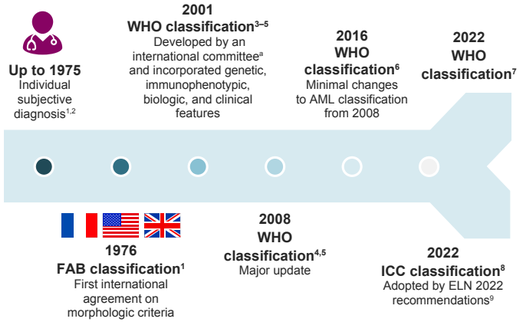
How has the classification of acute myeloid leukemia (AML) evolved?

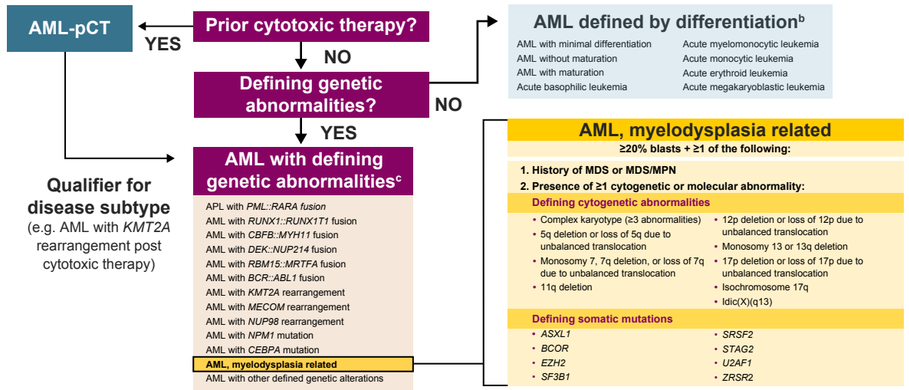
In 2022, the WHO 2016 classification of myeloid neoplasms and acute leukemias was replaced by 2 different international classifications



Categories of AML defined in the 2022 classifications evolved in several ways to reflect improved understanding of the molecular pathogenesis of AML[7,8]

- Changes in the blast count threshold used to define AML
- Alterations in qualifying criteria for certain categories
- Introduction of new categories and elimination of others
- Requirements for additional workup (diagnostic qualifiers)

The WHO 2022 classification of AML[7]



Major changes in the WHO 2022 classification of AML[7]

Blast cutoffs have been eliminated for most AML types with defining genetic alterations[d]

- 20% blast cutoff retained to delineate MDS from AML in cases without defining genetic alterations
- MDS-IB2 may be regarded as AML equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate

AML is now broadly separated into 2 main groups, each with multiple subsections (AML-NOS eliminated as a category)

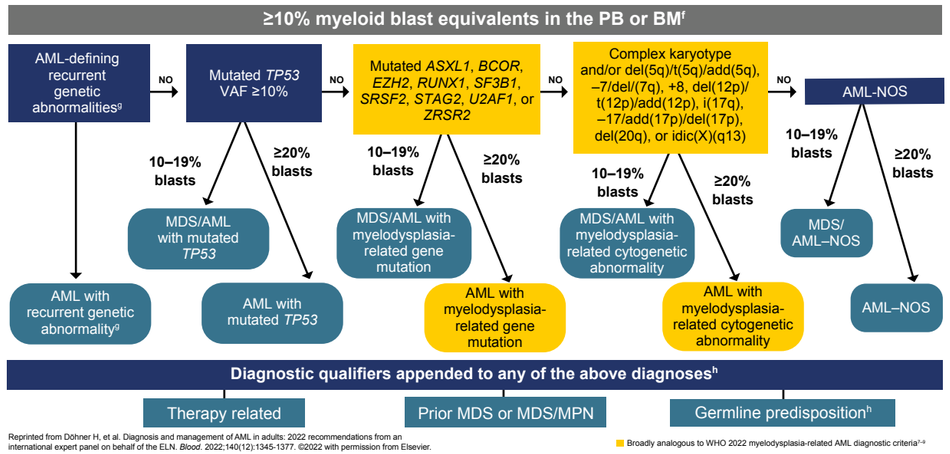
- AML with defining genetic abnormalities (no 20% blast requirement, except for *CEBPA* mutation, *BCR::ABL1*, and AML-MR)
- AML defined by differentiation (≥20% blasts)

Several of the main groups from WHO 2016[6] are now removed or altered[7]

- AML-MRC is replaced by AML-MR and included under "AML with defining genetic abnormalities"
- t-AML is no longer considered a distinct disease entity; t-AML is replaced by "MN-pCT" and used to qualify diagnoses according to relevant myeloid disease type (e.g. AML with *KMT2A* rearrangement post cytotoxic therapy)
- AML with rare fusions is incorporated as subtypes under "AML with other defined genetic alterations"
- AML with somatic *RUNX1* mutation has been removed

AML with *TP53* mutation is not considered a distinct entity[7] (no change from WHO 2016[6] but differs from ICC 2022[8])

The ICC 2022 classification of AML[8,9,e]



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Broadly analogous to WHO 2022 myelodysplasia-related AML diagnostic criteria[7–9]

Major changes in the ICC 2022 classification of AML[8]

Changes with regard to the blast thresholds defining AML

- AML with recurrent genetic abnormalities requires ≥10% blasts
- Other categories: Cases with 10%–19% blasts now designated "MDS/AML" (MDS-EB2 now eliminated); cases with ≥20% blasts are designated "AML"; the term "MDS/AML" better reflects the genetic and clinical continuum of cases

Introduction of new genetically defined entities

- AML with mutated *TP53*
- AML with myelodysplasia-related gene mutations (strongly associated with secondary AML arising from prior myeloid neoplasia)

Retained category

- AML with myelodysplasia-related cytogenetic abnormalities (minor changes made)

Antecedent AML history

- The classification now describes prior MDS or MDS/MPN and prior therapy (chemotherapy, radiotherapy, immune interventions) as "qualifiers" to the diagnosis, rather than as separate categories
- As a consequence of the new genetically defined entities and progression from MDS or MDS/MPN becoming diagnostic qualifiers, the category AML-MRC was eliminated

Key differences between the WHO 2016, WHO 2022, and ICC 2022 classifications of AML

	WHO 2016[6]	WHO 2022[7]	ICC 2022[8,9]
20% blast threshold	✓ ≥20% PB or BM blasts define AML	✗ ≥20% blasts define AML for ✓ the following only: *CEBPA* mutation, *BCR::ABL1*, **AML-MR**	✗ ≥20% blasts for AML with *BCR::ABL1* ≥10% for other subtypes (AML or MDS/AML)
Therapy-related myeloid neoplasms (including t-AML)	✓ Distinct entity	○ Diagnostic qualifier (diagnostic workup required)	○ Diagnostic qualifier (diagnostic workup required)
AML with multilineage dysplasia	✓ Criterion for AML-MRC *Requires exclusion of recurrent genetic abnormalities, NPM1 mutation, and biCEBPA. Presence of an MDS-related cytogenetic abnormality with the exception of del(9q)*	✗ Not included	✗ Not included
History of MDS or MDS/MPN	✓ Criterion for AML-MRC *Requires exclusion of recurrent genetic abnormalities, NPM1 mutation, and biCEBPA*	✓ Criterion for AML-MR	○ Diagnostic qualifier (diagnostic workup required)
Complex karyotype	✓ ≥3 cytogenetic abnormalities *Sufficient to diagnose AML-MRC when ≥20% PB or BM blasts are present and prior therapy has been excluded*	✓ ≥3 cytogenetic abnormalities *For defining AML-MR*	✓ ≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining, recurring genetic abnormalities *AML with myelodysplasia-related cytogenetic abnormalities 10%–19% (MDS/AML) and ≥20% (AML)*
Secondary AML-type genetic mutations	✗ Not included	✓ Criterion for AML-MR ***8 genes:*** *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*	✓ Criterion for AML with myelodysplasia-related gene mutations[8,9] ***9 genes:*** *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2. Requires exclusion of recurrent genetic abnormalities (including NPM1 mutation, in-frame CEBPA mutation) and TP53 mutation*
Myelodysplasia-related cytogenetic abnormalities	✓ Criterion for AML-MRC *Requires exclusion of recurrent genetic abnormalities, NPM1 mutation, and biCEBPA. Presence of an MDS-related cytogenetic abnormality with the exception of del(9q)*	✓ Criterion for AML-MR	✓ Criterion for AML with myelodysplasia-related cytogenetic abnormalities[8,9] *Requires exclusion of recurrent genetic abnormalities (including NPM1 mutation, in-frame CEBPA mutation) TP53 mutation, and myelodysplasia-related gene mutations*
AML with *TP53* mutation	✗ No distinct entity	✗ No distinct entity	✓ Distinct entity[8]

References: 1. Bennet JM, et al. *Br J Haematol*. 1976;33(4):451-458. **2.** Harris NL, et al. *J Clin Oncol*. 1999;17(12):3835-3849. **3.** Vardiman JW, et al. *Blood*. 2002;100(7):2292-2302. **4.** Swerdlow SH, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. International Agency for Research on Cancer; 2008. **5.** Arber DA, et al. *Am J Hematol*. 2022;97(5):514-518. **6.** Arber DA, et al. *Blood*. 2016;127(20):2391-2405. **7.** Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. **8.** Arber DA, et al. *Blood*. 2022;140(11):1200-1228. **9.** Döhner H, et al. *Blood*. 2022;140(12):1345-1377.

Abbreviations: AML, acute myeloid leukemia; AML-MR, acute myeloid leukemia, myelodysplasia related; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; AML-pCT, acute myeloid leukemia post cytotoxic therapy; APL, acute promyelocytic leukemia; bi, biallelic; BM, bone marrow; bZIP, basic leucine zipper domain; CML, chronic myeloid leukemia; ELN, European LeukemiaNet; FAB, French-American-British; ICC, International Consensus Classification; MDS, myelodysplastic syndrome; MDS-EB2, myelodysplastic syndrome with excess blasts; MDS-IB2, myelodysplastic syndrome with increased blasts; MN-pCT, myeloid neoplasm (MDS, MDS/MPN, and AML) post cytotoxic therapy; MPAL, mixed-phenotype acute leukemia; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; PB, peripheral blood; t-AML, therapy-related acute myeloid leukemia; VAF, variant allele frequency; WHO, World Health Organization.

Footnotes: [a]Comprising leading international pathologists, oncologists, hematologists, and geneticists.[5] [b]Shared diagnostic criteria include: (1) ≥20% blasts required (except for acute erythroid leukemia); (2) must not meet criteria for MPAL (relevant for AML with minimal differentiation); (3) must not meet diagnostic criteria for MN-pCT; and (4) no prior history of MPN. Note that the diagnosis of acute erythroid leukemia supersedes AML-MR. [c]AML with *BCR::ABL1*, AML with *CEBPA* mutation, and AML-MR are the only types that require ≥20% blasts for diagnosis; the definition of AML with *CEBPA* mutation includes biallelic mutation (bi*CEBPA*) and single mutations in the bZIP region (smbZIP-*CEBPA*); AML with somatic *RUNX1* mutation is not recognized as a distinct disease type due to lack of sufficient unifying characteristics. [d]Blast cutoff removal will require a correlation between morphologic changes and molecular genetic findings to ensure that the defining abnormality is driving the disease pathology. [e]The classification is hierarchical (i.e. AML with recurrent genetic abnormalities takes precedence over all other categories); among the remaining categories, AML with *TP53* mutation supersedes AML with myelodysplasia-related gene mutations, and the latter supersedes AML with myelodysplasia-related cytogenetic abnormalities. [f]Myeloblasts, monoblasts, and megakaryoblasts are included in the blast count. Monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents in AML with monocytic or myelomonocytic differentiation, as well as promyelocytes in the setting of *PML::RARA* or variant *RARA* rearrangement. Cases with prior diagnosis of MPN are excluded and are classified as in the accelerated phase (10%–19% blasts) or blast phase (≥20% blasts) MNP. For patients who already have a history of MDS/MPN (e.g. chronic myelomonocytic leukemia), the diagnosis of MDS/MPN should be retained until there are ≥20% blasts/blast equivalents; however, once an AML-defining recurrent genetic abnormality (e.g. *KMT2A* rearrangement or *NPM1* mutation) is detected and the blast count is ≥10%, AML-type therapy is recommended. [g]AML-defining recurrent genetic abnormalities are t(15;17)(q24.1;q21.2)/*PML::RARA*; t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*; inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*; t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*; t(6;9)(p22.3;q34.1)/*DEK::NUP214*; inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*; *NPM1* mutation; in-frame bZIP-*CEBPA* mutation; t(9;22)(q34.1;q11.2)/*BCR::ABL1*; other recurrent rearrangements involving *RARA*, *KMT2A*, *MECOM*, as well as other rare rearrangements as listed in Table 1 of Döhner H, et al.[9] The entity is named with the specific genetic abnormality. Cases with *BCR::ABL1* rearrangement and 10%–19% blasts are classified as CML in accelerated phase, and cases with history of CML and ≥20% blasts are classified as CML in myeloid blast phase. [h]Examples of how to append diagnostic qualifiers: AML with myelodysplasia-related cytogenetic abnormality, therapy related; AML with myelodysplasia-related gene mutation, prior MDS; AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation (i.e. gene or syndrome should be specified).

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