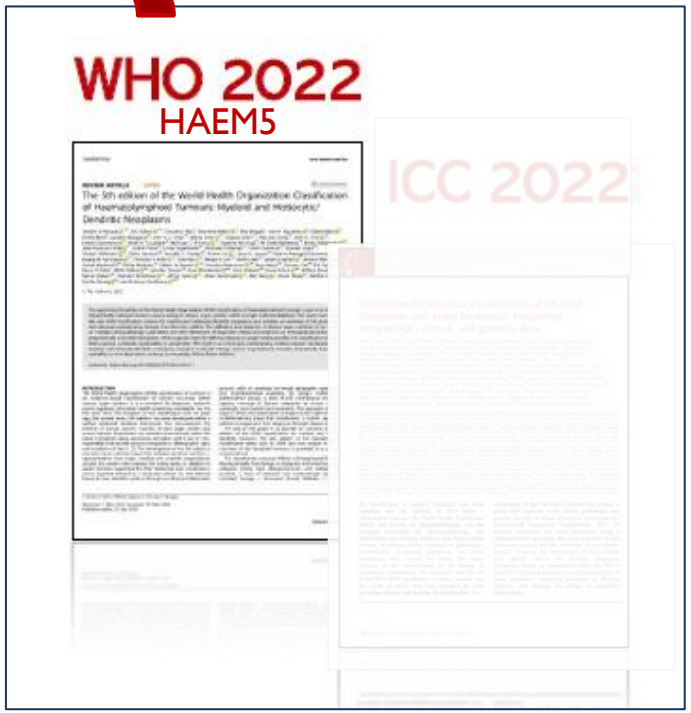
WHO-HAEM 4R
2017



Adapted from MS. Lim, BJH, 2023 (203): 349-.50

CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES



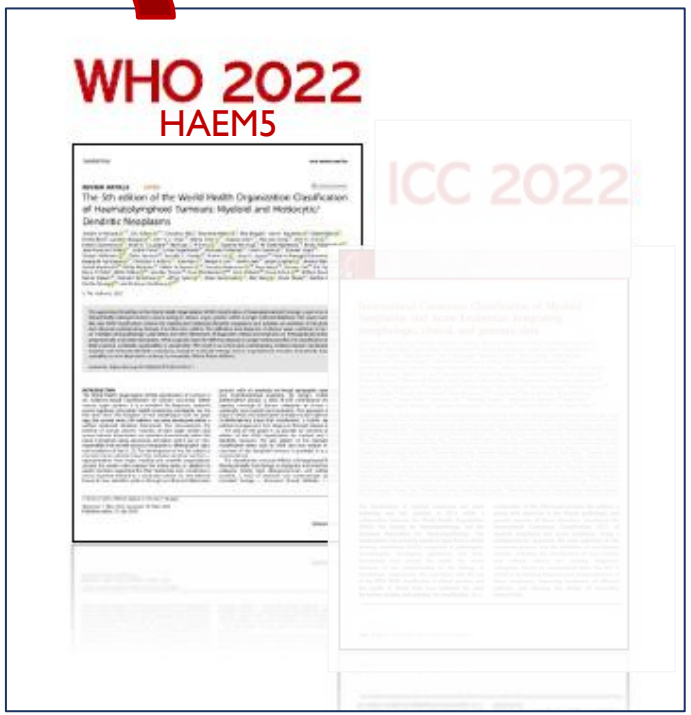


https://tumourclassification.iarc.who.int/home
Khoury JD. Et al. Leukemia 2022 (36); 1703-1719.
Allegio R et al. Leukemia 2022 (36): 1720-1748.

CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

Haematolymphoid Tumours (5th ed.)

1. Forewords and Introductions
2. Myeloid proliferations and neoplasms
3. Histiocytic/Dendritic cell neoplasms
4. B-cell lymphoid proliferations and lymphomas
5. T-cell and NK-cell lymphoid proliferations and lymphomas
6. Stroma-derived neoplasms of lymphoid tissues
7. Genetic tumour syndromes



https://tumourclassification.iarc.who.int/home
Khoury JD. et al. Leukemia 2022 (36):1703-1719.
Allegio R et al. Leukemia 2022 (36):1720-1748.

CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

Arber DA. et al. Blood 2022, 140 (11):1200-1228.
Campo E. et al. Blood 2022, 140 (11):1229-1253.

CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

Question: Which classification do you use in your daily practice?

- Only ICC 2022
- Only 5th WHO
- Both ICC 2022 and 5th WHO
- None of both / other

MAJOR CATEGORIES OF MYELOID NEOPLASMS AND ACUTE MYELOID LEUKEMIAS

WHO 2022 – HAEM5

- Myeloid precursor lesions
- Myeloproliferative neoplasms
- Mastocytosis
- Myelodysplastic neoplasms
- Myelodysplastic/myeloproliferative neoplasms
- Acute myeloid leukaemia
- Myeloid neoplasms, secondary
- Myeloid/lymphoid neoplasms
- Acute leukaemias of mixed or ambiguous lineage
- Dendritic cell and histiocytic neoplasms

ICC 2022

- Myeloproliferative neoplasms
- Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions
- Mastocytosis
- Myelodysplastic/myeloproliferative neoplasms
- Premalignant clonal cytopenias and MDS
- Pediatric disorders and/or germline mutation associated disorders
- Acute myeloid leukaemia
- Myeloid proliferation associated with Down Syndrome
- Blastic plasmocytoid dendritic cell neoplasm
- Acute leukemia of ambiguous lineage

MYELOPROLIFERATIVE NEOPLASMS (MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
CML, *BCR::ABL1* positive	CML	CML
PV	PV	PV
ET	ET	ET
PMF	PMF	PMF
CNL	CNL	CNL
CEL, NOS	CEL	CEL, NOS
MDS/MPN ←	JMML	→ Pediatric disorders
MPN, unclassifiable	MPN, NOS	MPN, unclassifiable

MYELOPROLIFERATIVE NEOPLASMS (MPN): CML

HAEM 4R	HAEM 5	ICC 2022
CML, *BCR::ABL1* positive	CML	CML

- Chronic phase (CP)
- Blast phase (BP)
  - ≥20% blasts in PB or BM
  - extramedullary proliferation of blasts
  - presence of bona fide lymphoblasts in PB or BM (even if <10%)

- Accelerated phase (AP): now called **'high-risk chronic phase'**

FEATURES IN CHRONIC PHASE ASSOCIATED WITH INCREASED RISK OF DISEASE PROGRESSION

At diagnosis
- High ELTS score
- 10–19% blasts in the peripheral blood and/or bone marrow[ab]
- ≥20% basophils in the peripheral blood
- ACA in Ph+ cells, including 3q26.2 rearrangements, -7, isochromosome 17q, complex karyotype
- ACA in Ph+ cells, including +8, 11q23 rearrangements, +19, +21, additional Ph+
- Clusters of small megakaryocytes, associated with significant reticulin and/or collagen fibrosis

Emerging on treatment
- Resistance to TKI as defined by ELN 2020, including loss of prior responses, emergence of ACA and BCR::ABL1 kinase domain mutations

MYELOPROLIFERATIVE NEOPLASMS (MPN): CML

HAEM 4R	HAEM 5	ICC 2022
CML, *BCR::ABL1* positive	CML	CML

- Chronic phase (CP)
- Accelerated phase (AP)
- Blast phase (BP)

DIAGNOSTIC CRITERIA FOR AP AND BP CML

Accelerated phase	Blast phase
Bone marrow or peripheral blood blasts 10%-19%	Bone marrow or peripheral blood blasts ≥ 20%
Peripheral blood basophils ≥ 20%	Myeloid sarcoma[‡]
Presence of additional clonal cytogenetic abnormality in Ph+ cells (ACA)[*]	Presence of morphologically apparent lymphoblasts (>5%) warrants consideration of lymphoblastic crisis[‡]

[*]Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2.
[†]Extramedullary blast proliferation.
[‡]Immunophenotypic analysis is required to confirm lymphoid lineage.

MYELOPROLIFERATIVE NEOPLASMS (MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
PV	PV	PV
ET	ET	ET
CNL	CNL	CNL
CEL, NOS	CEL	CEL, NOS
PMF	PMF	PMF

=> Major diagnostic criteria established in the previous WHO edition (HAEM 4R) remain, only minor changes.

MPN: POLYCYTHEMIA VERA

HAEM 4R	HAEM 5	ICC 2022
PV	PV	PV

DIAGNOSIS OF PV REQUIRES EITHER ALL 3 MAJOR CRITERIA OR THE FIRST 2 MAJOR CRITERIA PLUS THE MINOR CRITERION.

Major criteria

- ↑ Hb concentration (> 16.5 g/dL (men); > 16.0 g/dL (women)) or ↑ Hct (>49% (men); >48% (women)) or ↑ RBC mass
- BM biopsy: age-adjusted hypercellularity with trilineage growth (panmyelosis), prominent erythroid, granulocytic, and increased pleomorphic mature megakaryocytic without atypie
- Presence of *JAK2* V617F or *JAK2* exon 12 mutation

Minor criterion

- Subnormal serum erythropoietin level

MPN: POLYCYTHEMIA VERA

HAEM 4R	HAEM 5	ICC 2022
PV	PV	PV

DIAGNOSIS OF PV REQUIRES EITHER ALL 3 MAJOR CRITERIA OR THE FIRST 2 MAJOR CRITERIA PLUS THE MINOR CRITERION.

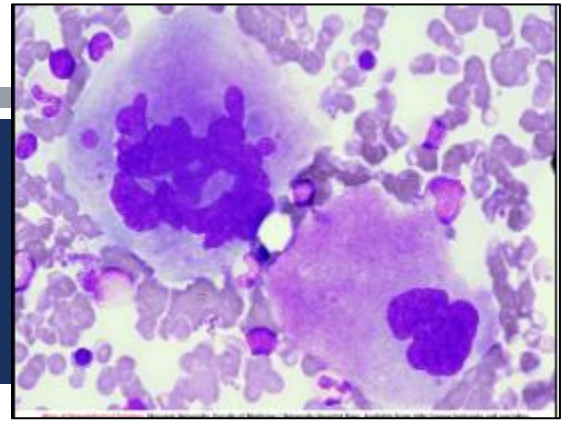
Major criteria

- ↑ Hb concentration (> 16.5 g/dL (men); > 16.0 g/dL (women)) or ↑ Hct (>49% (men); >48% (women)) ~~or ↑ RBC mass~~
- BM biopsy: age-adjusted hypercellularity with trilineage growth (panmyelosis), prominent erythroid, granulocytic, and increased pleomorphic mature megakaryocytic without atypie
- Presence of *JAK2* V617F or *JAK2* exon 12 mutation

Minor criterion

- Subnormal serum erythropoietin level

MPN: ESSENTIAL THROMBOCYTOSIS



HAEM 4R	HAEM 5	ICC 2022
ET	ET	ET

DIAGNOSIS OF ET REQUIRES EITHER ALL MAJOR CRITERIA OR THE FIRST 3 MAJOR CRITERIA PLUS THE MINOR CRITERION.

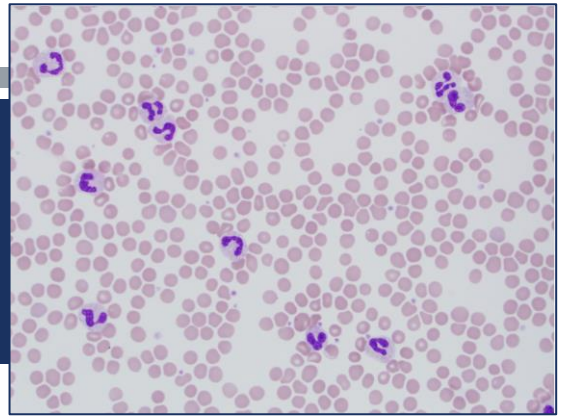
Major criteria

- Platelet count ≥450 x10e9/L
- Bone marrow biopsy showing proliferation mainly of MgK lineage, with increased numbers of enlarged, mature MgK with hyperlobulated staghorn-like nuclei, infrequently dens clusters; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis
- Diagnostic criteria for *BCR::ABL1* positive CML, PV, PMF or other myeloid neoplasms are not met
- *JAK2*, *CALR*, or *MPL* mutation

Minor criterion

- Presence of clonal markers OR absence of evidence of reactive thrombocytosis

MPN: CHRONIC NEUTROPHILIC LEUKEMIA



HAEM 4R	HAEM 5	ICC 2022
CNL	CNL	CNL

DIAGNOSTIC CRITERIA FOR CHRONIC NEUTROPHILIC LEUKEMIA

Peripheral bood

- WBC ≥25 x 10e9/L
- Segmented + banded neutrophils ≥80%
- Neutrophil precursors (pro-, myelocytes, meta-) <10%
- Circulating blasts rarely seen
- No significant dysgranulopoiesis
- Monocyte count <10%, absolute # not meeting criteria CMML

Bone marrow

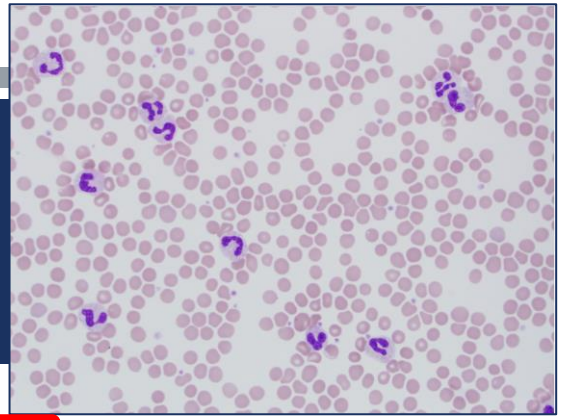
- Hypercellular with increased neutrophil granulocytes in % and absolute number, showing normal maturation

- Not meeting diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, PMF

- No rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, and no *PCM1-JAK2* fusion

- ***CSF3R* T618I** or another *CSF3R* mutation
  or
  persistent neutrophilia (≥3 months), splenomegaly, and no identifiable cause of reactive neutrophilia including absence of a PC neoplasm, or if present, demonstration of clonality of myeloid cells by cytogenetic/molecular studies

MPN: CHRONIC NEUTROPHILIC LEUKEMIA



HAEM 4R	HAEM 5	ICC 2022
CNL	CNL	CNL

DIAGNOSTIC CRITERIA FOR CHRONIC NEUTROPHILIC LEUKEMIA

Peripheral bood

- WBC ≥13 x 10e9/L (≥ 25 x 10e9/L if no *CSF3R* mutation)
- Segmented + banded neutrophils ≥80%
- Neutrophil precursors (pro-, myelocytes, meta-) <10%
- Circulating blasts rarely seen*
- No significant dysgranulopoiesis
- Monocyte count <10%

Bone marrow

- Hypercellular with increased neutrophil granulocytes in % and absolute number, showing normal maturation

- Not meeting diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, PMF

- No rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, and no *PCM1-JAK2* fusion

- *CSF3R* T618I or another *CSF3R* mutation

  or

  persistent neutrophilia (≥3 months), splenomegaly, and no identifiable cause of reactive neutrophilia including absence of a PC neoplasm, or if present, demonstration of clonality of myeloid cells by cytogenetic/molecular studies

MPN: PRIMARY MYELOFIBROSIS

HAEM 4R	HAEM 5	ICC 2022
PMF	PMF	PMF

PRE-FIBROTIC / EARLY STAGE PRIMARY MYELOFIBROSIS requires all 3 major criteria and at least 1 minor criterion.

Major criteria

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade > 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
2. WHO criteria for *BCR-ABL1*–positive chronic myeloid leukaemia, polycythaemia vera, essential thrombocythaemia, myelodysplastic syndromes, or other myeloid neoplasms are not met
3. *JAK2*, *CALR*, or *MPL* mutation OR
   Presence of another clonal marker OR
   Absence of minor reactive bone marrow reticulin fibrosis

Minor criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

- Anaemia not attributed to a comorbid condition
- Leukocytosis ≥ 11 × 10^9/L
- Splenomegaly detected clinically and/or by imaging
- LDH above the upper limit of the institutional reference range
- Leukoerythroblastosis

OVERT PRIMARY MYELOFIBROSIS requires all 3 major criteria and at least 1 minor criterion.

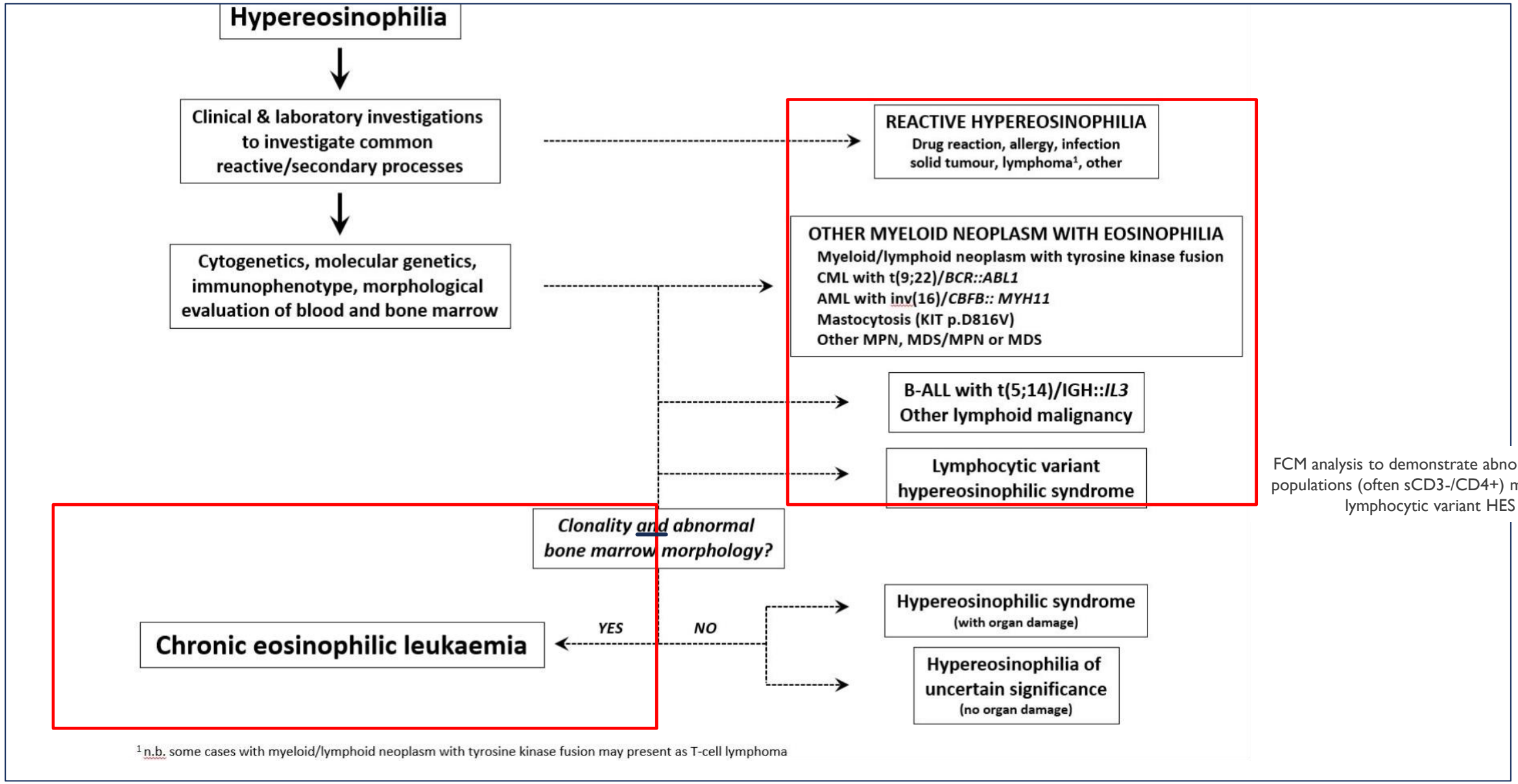
Major criteria

1. Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3
2. WHO criteria for essential thrombocythaemia, polycythaemia vera, *BCR-ABL1*–positive chronic myeloid leukaemia, myelodysplastic syndrome, or other myeloid neoplasms are not met
3. JAK2, CALR, or MPL mutation OR
   Presence of another clonal marker OR
   Absence of reactive myelofibrosis

Minor criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

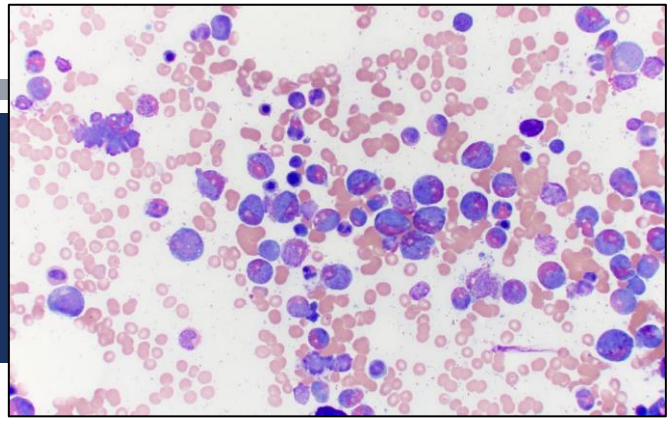
- Anaemia not attributed to a comorbid condition
- Leukocytosis ≥ 11 × 10^9/L
- Splenomegaly detected clinically and/or by imaging
- LDH above the upper limit of the institutional reference range
- Leukoerythroblastosis



FCM analysis to demonstrate abnormal T cell populations (often sCD3-/CD4+) may identify lymphocytic variant HES

https://tumourclassification.iarc.who.int/home

MPN: CHRONIC EOSINOPHILIC LEUKEMIA



HAEM 4R	HAEM 5	ICC 2022
CEL, NOS	CEL	CEL, NOS

ESSENTIAL *(Note 1)*

- peripheral blood eosinophilia >1.5 x 10^9/L on at least 2 occasions over an interval of at least 4 weeks
- evidence of clonality (*Note 2*);
- abnormal bone marrow morphology;
- WHO criteria for other myeloid or lymphoid neoplasms not met, including MPN, MDS/MPN, MDS, MLN-eo, mastocytosis, AML

Note 1: criteria have changed since the 4th Edition,

(1) specifically a reduction in the time interval required to define sustained HE from 6 months to 4 weeks

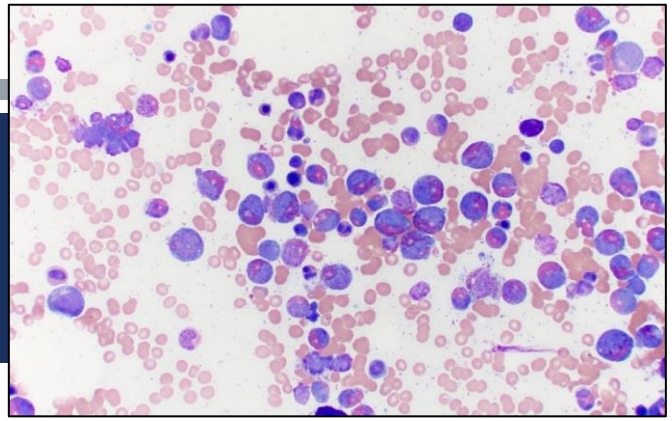
(2) requirement for both clonality and abnormal bone marrow morphology,

(3) removal of the possibility to define CEL-NOS by increased blasts (≥ 2% in peripheral blood or 5–19% in bone marrow) as an alternative to clonality.

Note 2: the possibility of CHIP should be considered

https://tumourclassification.iarc.who.int/home

MPN: CHRONIC EOSINOPHILIC LEUKEMIA



HAEM 4R	HAEM 5	ICC 2022
CEL, NOS	CEL	CEL, NOS

1, Peripheral blood hypereosinophilia (eosinophil count ≥ 1.5 × 10^9/L and eosinophils ≥ 10% of white blood cells)
2. Blasts constitute < 20% cells in peripheral blood and bone marrow, not meeting other diagnostic criteria for AML*
3. No tyrosine kinase gene fusion including *BCR::ABL1*, other *ABL1*, *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, or *FLT3* fusions
4. Not meeting criteria for other well-defined MPN; chronic myelomonocytic leukemia, or SM†
5. BM shows increase cellularity with dysplastic MgK with or without dysplastic features in other lineages and often significant fibrosis, associated with an eosinophilic infiltrate or increased blast ≥ 5% in BM and/or ≥ 2% in PB
6. Demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s)‡
The diagnosis of CEL requires all 6 criteria.

* AML with recurrent genetic abnormalities with < 20% blasts is excluded.
† Eosinophila can be seen in association with SM. However, "true" CEL, NOS may occur as SM-AMN (SM with an associated myeloid malignancies).
‡ In the absence of a clonal cytogenetic abnormality and/or somatic mutation(s) or increased blasts, bone marrow findings supportive of the diagnosis will suffice in the presence of persistent eosinophilia, provided other causes of eosinophilia having been excluded.

SYSTEMIC MASTOCYTOSIS

WHO HAEM 5

Major criterion:

- Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of BM and/or other extracutaneous organ(s).

Minor criteria

- >25% of all mast cells are atypical cells (type I or type II) on BM smears or are spindle-shaped in dense and diffuse mast cell infiltrates in sections of BM or other extracutaneous organ(s).
- Activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT* in BM or another extracutaneous organ(s).
- Mast cells in BM, blood, or another extracutaneous organ(s) aberrantly express one or more of the following antigens: CD2, CD25, CD30 (either FCM or IH)
- Baseline serum tryptase concentration >20 ng/mL in the absence of a myeloid AHN. In the case of a known HαT, the tryptase level could be adjusted.

ICC 2022

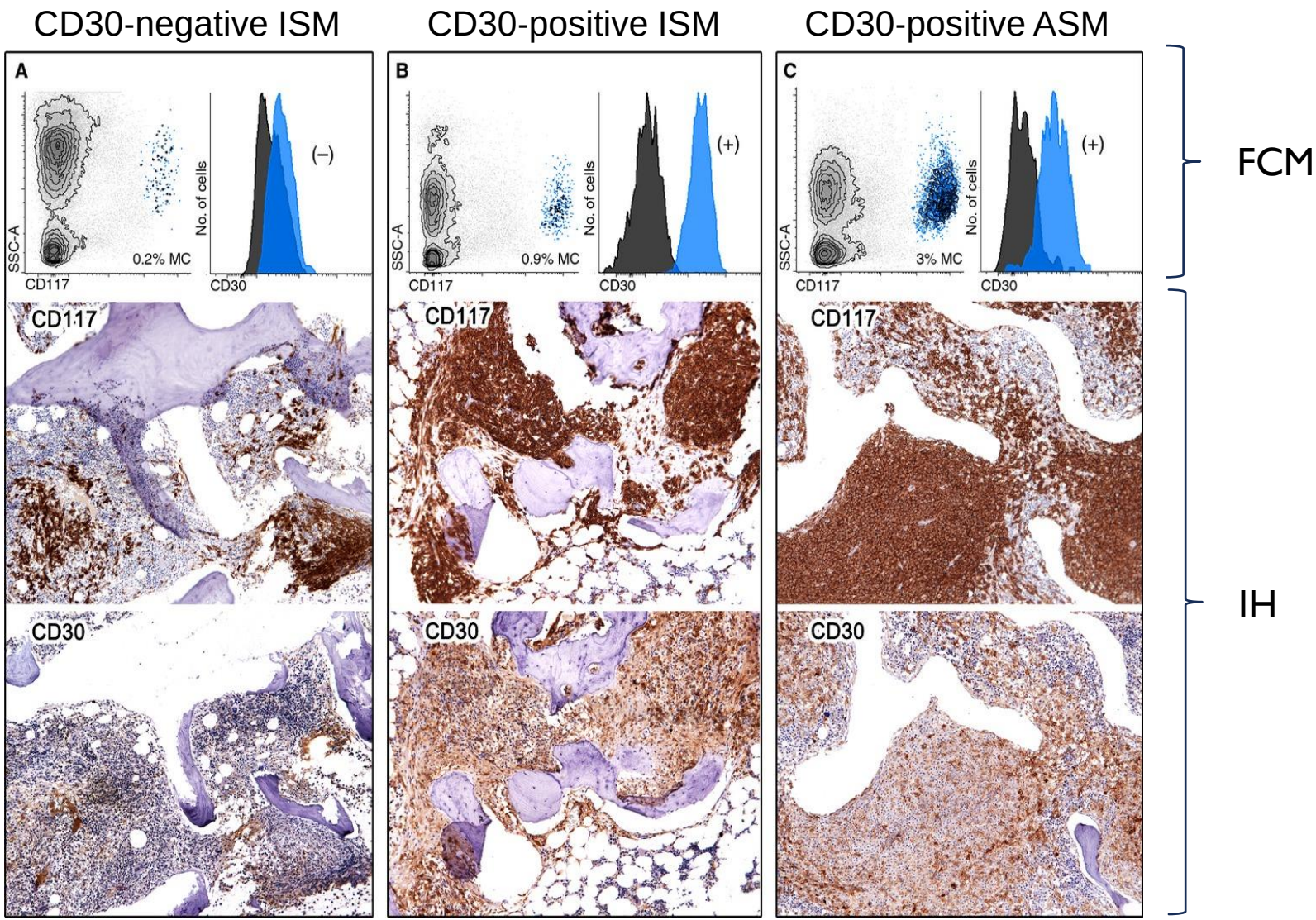
Major criterion

- Multifocal dense infiltrates of tryptase- and/or CD117 positive mast cells (≥ 15 mast cells in aggregates) detected in sections of BM and/or other extracutaneous organ(s)

Minor criteria

- In BM biopsy or in section of other extracutaneous organs >25% of mast cells are spindle shaped or have an atypical immature morphology
- KIT D816V mutation or other activating KIT mutation detected in BM, peripheral blood, or other extracutaneous organs
- Mast cells in BM, peripheral blood or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to mast cell markers
- Elevated serum tryptase level, persistently >20 ng/mL. In cases of SM-AMN an elevated tryptase does not count as a SM minor criterion

at least 1 major and 1 minor or 3 minor criteria are fulfilled

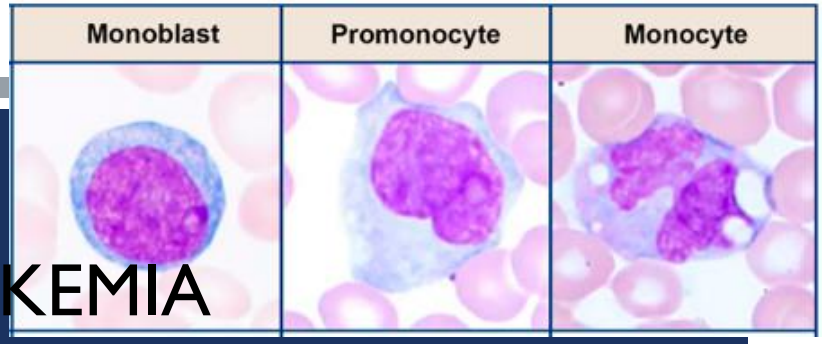


Morgado et al. Histopathology (2013)

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
CMML	CMML	CMML
-	-	Clonal cytopenia with monocytosis of undetermined significance (CCMUS)
-	-	Clonal monocytosis of undetermined significance (CMUS)
JMML	- → MPN	- → Pediatric disorders
aCML, *BCR::ABL1* negative	MDS/MPN with neutrophillia	aCML
-	MDS/MPN with thrombocytosis and *SF3B1* mutation	MDS/MPN with thrombocytosis and *SF3B1* mutation
MDS/MPN with ringsideroblasts and thrombocytosis	-	MDS/MPN with ringsideroblasts and thrombocytosis, NOS
MDS/MPN, unclassifiable	MDS/MPN, NOS	MDS/MPN, NOS *provisional entity* *MDS/MPN with i(17q)*

MDS/MPN: CHRONIC MYELOMONOCYTIC LEUKEMIA



HAEM 4R	HAEM 5	ICC
CMML	CMML	CMML

DIAGNOSTIC CRITERIA FOR CHRONIC MYELOMONOCYTIC LEUKEMIA

Pre-requisite criteria

1. Persistent absolute (≥ 0.5 × 10^9/L) and relative (≥ 10%) peripheral blood monocytosis.
2. Blasts/blast equivalent constitute < 20% in PB and BM.
3. Not meeting diagnostic criteria of CML or other MPN.[2]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangements (e.g. *PDGFRA, PDGFRB, FGFR1*, or *JAK2).*[3]

Supporting criteria

1. Dysplasia involving ≥ 1 myeloid lineages.[4]
2. Acquired clonal cytogenetic or molecular abnormality.[5]
3. Abnormal partitioning of peripheral blood monocyte subsets.

Requirements for diagnosis

Pre-requisite criteria must be present in all cases

If monocytosis is ≥ 1 × 10^9/L: ≥1 supporting criteria must be met

If monocytosis is <1 × 10^9/L: supporting criteria 1 + 2 must be met

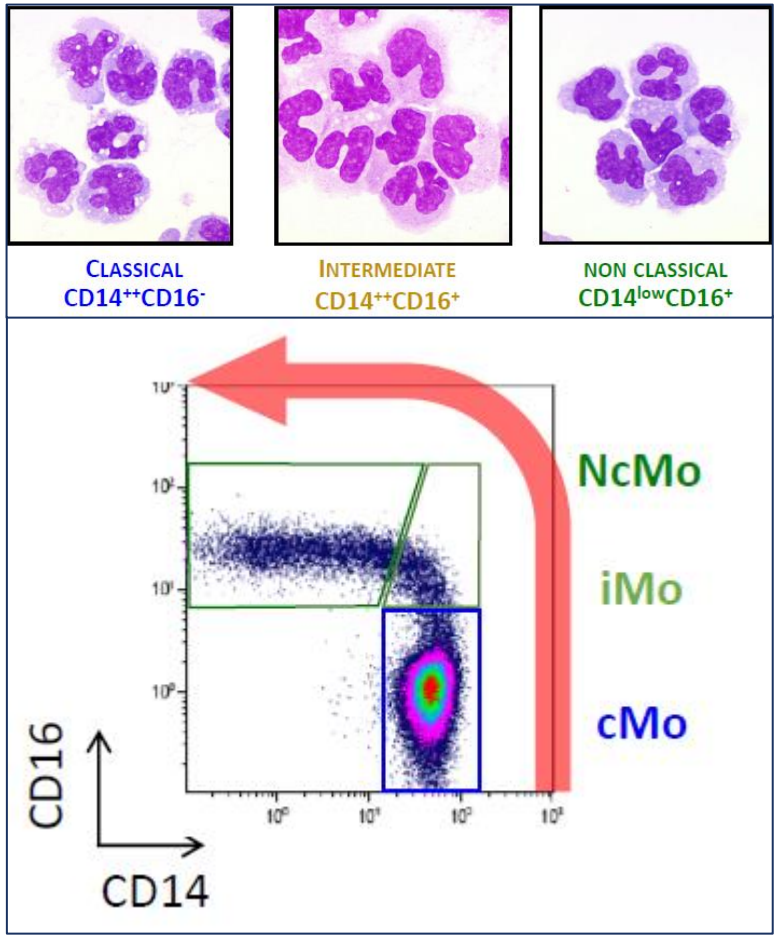
Recommended minimal gene set for mutation profiling in the workup of patients for CMML

Pathway	Gene	Frequency (%)
Epigenetic regulation	***TET2***	29-61
	ASXL1*	32-44
	DNMT3A	2-12
	*EZH2**	5-13
	IDH1	1-2
	IDH2	6-7
	*BCOR**	6-7
Spliceosome	***SRSF2****	29-52
	*U2AF1**	4-10
	*SF3B1**	6-10
	*ZRSR2**	4-8
Cellular signaling	*CBL**	8-22
	*KRAS**	7-16
	*NRAS**	4-22
	NF1	6-7
	JAK2	1-10
Other	*RUNX1**	8-23
	*SETBP1**	4-18
	NPM1	1-3
	FLT3	1-3

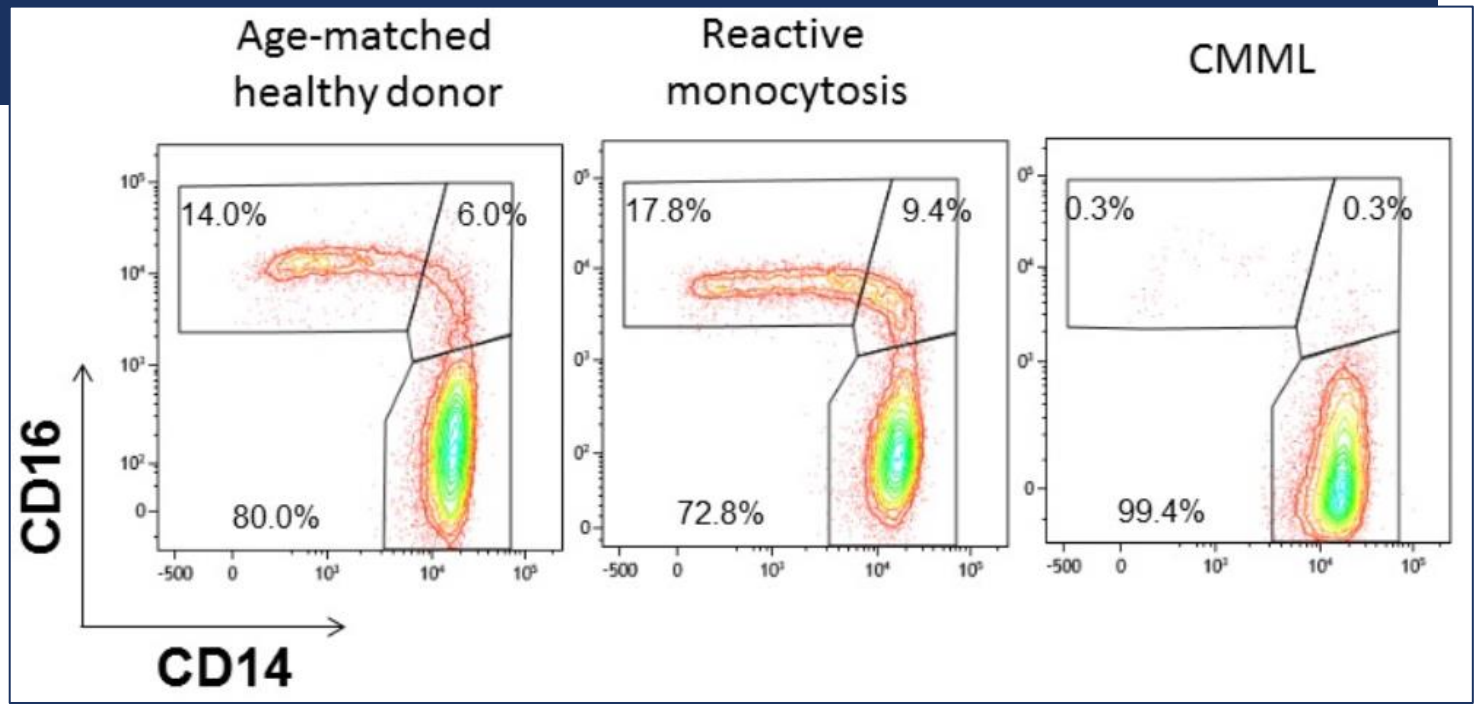
*Mutations involving one or more of these genes is required to meet supporting criterion #2 if absolute monocytosis is ≥0.5 but <1 × 10^9/L.

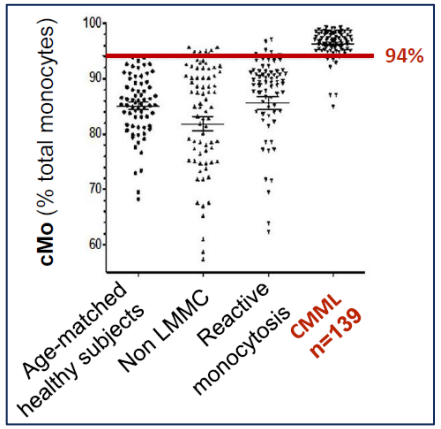
https://tumourclassification.iarc.who.int/home

MULTIPARAMETRIC FLOW ANALYSIS OF PERIPHERAL BLOOD MONOCYTE SUBSETS.



MONOCYTE SUBSETS IN CMML





The relative accumulation of classical monocytes distinguishes CMML from reactive monocytosis (cMo ≥ 94%) in PB

https://tumourclassification.iarc.who.int/home

Selimoglu-Buet, Wagner-Balon et al. Blood 2015.

MDS/MPN: CMML

HAEM 4R	HAEM 5	ICC 2022
CMML	CMML	CMML

DIAGNOSTIC CRITERIA CMML
Monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Cytopenia (thresholds same as MDS)*
Blasts (including promonocytes) < 20% of the cells in blood and bone marrow
Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of ≥10% allele frequency†
In cases without evidence of clonality, • monocytes ≥ 1.0 × 10^9/L and > 10% of the WBC, and • increased blasts (+promonocytes),‡ or morphologic dysplasia, or • abnormal immunophenotype consistent with CMML would be required for its diagnosis.
BM examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of AML, MPN or other conditions associated with monocytosis§
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

MDS/MPN: CMML (WHO HAEM5 – ICC 2022)

Subtyping criteria

- Myelodysplastic CMML (**MD-CMML**): WBC count < 13×10^9/L
- Myeloproliferative CMML (**MP-CMML**): WBC count ≥ 13×10^9/L

Subgrouping criteria*

- ~~CMML-0: < 2% in peripheral blood and < 5% in bone marrow, no Auer rods~~
- **CMML-1**: < 5% in peripheral blood or < 10% in bone marrow, no Auer rods
- **CMML-2**: 6-19% in peripheral blood or 10-19% in bone marrow, or Auer rods

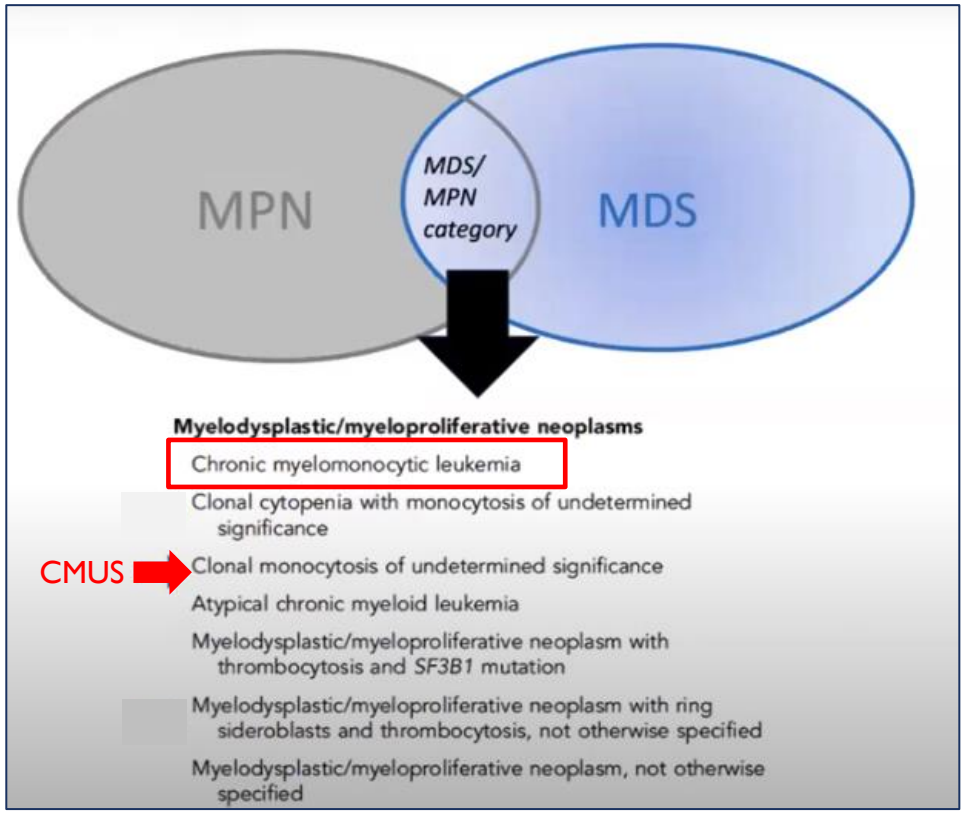
*based on percentage of blasts (myeloblasts and monoblasts) and blast equivalent cells (promonocytes)

WHO Haem 5:
MPN at presentation + evolution to CMML-like disease phenotype => disease progression (**not be reclassified as CMML)**
MDS at presentation + subsequently meet the diagnostic criteria of CMML => **may be reclassified as CMML**

MDS/MPN: CMML

HAEM 4R	HAEM 5	ICC 2022
CMML	CMML	CMML precursor condition: CMUS

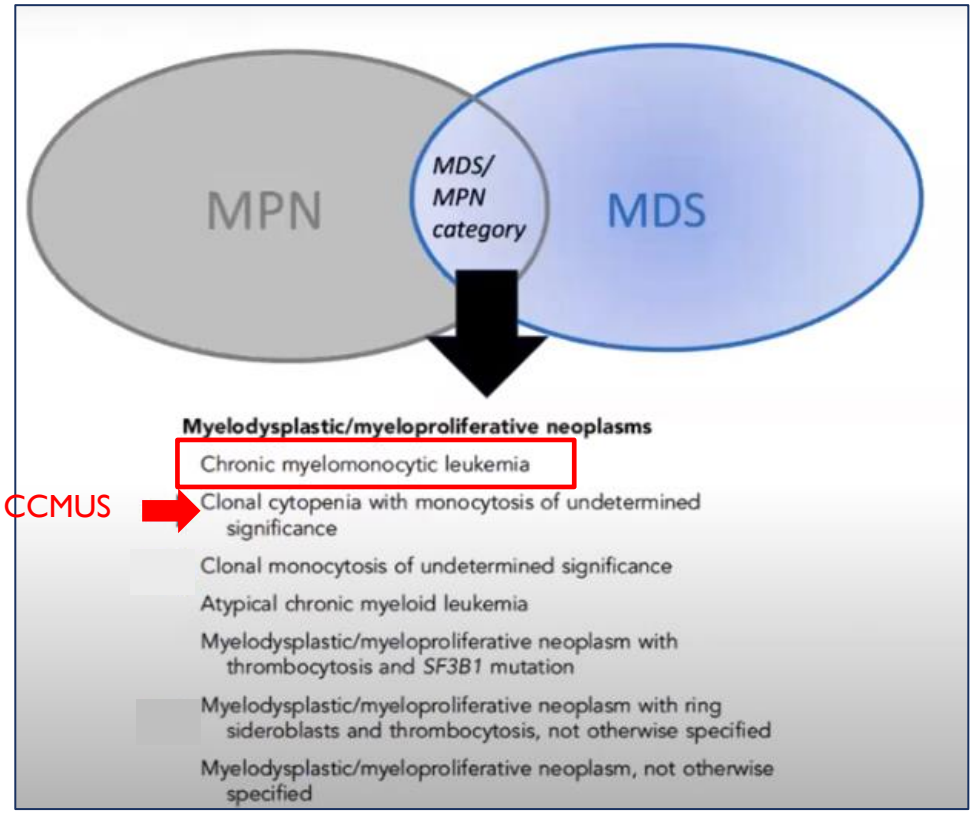
DIAGNOSTIC CRITERIA CMUS
Persistent monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on BM examination‡
No criteria for a myeloid or other hematopoietic neoplasm
No reactive condition that would explain a monocytosis



MDS/MPN: CMML

HAEM 4R	HAEM 5	ICC 2022
CMML	CMML	CMML precursor condition: CMUS /CCMUS

DIAGNOSTIC CRITERIA CMUS
Persistent monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on BM examination‡
No criteria for a myeloid or other hematopoietic neoplasm
No reactive condition that would explain a monocytosis



JUVENILE MYELOMONOCYTIC LEUKEMIA

HAEM 4R	HAEM 5	ICC 2022
JMML => MDS/MPN	JMML => MPN	JMML => Pediatric and/or germline associated disorders

Clinical, hematological, and laboratory criteria (all 5 required)

- Peripheral blood monocyte count ≥ 1 x 10^9/L
- Blast and promonocyte in PB and BM < 20%
- Clinical evidence of organ infiltration, mostly splenomegaly
- No Ph chromosome or *BCR-ABL1* fusion
- No *KMT2A (MLL1)* gene rearrangement

Genetic criteria (any 1 criterion is sufficient)

- Mutation in a component or a regulator of the canonical RAS pathway:
  - Clonal somatic mutation in *PTPN11, KRAS, or NRAS*[a]
  - Clonal somatic or germline *NF1* mutation and LOH or compound heterozygosity of *NF1*
  - Clonal somatic or germline *CBL* mutation and LOH of *CBL*[b]
- Non-canonical clonal RAS pathway pathogenic variant[c] or fusions causing activation of genes upstream of the RAS pathway, such as *ALK*, *PDGFR-B*, *ROS1*, among others.

Other criteria

Cases not meeting any of the genetic criteria listed above (or when genetic testing is not available) must meet following criteria in addition to aforementioned clinical, haematological, and laboratory criteria: ≥2 of the following

- Increased haemoglobin F for age
- Myeloid (promyelocytes, myelocytes, metamyelocytes) and erythroid precursors on peripheral blood smear
- Thrombocytopenia with hypercellular marrow often showing decreased number of megakaryocytes. Dysplastic features may or may not be evident.
- Hypersensitivity of myeloid progenitors to GM-CSF as tested in clonogenic assays in methylcellulose or by measuring STAT5 phosphorylation in the absence or with low dose of exogenous GM-CSF.

JUVENILE MYELOMONOCYTIC LEUKEMIA

HAEM 4R	HAEM 5	ICC 2022
JMML => MDS/MPN	JMML => MPN	JMML => Pediatric and/or germline associated disorders

Clinical and hematological features (the first 2 features are present in most cases; the last 2 are required)

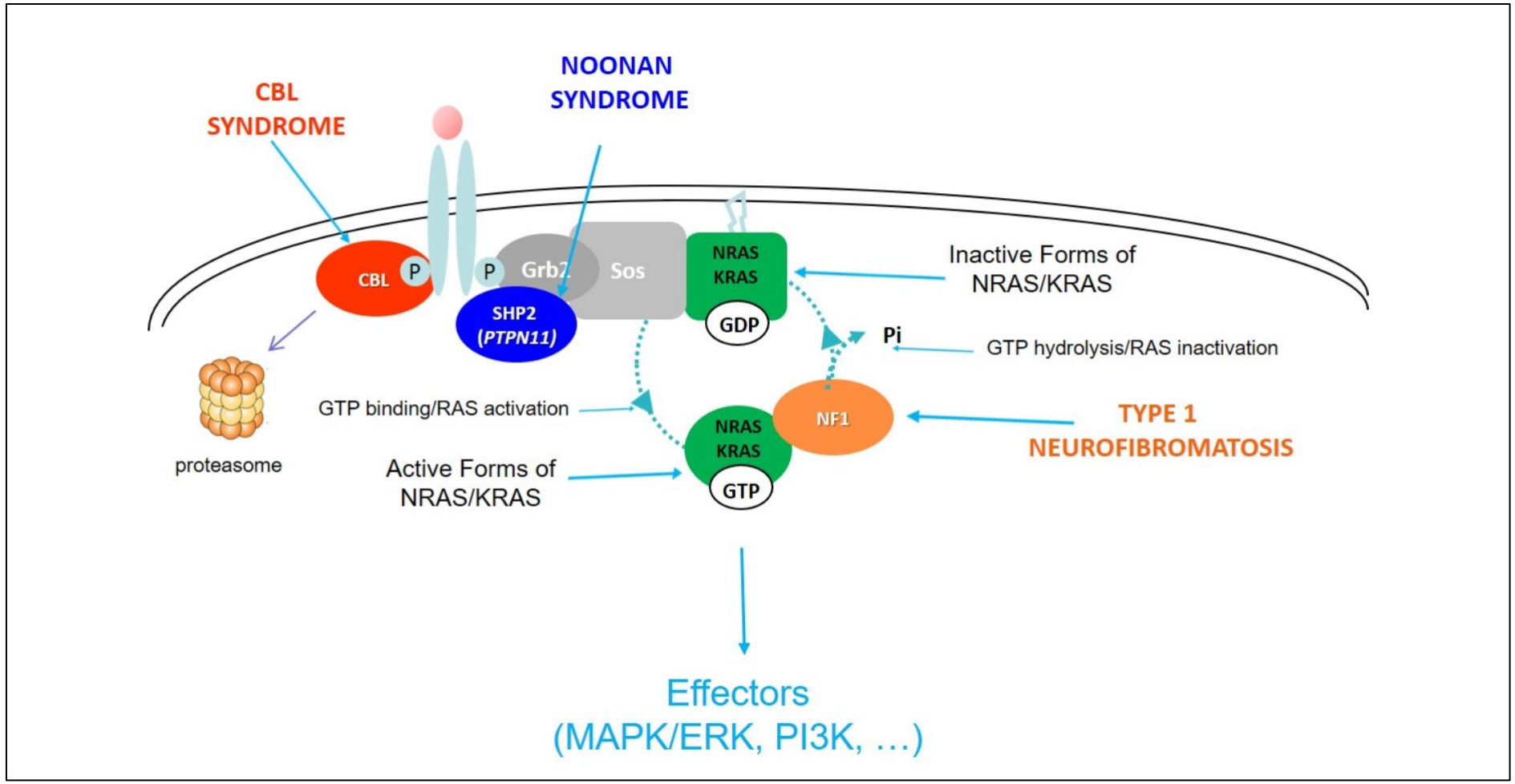
- PB monocyte count ≥ 1 × 10^9/L*
- Splenomegaly†
- Blast percentage in PB and BM < 20%
- Absence of *BCR::ABL1*

Genetic studies (1 finding required)

- Somatic mutation in *PTPN11* or *KRAS* or *NRAS* or *RRAS*
- Germline *NF1* mutation and LOH of *NF1* or clinical diagnosis of neurofibromatosis type
- Germline *CBL* mutation and LOH of *CBL*§

*This monocyte threshold is not reached in approximately 7% of cases.
†Splenomegaly is absent in 3% of cases at presentation.
‡Germline mutations (indicating Noonan syndrome) need to be excluded.
§Occasional cases with heterozygous splice site mutations.

BASIC RAS PATHWAY JMML



MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
aCML, *BCR::ABL1* negative	MDS/MPN with neutrophillia	aCML

ESSENTIAL
• PB leukocytosis ≥13 × 10^9/ L, with neutrophilia and ≥10% circulating immature myeloid cells (promyelocytes, myelocytes and metamyelocytes), as well as neutrophilic dysplasia. • Hypercellular BM with granulocytic predominance and granulocytic dysplasia, with or without dysplasia in the megakaryocytic and erythroid lineages. • <20% blasts in PB and BM. • Not meeting diagnostic criteria for MPN (specifically, exclusion of *BCR::ABL1* fusion)[1], myeloid neoplasms with eosinophilia and defining gene rearrangement, CMML, or MDS/MPN with *SF3B1* mutation and thrombocytosis.
DESIRABLE
• Detection of *SETBP1* and/or *ETNK1* mutations. • Absence of mutations in *JAK2, CALR, MPL*, and *CSF3R*.[2]

[1] The diagnosis of MDS/MPN-N requires exclusion of BCR::ABL1 fusion, which requires careful evaluation to exclude cryptic rearrangements and/or alternate BCR::ABL1 transcripts by available methodologies (e.g. cytogenetics, in situ hybridization, or PCR-based assays).
[2] Mutations in these genes are uncommon in MDS/MPN-N and should prompt morphologic review to exclude alternative diagnoses.

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
aCML, *BCR::ABL1* negative	MDS/MPN with neutrophillia	aCML

DIAGNOSTIC CRITERIA
• Leukocytosis ≥ 13 × 10^9/L, due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes and metamyelocytes), the latter constituting ≥ 10% of the leukocytes
• Cytopenia (thresholds same as for MDS)
• Blasts < 20% of the cells in blood and bone marrow
• Dysgranulopoiesis, including the presence of abnormal hyposegmented and/or hypersegmented neutrophils ± abnormal chromatin clumping
• No or minimal absolute monocytosis; monocytes constitute < 10% of the peripheral blood leukocytes
• No eosinophilia; eosinophils constitute < 10% of the peripheral blood leukocytes
• Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
• No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions. The absence of MPN-associated driver mutations and the presence of ***SETBP1*** mutations in association with *ASXL1* provide additional support for a diagnosis of aCML

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN): MAJOR CATEGORIES

HAEM 4R	HAEM 5	ICC 2022
-	MDS/MPN with thrombocytosis and *SF3B1* mutation	MDS/MPN with thrombocytosis and *SF3B1* mutation
MDS/MPN-RS-T	-	MDS/MPN-RS-T, NOS

Diagnostic criteria (counts/cytology):

- Anemia
- Dysplasia, especially dyserythropoiesis
- Thrombocytosis ≥ 450x10e9L
- Blasts <1% in PB and <5% in BM

SIGNIFICANT CHANGES:

- MDS/MPN-RS-T => **MDS/MPN with *SF3B1* and thrombocytosis** (WHO and ICC)
  - ⇒ ICC: RS not required, *SF3B1*≥10% VAF (isolated or with other abnormal cytogenetics and/or myeloid neoplasm associated mutation)
  - ⇒ WHO: ≥15% RS, no minimum VAF
- rare MDS/MPN-RS-T lacking *SF3B1* mutations
  - ⇒ **MDS/MPN-RS-T, NOS** (ICC): requires ≥15% RS
  - ⇒ MDS/MPN with *SF3B1* and thrombocytosis, if ≥15% RS (WHO)

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

WHO-HAEM4	International consensus classification (ICC)	WHO-HAEM5
Acute promyelocytic leukemia with *PML::RARA*	Acute promyelocytic leukemia with t(15;17)(q24.1;q21.2)/*PML::RARA)* (≥10% blasts)	Acute promyelocytic leukemia with *PML::RARA* fusion[a]
	APL with other *RARA* rearrangements[b] (≥ 10% blasts)	
AML with t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1*	AML with t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1)* (≥ 10% blasts)	AML with *RUNX1::RUNX1T1* fusion[a]
AML with inv(16)(p13.1q22) or t(16;16)(p13.1q22)/*CBFB::MYH11)*	AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11)* (≥ 10% blasts)	AML with *CBFB::MYH11* fusion[a]
AML with t(9;11) (p21.3;q23.3)/ MLLT3::*KMT2A*	AML with t(9;11) (p21.3;q23.3)/*MLLT3::KTM2A)* (≥ 10% blasts)	AML with *KMT2A* rearrangement[a]
	AML with other *KMT2A* rearrangements (≥ 10% blasts)[c]	AML with *KMT2A* rearrangements[a]
AML with t (6;9) (p23;q34.1)/*DEK::NUP214*	AML with t (6;9) (p22.3;q34.1)/*DEK::NUP214)* (≥ 10% blasts)	AML with *DEK::NUP214* fusion[a]
AML with inv(3)(q21.3q26.2) or t(3;3) (q21.3;q26.2)/*GATA2::MECOM(EVI1)*	AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM (EVI1)* (≥ 10% blasts)	AML with *MECOM* rearrangements[a]
	AML with other *MECOM* rearrangements (≥ 10% blasts)[d]	AML with *MECOM* rearrangements[a]
	AML with other rare recurring translocations (≥ 10% blasts), including *NUP98* rearrangement and *RBM15::MRTF1* fusion (Table S2)	AML with other defined genetic alterations (rare fusions)[a]
AML with t (9;22) (q34.1;q11.2)/BCR::ABL1	AML with t (9;22) (q34.1;q11.2)/ *BCR:: ABL1)* (≥ 20% blasts)	AML with *BCR::ABL1* fusion (≥ 20% blasts)
AML with mutated *NPM1*	AML with mutated *NPM1* (≥ 10% blasts)	AML with *NPM1* mutation[a]
AML with biallelic mutation of *CEBPA*	AML with in-frame bZIP *CEBPA* mutations (≥ 10% blasts)	AML with *CEBPA* mutation (≥ 20% blasts)
	AML with mutated *TP53*† (≥ 20% blasts)	
Not considered (AML with mutated *RUNX1*)	AML with myelodysplasia-related gene mutations (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *or ZRSR2*) (≥ 20% blasts)	AML, myelodysplasia-related (≥ 20% blasts)
AML with myelodysplasia-related changes (MRC)	AML with myelodysplasia-related cytogenetic abnormalities (≥ 20% blasts)[e]	AML, myelodysplasia-related (≥ 20% blasts)
AML not otherwise specified (NOS)	AML not otherwise specified (NOS)(≥ 20% blasts)	AML, defined by differentiation (≥20% blasts)[f]
Myeloid sarcoma	Myeloid sarcoma	Myeloid sarcoma

KEY CHANGES:
↑ genetic defined entities

Faline P. et al. 2023;98(3):481

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17) (q24.1;q21.2)/*PML::RARA*	≥10%	[illegible]	[illegible]
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
AML with other *MECOM* rearrangements			
AML with other rare recurring translocations	≥10%	AML with other defined genetic alterations	no threshold
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*		AML with *NPM1::MLF1*	
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*		AML with *KAT6A::CREBBP*	
AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBB*		AML with *MNX1::ETV6*	
AML with t(1;22)(p13.3;q13.1)/*RBM15::MRTF1*		AML with *FUS::ERG*	
AML with t(5;11)(q35.2;p15.4/*NUP98::NSD1*		AML with *RUNX1T3(CBFA2T3)::GLIS2*	
AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*			
AML with NUP98 and other partners			
AML with t(7;12)(q36.3;p13.2)/ETV6::MNX1			
AML with t(10;11)(p12.3;q14.2)/PICALM::MLLT10			
AML with t(16;21)(p11.2;q22.2)/FUS::ERG			
AML with t(16;21)(q24.3;q22.1)/RUNX1::CBFA2T3			
AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2*			
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*	≥20%	AML with *BCR:: ABL1* fusion	>20%
AML with mutated *NPM1*	≥10%	AML with *NPM1* mutation	no threshold
AML with in-frame bZIP *CEBPA* mutations	≥10%	AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations [§]	≥20%	**AML, myelodysplasia-related**	≥20%
AML with myelodysplasia-related cytogenetic abnormalities [#]			
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

KEY CHANGES:
Cut-off value for % of blasts

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17)(q24.1;q21.2)/*PML::RARA*	≥10%	Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
AML with other *MECOM* rearrangements			
AML with other rare recurring translocations	≥10%	AML with other defined genetic alterations	no threshold
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*		AML with *NPM1::MLF1*	
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*		AML with *KAT6A::CREBBP*	
AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBB*		AML with *MNX1::ETV6*	
AML with t(1;22)(p13.3;q13.1)/*RBM15::MRTF1*		AML with *FUS::ERG*	
AML with t(5;11)(q35.2;p15.4/*NUP98::NSD1*		AML with *RUNX1T3(CBFA2T3)::GLIS2*	
AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*			
AML with NUP98 and other partners			
AML with t(7;12)(q36.3;p13.2)/ETV6::MNX1			
AML with t(10;11)(p12.3;q14.2)/PICALM::MLLT10			
AML with t(16;21)(p11.2;q22.2)/FUS::ERG			
AML with t(16;21)(q24.3;q22.1)/RUNX1::CBFA2T3			
AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2*			
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*	≥20%	AML with *BCR:: ABL1* fusion	≥20%
AML with mutated *NPM1*	≥10%	AML with *NPM1* mutation	no threshold
AML with in-frame bZIP *CEBPA* mutations	≥10%	AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations §	≥20%	**AML, myelodysplasia-related**	≥20%
AML with myelodysplasia-related cytogenetic abnormalities #			
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

KEY CHANGES:
Cut-off value for % of blasts

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17) (q24.1;q21.2)/*PML::RARA*	≥10%	Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
AML with other *MECOM* rearrangements			
AML with other rare recurring translocations	≥10%	AML with other defined genetic alterations	no threshold
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*		AML with *NPM1::MLF1*	
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*		AML with *KAT6A::CREBBP*	
AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBB*		AML with *MNX1::ETV6*	
AML with t(1;22)(p13.3;q13.1)/*RBM15::MRTF1*		AML with *FUS::ERG*	
AML with t(5;11)(q35.2;p15.4/*NUP98::NSD1*		AML with *RUNX1T3(CBFA2T3)::GLIS2*	
AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A*			
AML with NUP98 and other partners			
AML with t(7;12)(q36.3;[illegible]			
AML with t(10;11)(p12.3[illegible]			
AML with t(16;21)(p11.2[illegible]			
AML with t(16;21)(q24.3[illegible]			
AML with inv(16)(p13.3[illegible]			
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*	[illegible]	[illegible]	≥20%
AML with mutated *NPM1*	≥10%	AML with *NPM1* mutation	no threshold
AML with in-frame bZIP *CEBPA* mutations	≥10%	AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations §	≥20%	**AML, myelodysplasia-related**	≥20%
AML with myelodysplasia-related cytogenetic abnormalities #			
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

WHO 4R: biallelic mutation
WHO 5: biallelic mutations in *CEBPA*, or a single mutation located in the bZIP region
ICC: no requirement of bilallelic mutation

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
		AML with defining genetic abnormalities	
		Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
		AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations § **AML with myelodysplasia-related cytogenetic abnormalities #**	≥20%	AML, myelodysplasia-related	≥20%
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

Diagnosis of AML-MR requires following 3 criteria:

- *≥ 20% blasts in blood or marrow*
- *Presence of at least one of the following:*
  - History of MDS or MDS/MPN
  - One or more cytogenetic or molecular abnormalities
- *Absence of the following:*
  - History of exposure to cytotoxic therapy
  - History of myeloproliferative neoplasm
  - Criteria for AML with defining genetic abnormalities
  - Criteria for myeloid neoplasms associated with germline predisposition

Defining cytogenetic abnormalities

- Complex karyotype (≥ 3 abnormalities)
- 5q deletion or loss of 5q due to unbalanced translocation
- -7, 7q deletion, or loss of 7q due to unbalanced translocation
- 11q deletion
- 12p deletion or loss of 12p due to unbalanced translocation
- Monosomy 13 or 13q deletion
- 17p deletion or loss of 17p due to unbalanced translocation
- Isochromosome 17q
- idic(X)(q13)

***Defining somatic mutations**: ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17) (q24.1;q21.2)/*PML::RARA*	≥10%	Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
		AML with other defined genetic alterations	no threshold
		AML with *NPM1::MLF1*	
		AML with *KAT6A::CREBBP*	
		AML with *MNX1::ETV6*	
		AML with *FUS::ERG*	
		AML with *BCR:: ABL1* fusion	≥20%
		AML with *NPM1* mutation	no threshold
		AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations §	≥20%	**AML, myelodysplasia-related**	≥20%
AML with myelodysplasia-related cytogenetic abnormalities #			
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

Cytogenetic abnormalities:

- complex karyotype
- del(5q)/t(5q)/add(5q)
- -7/del(7q)
- +8
- del(12p)/t(12p)/add(12p)
- i(17q)
- -17/add(17p) or del(17p),
- del(20q)
- idic(X)(q13)

Gene mutations:

ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2

AML with RUNX1 (provisional entity in WHO 4R)

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17) (q24.1;q21.2)/*PML::RARA*	≥10%	Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
AML with other *MECOM* rearrangements			
AML with other rare recurring translocations	≥10%	AML with other defined genetic alterations	no threshold
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*		AML with *NPM1::MLF1*	
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*		AML with *KAT6A::CREBBP*	
AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBB*		AML with *MNX1::ETV6*	
AML with t(1;22)(p13.3;q13.1)/*RBM15::MRTF1*		AML with *FUS::ERG*	
AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2*			
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*	≥20%	AML with *BCR:: ABL1* fusion	≥20%
AML with mutated *NPM1*	≥10%	AML with *NPM1* mutation	no threshold
AML with in-frame bZIP *CEBPA* mutations	≥10%	AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations §	≥20%	AML, myelodysplasia-related	≥20%
AML with myelodysplasia-related cytogenetic abnormalities #			
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

KEY CHANGES:

1) removal of morphology alone as a diagnostic premise
2) update of defining cytogenetic criteria
3) mutation-based definition

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelo			no threshold
Acute promyelo			
AML with t(8;2			no threshold
AML with inv(			no threshold
AML with t(9;1			no threshold
AML with othe			
AML with t (6;9			no threshold
AML with inv(3			no threshold
AML with othe			
AML with othe			no threshold
AML with t(			
AML with t(			
AML with t(			
AML with t(			
AML with t(			
AML with t			
AML with N			
AML with t			
AML with t			
AML with t			
AML with t			
AML with i			
AML with t(9;22)(q34.1;q11.2)/ *BCR::ABL1*	≥20%	AML with *BCR::ABL1* fusion	≥20%
AML with mutated *NPM1*	≥10%	AML with *NPM1* mutation	no threshold
AML with in-frame bZIP *CEBPA* mutations	≥10%	AML with *CEBPA* mutation	≥20%
AML with mutated *TP53* **	≥20%	-	
AML with myelodysplasia-related gene mutations § **AML with myelodysplasia-related cytogenetic abnormalities** #	≥20%	**AML, myelodysplasia-related**	≥20%
AML, not otherwise specified	≥20%	**AML, defined by differentiation**	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

International Consensus Classification (ICC)		2022 WHO Classification	
AML subtypes	*Blasts* *	*AML subtypes*	*Blasts* *
AML with recurrent genetic abnormalities		**AML with defining genetic abnormalities**	
Acute promyelocytic leukemia with t(15;17) (q24.1;q21.2)/*PML::RARA*	≥10%	Acute promyelocytic leukemia with *PML::RARA* fusion	no threshold
Acute promyelocytic leukemia with other *RARA* rearrangements			
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥10%	AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* fusion	no threshold
AML with inv(16)(p13.1;q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11*	≥10%	AML with *CBFB::MYH11* fusion	no threshold
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KTM2A*	≥10%	AML with *KTM2A* rearrangement	no threshold
AML with other *KMT2A* rearrangements			
AML with t (6;9)(p22.3;q34.1)/*DEK::NUP214*	≥10%	AML with *DEK::NUP214* fusion	no threshold
AML with inv(3)(q21.3q;26.2) or t(3;3)(q21.3;q26.2)/*GATA2::MECOM*	≥10%	AML with *MECOM* rearrangements	no threshold
AML with other *MECOM* rearrangements			
AML with other rare recurring translocations	≥10%	AML with other defined genetic alterations	no threshold
AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*		AML with *NPM1::MLF1*	
AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1*		AML with *KAT6A::CREBBP*	
AML with myelodysplasia-related cytogenetic abnormalities #			
AML, not otherwise specified	≥20%	AML, defined by differentiation	≥20%
Myeloid sarcoma	n.a	**Myeloid sarcoma**	n.a

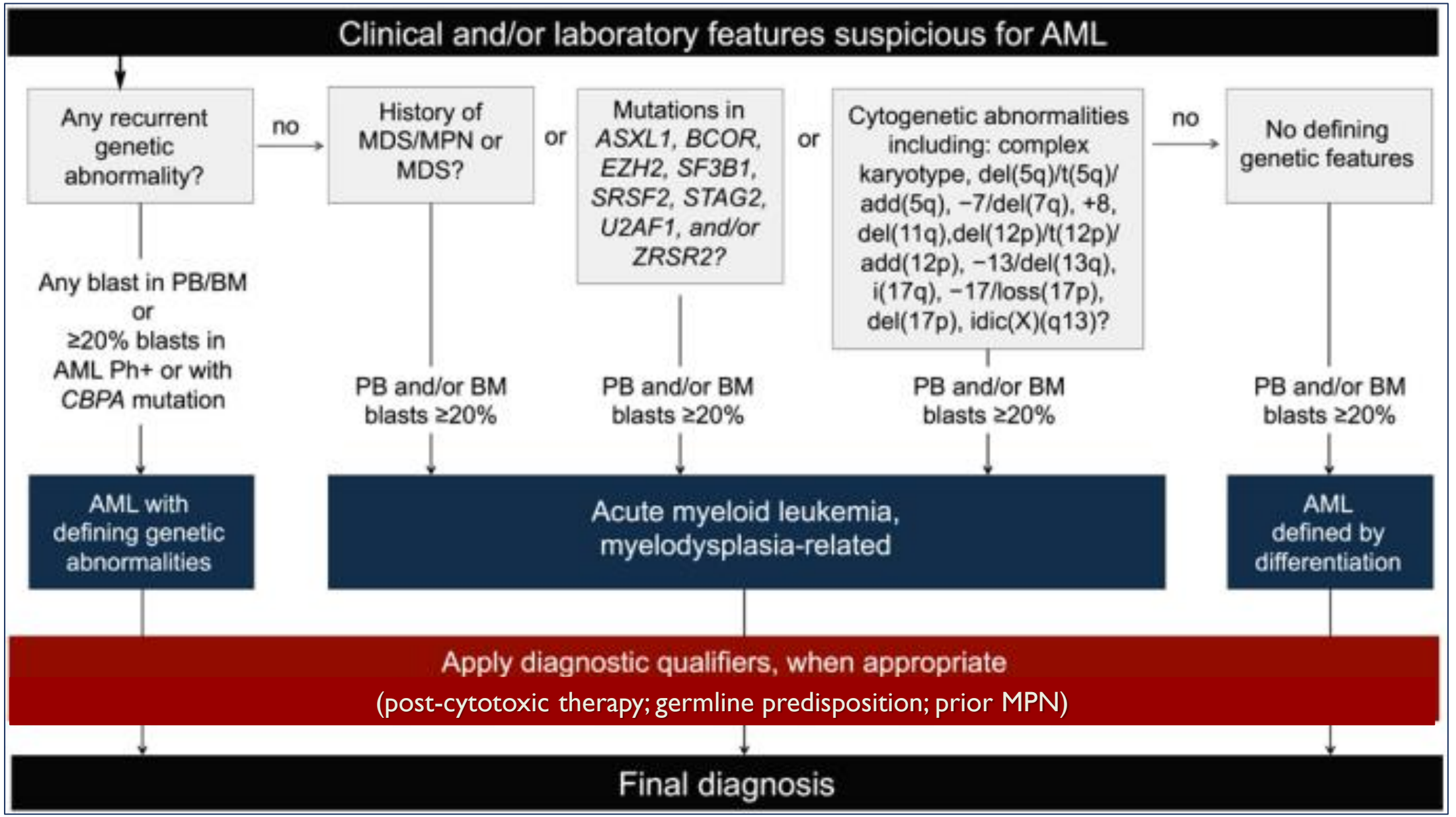
Previously used morphologic or cytochemical subtypes of AML, NOS : limited prognostic significance, but pathologists may continue to subclassify if desired.

Pure erythroid leukemia is typically associated with *TP53* mutations => *classified as "AML with TP53 mutations"*

Acute myeloid leukaemia, defined by differentiation

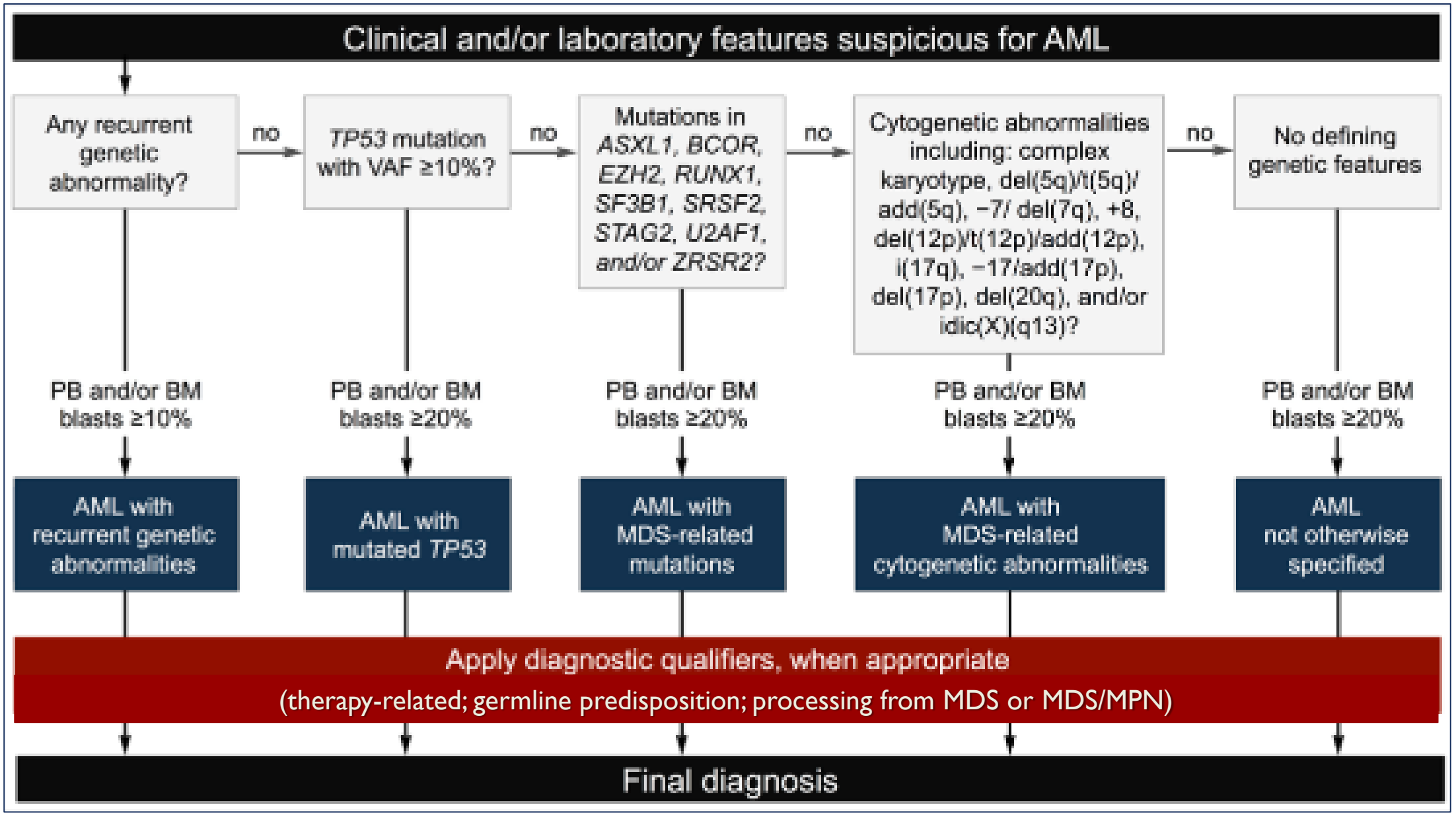
- Acute myeloid leukaemia with minimal differentiation
- Acute myeloid leukaemia without maturation
- Acute myeloid leukaemia with maturation
- Acute basophilic leukaemia
- Acute myelomonocytic leukaemia
- Acute monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryoblastic leukaemia

AML CLASSIFICATION DIAGNOSTIC FLOW-CHART: WHO 2022



Pizzi M. et al Hemato **2023**

AML CLASSIFICATION DIAGNOSTIC FLOW-CHART: ICC 2022



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CLASSIFICATION OF MDS

WHO-HAEM4	ICC	WHO-HAEM5
NA	Clonal cytopenia of undetermined significance (CCUS)	Clonal cytopenia of undetermined significance (CCUS)
MDS with ring sideroblasts	MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with isolated del(5q)	MDS with del(5q)	MDS with low blasts and isolated 5q deletion
NA	MDS with mutated *TP53*	MDS with biallelic *TP53* inactivation
NA	MDS, NOS without dysplasia	NA
MDS with single lineage dysplasia	MDS, NOS with single lineage dysplasia	Definition of lineage dysplasia, optional
MDS with multilineage dysplasia	MDS, NOS with multilineage dysplasia	D
	NA	M
	NA	M
MDS-EB-1 (5%–9% blasts)[a]	MDS with excess blasts (5%–9% blasts)[a]	MDS with increased blasts (MDS-IB1) (5%–9% blasts)[a]
MDS-EB-2 (10%–19% blasts)[a]	MDS/AML (10%–19% blasts)[a]	MDS with increased blasts (MDS-IB2) (10%–19% blasts)[a]
NA	MDS/AML with mutated *TP53*	NA
NA	MDS/AML with myelodysplasia-related mutations	NA
NA	MDS/AML with myelodysplasia-related cytogenetic abnormalities	NA
NA	MDS/AML NOS	NA
NA	NA	MDS with fibrosis

IMPORTANT CHANGES

WHO: MYELODYSPLASTIC NEOPLASM

Faline P. et al. 2023;98(3):481

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	MDS with low blasts and isolated 5q deletion
MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with mutated *TP53* [a]	MDS with biallelic *TP53* inactivation [a]
MDS not otherwise specified (MDS-NOS) [b] - MDS-NOS, with single lineage dysplasia - MDS-NOS, with multilineage dysplasia - MDS-NOS, without dysplasia [c]	MDS with low blasts [b] - with single lineage dysplasia (*optional*) - with multilineage dysplasia (*optional*)
-	MDS, hypoplastic [d]
MDS with excess blasts [e]	MDS with increased blasts 1 [e]
MDS/AML [f] - MDS/AML with MDS-related cytogenetic abnormalities - MDS/AML with MDS-related gene mutations - MDS/AML with mutated *TP53* - MDS/AML not otherwise specified	MDS with increased blasts 2 [f]
	MDS with increased blast and fibrosis [g]

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)
Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	MDS with low blasts and isolated 5q deletion
MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with mutated *TP53* [a]	MDS with biallelic *TP53* inactivation [a]
MDS not otherwise specified	
- MDS-NOS, with single	plasia (*optional*)
- MDS-NOS, with multil	lasia (*optional*)
- MDS-NOS, without dy	
-	MDS, hypoplastic [d]
MDS with excess blasts [e]	MDS with increased blasts 1 [e]
MDS/AML [f]	
- MDS/AML with MDS-related cytogenetic abnormalities	
- MDS/AML with MDS-related gene mutations	MDS with increased blasts 2 [f]
- MDS/AML with mutated *TP53*	
- MDS/AML not otherwise specified	
	MDS with increased blast and fibrosis [g]
Childhood MDS	
Childhood MDS with low blasts (cMDS-LB)	
Childhood MDS with increased blasts (cMDS-IB)	

MDS with defining genetic abnormalities

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	MDS with low blasts and isolated 5q deletion
MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with mutated *TP53* [a]	MDS with biallelic *TP53* inactivation [a]

MDS not otherwise specified

- MDS-NOS, with single
- MDS-NOS, with multil
- MDS-NOS, without dysplasia

plasia (*optional*)

lasia (*optional*)

MDS with defining genetic abnormalities

ESSENTIAL

- Anaemia, with or without other **cytopenias** (≥1) with or without thrombocytosis;
- **Dysplasia** (≥1 lineage) involving megakaryocytes, with or without dysplasia involving other lineages;
- **Blasts <5% in BM and <2% in PB**;
- Detection of **5q deletion**, isolated or with 1 other cytogenetic aberration other than -7 or del(7q);

- *Not fulfilling* diagnostic criteria of AML, MDS with biallelic *TP53* inactivation, MDS with increased blasts, or MDS/MPN.

- Presence of *SF3B1* or a *TP53* mutation (except multi-hit) does not per se override the diagnosis of MDS-5q.

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	MDS with low blasts and isolated 5q deletion
MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with mutated *TP53* [a]	MDS with biallelic *TP53* inactivation [a]
MDS not otherwise specified	
- MDS-NOS, with single	plasia (*optional*)
- MDS-NOS, with multil	lasia (*optional*)
- MDS-NOS, without dysplasia	

MDS with defining genetic abnormalities

ESSENTIAL

- **Cytopenia** in ≥ 1 lineage, <u>without thrombocytosis</u>;
- Erythroid lineage **dysplasia** (≥ 1 lineage);
- **Blasts <5% in BM and <2% in PB**;
- WHO:
  - ***SF3B1* mutation**. If *SF3B1* mutation analysis is not available, demonstration of RS ≥15%;
  - *Absence* of del(5q), -7/del(7q), or complex karyotype.
  - *Not fulfilling* diagnostic criteria of AML, MDS with low blasts and 5q deletion, MDS with biallelic *TP53* inactivation, MDS with increased blasts, or any MDS/MPN type.
- ICC:
  - ***SF3B1* mutation** (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
  - *Absence* of del(5q), -7/del(7q), abn3q26.2 or complex karyotype.

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	MDS with low blasts and isolated 5q deletion
MDS with mutated *SF3B1*	MDS with low blasts and *SF3B1* mutation
MDS with mutated *TP53* [a]	MDS with biallelic *TP53* inactivation [a]

MDS with defining genetic abnormalities

ESSENTIAL

- **Cytopenia**;
- **Dysplasia:** threshold set as 10% for all lineages;
- **Blast percentage:**
  - WHO: <20%
  - ICC: 0-9% in blood and bone marrow
- ***TP53* mutations**:
  - WHO: Detection of one or more *TP53* mutations. In the presence of one *TP53* mutation, evidence of *TP53* copy loss or copy neutral LOH.
  - ICC: multi-hit *TP53* mutation or *TP53* (VAF >10%) and complex karyotype, often with loss of 17p

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]
MDS, morphologically defined	
MDS not otherwise specified (MDS-NOS) [b] - MDS-NOS, with single lineage dysplasia - MDS-NOS, with multilineage dysplasia - MDS-NOS, without dysplasia [c]	MDS with low blasts [b] - with single lineage dysplasia (*optional*) - with multilineage dysplasia (*optional*)
-	MDS, hypoplastic [d]
MDS with excess blasts [e]	MDS with increased blasts 1 [e]
MDS/AML [f] - MDS/AML with MDS-related cytogenetic abnormalities - MDS/AML with MDS-related gene mutations - MDS/AML with mutated *TP53* - MDS/AML not otherwise specified	MDS with increased blasts 2 [f]
	MDS with increased blast and fibrosis [g]
	Childhood MDS *Childhood MDS with low blasts* (cMDS-LB) *Childhood MDS with increased blasts* (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]

MDS, morphologically defined

MDS hypoplastic:

Essential:

- Cytopenia ≥1 lineage;
- Hypocellular BM (assessed on a trephine core biopsy, adjusted for age of the patient) not explained by drug/toxin exposure or pertinent nutritional deficiency;
- Dysplasia in myeloid and/or MgK lineages;
- <5% blasts in BM and <2% blasts in PB
- Not meeting criteria for MDS with defining genetic abnormalities or MDS with increased blasts.

Desirable:

- Detection of clonal cytogenetic and/or molecular abnormality.

MDS with low blasts [b]
- with single lineage dysplasia (*optional*)
- with multilineage dysplasia (*optional*)

MDS, hypoplastic [d]

MDS with increased blasts 1 [e]

MDS with increased blasts 2 [f]

MDS with increased blast and fibrosis [g]

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]

MDS, morphologically defined

MDS not otherwise specified (MDS-NOS) [b]

- MDS-NOS, with single lineage dysplasia
- MDS-NOS, with multilineage dysplasia
- MDS-NOS, without dysplasia [c]

MDS with excess blasts [e]

MDS/AML [f]

- MDS/AML with MDS-related cytogenetic abnormalities
- MDS/AML with MDS-related gene mutations
- MDS/AML with mutated *TP53*
- MDS/AML not otherwise specified

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]
MDS, morphologically defined	
MDS not otherwise specified (MDS-NOS) [b]	
- MDS-NOS, with single lineage dysplasia	
- MDS-NOS, with multilineage dysplasia	
- MDS-NOS, without dysplasia [c]	
MDS with excess blasts [e]	
MDS/AML [f]	
- MDS/AML with MDS-related cytogenetic abnormalities	
- MDS/AML with MDS-related gene mutations	
- MDS/AML with mutated *TP53*	
- MDS/AML not otherwise specified	

- Blasts: <2% PB and <5% BM
- MDS-NOS, without dysplasia: -7/del(7q) or complex karyotype

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]

MDS, morphologically defined

MDS not otherwise specified (MDS-NOS) [b]
- MDS-NOS, with single lineage dysplasia
- MDS-NOS, with multilineage dysplasia
- MDS-NOS, without dysplasia [c]

- Blasts: <2% PB and <5% BM
- MDS-NOS, without dysplasia: -7/del(7q) or complex karyotype

MDS with excess blasts [e]

- Blasts: 2-9% in PB and 5-9% in BM

MDS/AML [f]
- MDS/AML with MDS-related cytogenetic abnormalities
- MDS/AML with MDS-related gene mutations
- MDS/AML with mutated *TP53*
- MDS/AML not otherwise specified

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS

International Consensus Classification (ICC) Criteria	2022 WHO Classification Criteria
MDS with del(5q)	lated 5q deletion
MDS with mutated *SF3B1*	*3B1* mutation
MDS with mutated *TP53* [a]	tivation [a]

MDS, morphologically defined

MDS not otherwise specified (MDS-NOS) [b]
- MDS-NOS, with single lineage dysplasia
- MDS-NOS, with multilineage dysplasia
- MDS-NOS, without dysplasia [c]

- Blasts: <2% PB and <5% BM
- MDS-NOS, without dysplasia: -7/del(7q) or complex karyotype

MDS with excess blasts [e]

- Blasts: 2-9% in PB and 5-9% in BM

MDS/AML [f]
- MDS/AML with MDS-related cytogenetic abnormalities
- MDS/AML with MDS-related gene mutations
- MDS/AML with mutated *TP53*
- MDS/AML not otherwise specified

- Blasts: 10-19% in PB or BM

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

CLASSIFICATION OF MDS: ICC 2022

International Consensus Classification (ICC) Criteria | **2022 WHO Classification Criteria**

ICC diagnostic criteria for RCC

1. Persistent cytopenia

Number of cytopenias (1-3). Cytopenia is defined according to age-adjusted values for hemoglobin, absolute neutrophil count, and platelets

2. Manifestation of dysplasia

Dysplastic changes in at least 2 lineages or in ≥10% in 1 lineage

Typical dysplastic features of RCC (not all are required)

Specimen	Cellularity	Erythropoiesis	Granulopoiesis	Megakaryopoiesis*
Bone marrow aspirate		Nuclear budding Multinuclearity Megaloblastoid changes	Pseudo–Pelger-Huët cells Hypo- or agranularity	Separated nuclear lobes Round monolobated nucleus Micromegakaryocytes
Bone marrow biopsy	Patchy pattern in otherwise hypocellular marrow or rarely diffuse pattern in normo- or hypercellular marrow†	Patchy (few multifocal clusters or unifocal cluster) Left-shift Increased mitosis	Marked decrease	Marked decrease or aplasia Round monolobated nucleus Separated nuclear lobes Micromegakaryocytes

*Immunohistochemistry for megakaryocyte markers is required.

†Normo- or hypocellular RCC requires significant dysplasia in megakaryocytes (>30%).

3. Other required criteria

Blast percentage in peripheral blood <2% and bone marrow <5%

No prior cytotoxic chemotherapy or radiation therapy

No fibrosis

In ICC 2022: RCC in new section of pediatric disorders

Childhood MDS

Childhood MDS with low blasts (cMDS-LB)

Childhood MDS with increased blasts (cMDS-IB)

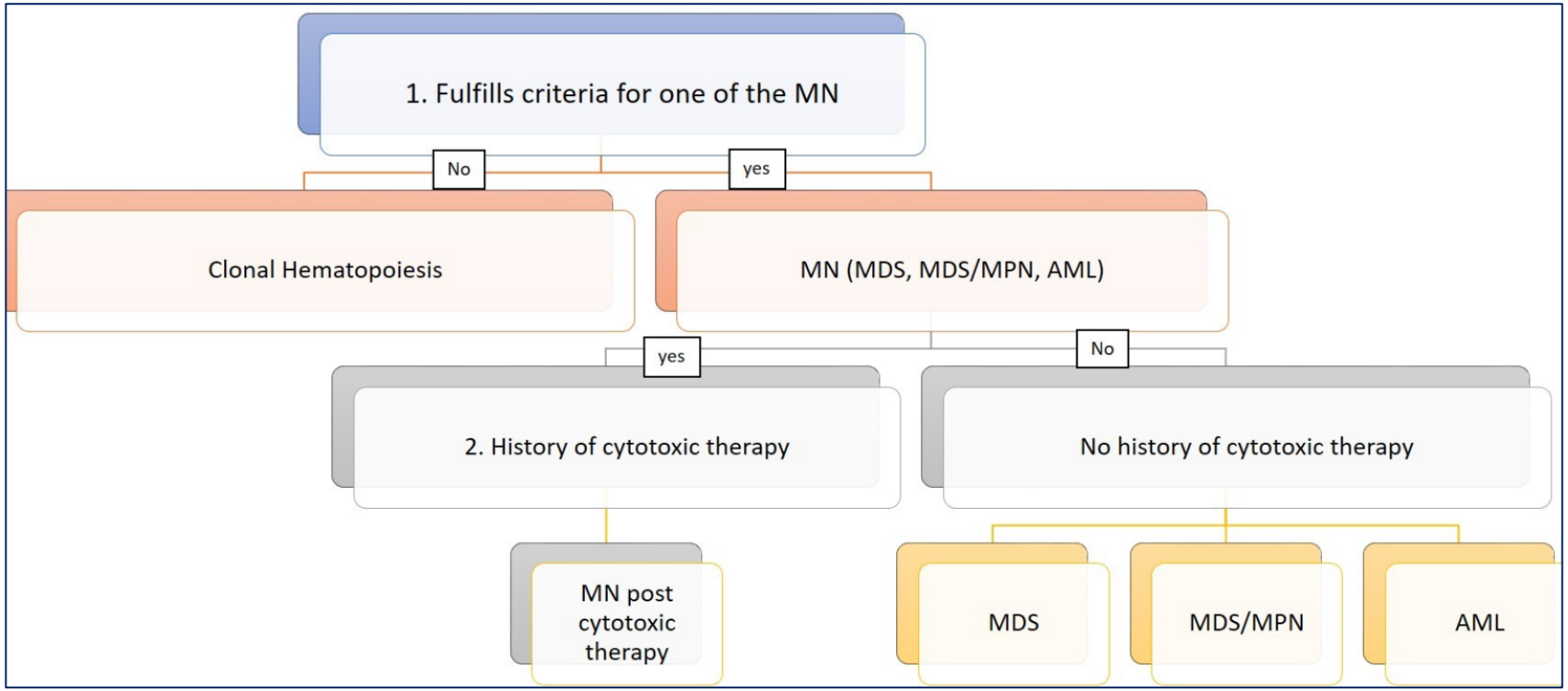
BLAST COUNTS IN MDS AND AML

- HAEM 4R: a 20% blast cut-off has been used
  - Exceptions for (t15;17), t(8;21) and inv(16)/t(16;16)
- Blast quantification can vary between : interobserver variability, blast/blast equivalents
- Blast cut-off is somewhat arbitrary, and the disease lie on a continuum
- May be influenced by sampling
- Newer therapies and clinical trials have shown to have efficacy in patients with 10-30% blasts

WHO HAEM 5 maintains a 20% cut-off between MDS and AML, BUT removes cut-off from most genetically defined AML

ICC 2022 favors having 10-19% blasts being diagnosed as MDS/AML, to reflecting the spectrum between AML and MDS

CLASSIFICATION SCHEMA FOR MN-pCT: WHO 2022



History of Cytotoxic therapy (cytotoxic agents listed below)

- **Alkylating agents** (Melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, procarbazine, carmustine, mitomycin C, thiotepa, lomustine)
- **Ionizing radiation therapy** (Large fields containing active bone marrow)
- **Topoisomerase II inhibitors** (Etoposide, teniposide, doxorubicin, daunorubicin, mitoxantrone, amsacrine, actinomycin)
- **Others**
  - Antimetabolites: thiopurines, mycophenolate mofetil, fludarabine
  - Antitubulin agents (usually in combination with other agents): vincristine, vinblastine, vindesine, paclitaxel, docetaxel
  - PARP1 inhibitors

Subtype(s)

- MDS, post cytotoxic therapy
- MDS/MPN, post cytotoxic therapy
- AML, post cytotoxic therapy

(WHO 4R: therapy-related MN)

https://tumourclassification.iarc.who.int/home

CLONAL HAEMATOPOIESIS

Both classifications now include clonal haematopoiesis

WHO HAEM 5

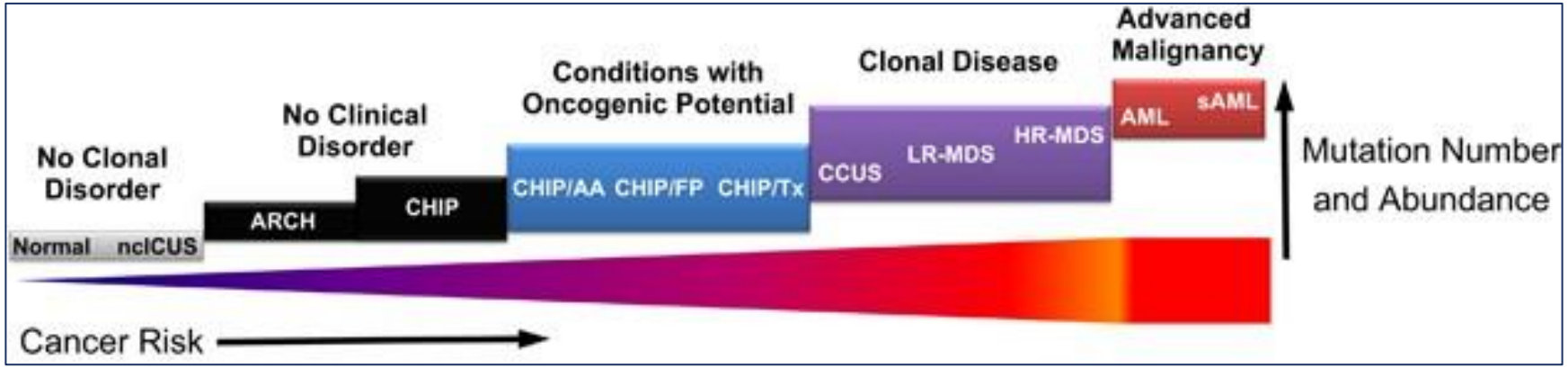
2. Myeloid proliferations and neoplasms

Myeloid precursor lesions
Clonal Haematopoiesis
Introduction
Clonal haematopoiesis
Clonal cytopenias of undetermined significance

ICC 2022

Premalignant clonal cytopenias and MDSs

Clonal cytopenia of undetermined significance (CCUS) and other pre-malignant clonal cytopenias



Bejar R, Leukemia, 2017

CLONAL HAEMATOPOIESIS

Idiopathic Cytopenia of Undetermined Significance (ICUS)	Clonal Hematopoiesis of Indeterminate Potential (CHIP)	Clonal Cytopenia of Undetermined Significance (CCUS)	MDS/AML
Cytopenia: Yes	Cytopenia: No	Cytopenia: Yes (≥4 months)	Cytopenia: Yes
Dysplasia: No/≤10	Dysplasia: No/≤10	Dysplasia: No/≤10	Dysplasia: Yes/≥10%
Mutations: No	Mutations: Yes	Mutations: Yes	Mutations: Yes
VAF: N/A	VAF: ≥2%	VAF: ≥2%	VAF: ?

Hb <13 g/dl (M) and <12 g/dL (F), ANC <1,8x10^9/L, PLT <150x 10^9/L

TET2, DNMT3A, ASXL1, SRSF2, ZRSR2, SF3B1, U2AF1, IDH1/2, RUNX1, EZH2, JAK2, CBL, KRAS, CUX1, TP53