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Review Articles

AML, Myelodysplasia-Related: Beyond Classification—Toward Precision Decision-Making

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Abstract. Acute myeloid leukemia, myelodysplasia-related (AML-MR), represents a genetically defined and clinically heterogeneous entity characterized by myelodysplasia-related gene (MRG) mutations, specific cytogenetic abnormalities, and frequently a previous history of myelodysplastic syndromes (MDS) or MDS/myeloproliferative neoplasm (MDS-MPN). The transition from the World Health Organization (WHO) 2016 classification to the 2022 WHO and International Consensus Classification (ICC) systems reflects a paradigm shift from morphology-based definitions toward genomics-driven disease entities. However, while diagnostic precision has improved, translation of these classifications into clinically actionable strategies remains incomplete. This review critically examines the biological and prognostic implications of MRG mutations, their interaction with key molecular subgroups such as *NPM1*- and *FLT3*-mutated AML, and their impact on therapeutic decision-making. We highlight unresolved issues, including the context-dependent prognostic value of MRG mutations, limitations of static risk stratification, and the need to integrate measurable residual disease (MRD), genomics, and patient fitness into therapeutic algorithms. At the clinical level, many studies have explored the sensitivity of AML-MR to various induction treatments in both younger and older AML patients, with significant improvements in survival. The main objective of these different induction therapy strategies is to achieve a complete remission with minimal toxicity, particularly in older patients, allowing patients to proceed to allogeneic hematopoietic stem cell transplantation, the only curative option so far.

Keywords: AML MDS-related; MDS/AML; WHO5; ICC; MRG Mutations; TP53.

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Introduction. The World Health Organization (WHO) classification of myeloid neoplasms has been revised several times to provide a progressively more accurate understanding of the cellular and molecular features underlying these tumors. Advances in techniques for exploring the human genome have enabled more precise characterization of the molecular abnormalities in myeloid neoplasms. These studies have revealed the extensive molecular heterogeneity of acute myeloid leukemia (AML), enabling classification into molecular subtypes distinguished by genetic alterations, prognosis, and therapeutic response. The widespread adoption of

gene analysis techniques, such as next-generation sequencing, has enabled the incorporation of genetic information into the diagnostic criteria for AML. Several recent studies have provided detailed analyses of the genetic abnormalities occurring in AML and a comprehensive census of the genes altered by structural changes or mutational events in AML.[1-3]

The new Classifications. The AML with myelodysplasia-related change (AML-MRC) in the 2016 WHO classification was based on a history of MDS or MDS/myeloproliferative neoplasms; morphologic dysplasia in >50% of cells in at least two lineages; and the presence of MDS-defining cytogenetic abnormalities.[4] Recent classifications have introduced new criteria for diagnosing AML with myelodysplasia-related changes (MRC), renaming it AML-MR (**Table1, 2** and **Figure 1**).

Diagnostic Evolution: Progress and Remaining Gaps. The redefinition of AML-MR in the WHO 2022 and ICC 2022 classifications represents a major conceptual advance. In contrast to WHO 2016, which relied heavily on morphological dysplasia, clinical history, and MDS-

Table 1. The table compares the main diagnostic changes between WHO 2016, WHO 2022, and ICC 2022.

Feature	WHO 2016	WHO 2022	ICC 2022
Terminology	AML with myelodysplasia-related changes (AML-MRC)	AML, myelodysplasia-related (AML-MR)	MDS/AML (AML-MR)
Role of morphology	Central criterion; dysplasia in ≥50% of cells in ≥2 lineages	Removed as a sole diagnostic criterion	Not sufficient as a standalone criterion
Clinical history	Prior MDS or MDS-MPN included	Prior MDS/MDS-MPN, included in diagnosis, but not essential for diagnosis in presence of MRG mutations/or Cytogenetics	Not relevant for diagnosis
Cytogenetics	MDS-related cytogenetic abnormalities define AML-MRC	MDS-related cytogenetic abnormalities remain relevant	MDS-related cytogenetic abnormalities remain relevant
Molecular genetics	Not part of the core definition	MRG mutations included as a diagnostic criterion	MRG mutations included RUNX1 also; TP53 mutated unique form
Blast threshold	Usually ≥20% blasts	Usually ≥20% blasts, with genetically defined exceptions	Introduces MDS/AML category for 10–19% blasts
Conceptual advance	Morphology- and history-based entity	Genomics-driven definition	Genomics-driven definition plus MDS/AML continuum

The WHO classification (2022 WHO) and the International Consensus Classification (ICC) of myeloid neoplasms were published in 2022 (**Tables 1, 2**). The two classifications renamed myelodysplastic syndromes as myelodysplastic neoplasms, prioritized genetic lesions, and recognized the limited reproducibility of morphology alone. Both confirmed the blast threshold for defining AML (>20% blasts); ICC introduced the range 10- 20% blasts to identify the MDS/AML subsection.[5,6]

Table 2. A WHO 5 Classification for AML-MR (Leukemia 2022); **B** International Consensus Classification of Acute Myeloid Leukemia and MDS/AML (Blood 2022).

A

Cytogenetic and molecular abnormalities defining acute myeloid leukaemia, myelodysplasia-related. WHO 5, Leukemia 2022

Defining cytogenetic abnormalities:

- Complex karyotype (≥3 abnormalities)
- 5q deletion or loss of 5q due to unbalanced translocation
- Monosomy 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, SF3B,1 SRSF2, STAG2, U2AF, ZRSR2.

B

ICC Classification of MDS/AML and AML MDS related. Blood 2022, (ref. 6)

- AML and MDS/AML with mutated TP53† 10-19% (MDS/AML) and ≥20% (AML)
- AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥20% (AML)
- Defined by mutations in ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,or ZRSR2
- AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥20% (AML)
- Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8,del(12p)/add(12p, i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(XXq13) clonal abnormalities
- AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥ 20% (AML)

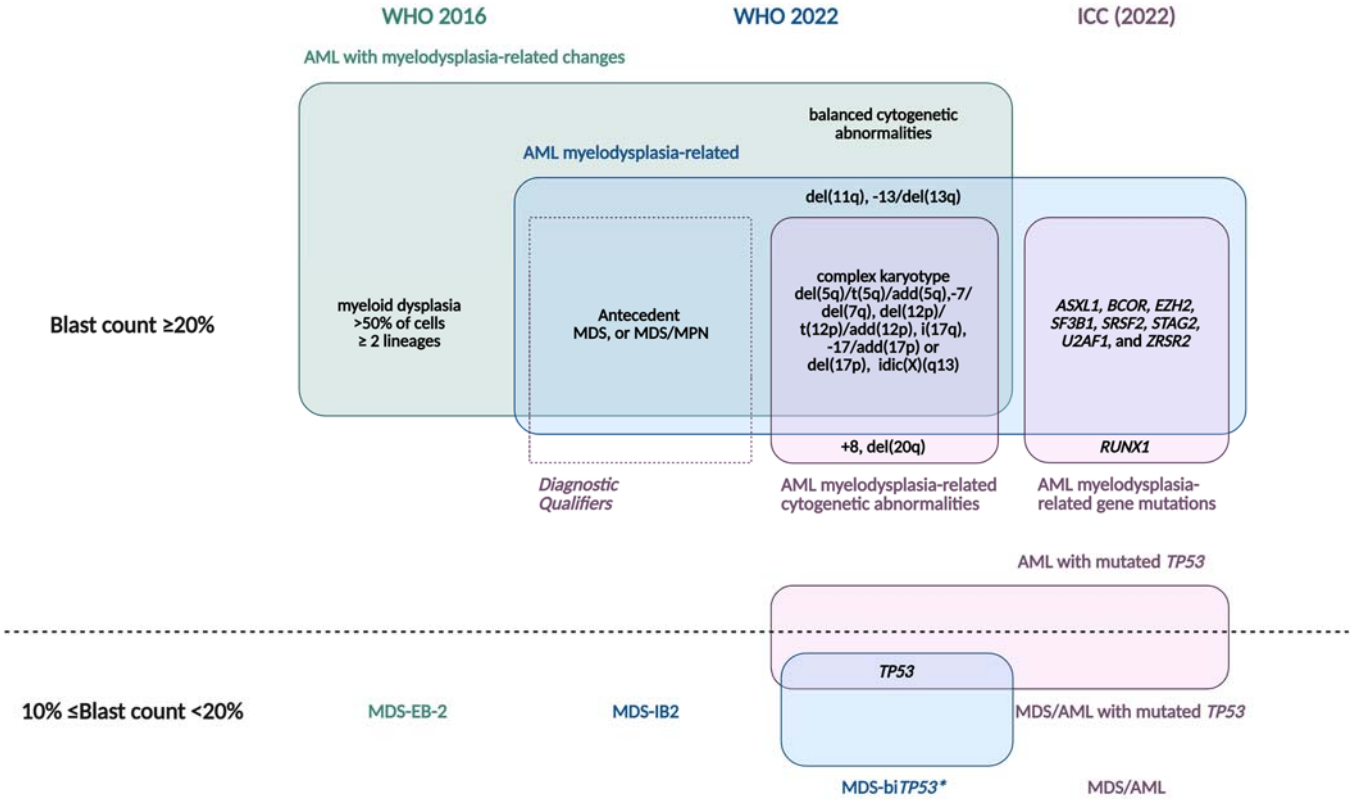

Figure 1. Diagnostic evolution: progress and remaining gaps: Evolution of the classification of myelodysplasia-related acute myeloid leukemia from 2016 to 2022. Schematic comparison of the criteria defining myelodysplasia-related AML across the WHO 2016 (in green), WHO 2022 (in blue), and ICC (in red) frameworks, based on blast count and genetic characteristics. Diagnostic subcategories are color-coded, while genetic characteristics are black-coded.

related cytogenetic abnormalities, the newer systems prioritize genetic lesions and recognize the limited reproducibility of morphology alone. The evolving diagnostic framework of AML-MR is summarized in **Table 1** and **Figure 1, 2**, highlighting the transition from morphology-based to genomics-driven classifications.[4–6] Morphologic dysplasia alone was excluded from the diagnostic criteria, while mutations in at least one of these myelodysplasia-related genes (*ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1,* and *ZSZR2*) were included.[5,6] In the 2022 ICC guidelines, one additional myelodysplasia-related gene was added, *RUNX1* (**Table 2A**, **Tables 2B**, **Figures 1** and **2**).[6]

The definition of AML/MDS-related from the original paper of Khoury et al.[6] says: The AML-MRR type is defined as a neoplasm with ≥20% blasts expressing a myeloid immunophenotype and harboring specific cytogenetic and molecular abnormalities associated with MDS, arising de novo or following a known history of MDS or MDS/MPN. Key changes include: (1) removal of morphology alone as a diagnostic criterion to make a diagnosis of AML-MR; (2) update of defining cytogenetic criteria; and, (3) introduction of a mutation-based definition based on a set of 8 genes – SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2, > 95% of which are present specifically in AML arising post MDS or MDS/MPN. The presence of one or more cytogenetic or molecular abnormalities listed in **Table 2** and/or history of MDS or MDS/MPN are required for diagnosing AML-MR. That means that MDS-related AML includes:

- AML with qualifying MR gene mutation(s), one or more of the eight WHO MR genes.
- AML with qualifying MR cytogenetic abnormality(ies).
- AML arising in a patient with a documented previous MDS or MDS/MPN, even if the AML does not carry one of the eight MR mutations or qualifying MR cytogenetic abnormalities. In contrast, ICC 2022 does not use a previous history of MDS or MDS/MPN alone to define an AML category. WHO 2022 uses a single umbrella category, AML-MR, encompassing qualifying MR gene mutations and MR cytogenetic abnormalities. ICC 2022 divides this biology into separate hierarchical entities, including AML with mutated TP53, AML with MR gene mutations, and AML with MR cytogenetic abnormalities. ICC also adds RUNX1 to the MR gene list.[5,6]

These revisions were largely driven by the seminal work of Lindsley et al., who demonstrated that mutations in a defined set of myelodysplasia-related genes were highly enriched in AML arising from antecedent MDS or following chemo/radiotherapy, identifying an MDS-related genetic signature in approximately 95% of such cases. The ICC adopts the same MDS gene mutations as

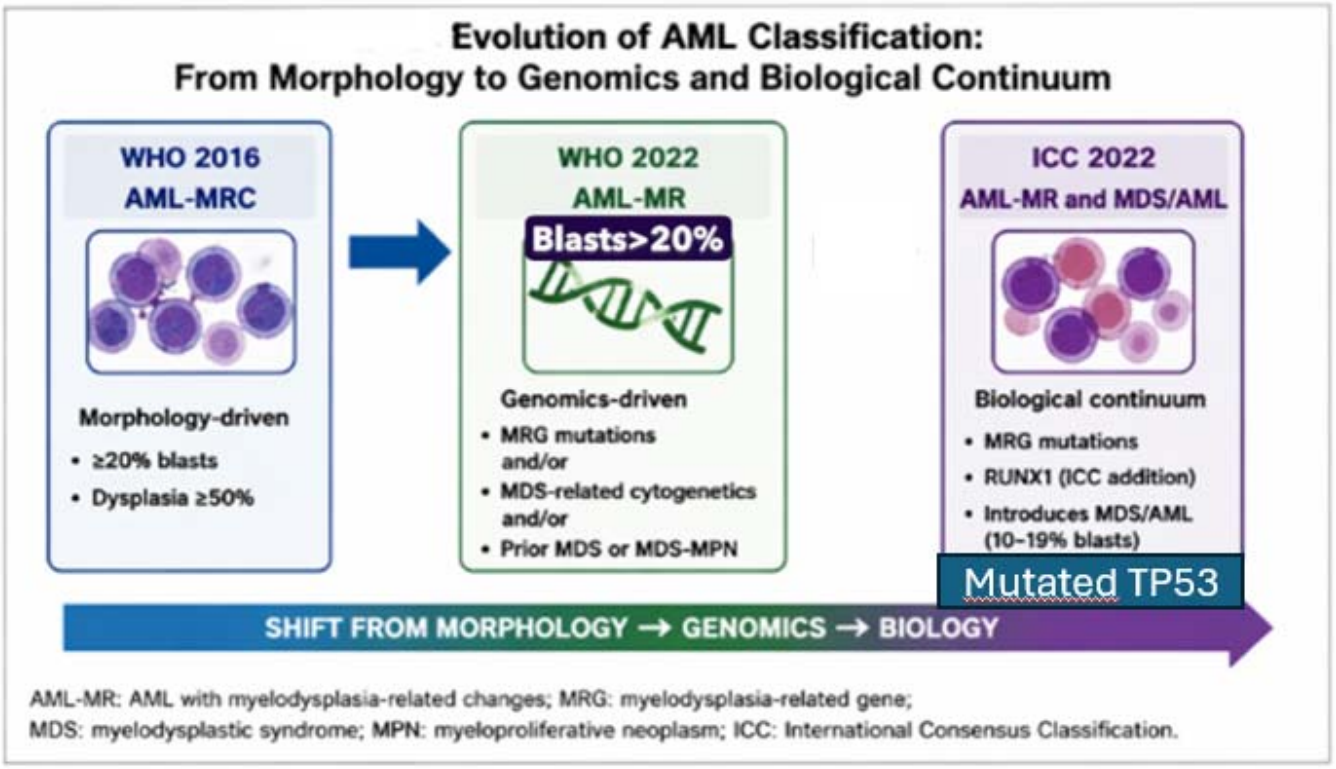

Figure 2. Evolution of AML-MR classification from a diagnostic point of view. The figure summarizes the transition from the WHO 2016 morphology-driven AML-MRC to the WHO 2022 genomics-driven AML-MR and to the ICC 2022 AML-MR/MDS-AML biological continuum. AML-MR: acute myeloid leukemia, myelodysplasia-related; AML-MRC: acute myeloid leukemia with myelodysplasia-related changes; MRG: myelodysplasia-related gene; MDS: myelodysplastic syndrome; MDS-MPN: myelodysplastic/myeloproliferative neoplasm; ICC: International Consensus Classification.[4–6]

the WHO, with the addition of RUNX1, which supersedes cytogenetics (AML with "MDR cytogenetic abnormality"), and encourages a diagnostic hierarchy prioritizing molecular testing (AML with "mutated TP53" and "MDR gene mutation") takes precedence (**Table 2B**). Furthermore, a point of discrepancy in the 2022 classifications concerns the biological boundaries between MDS and AML, as defined by the percentage of blasts (**Tables 1** and **2**, **Figure 1**).

The ICC introduced a new category: MDS/AML, defined by 10%-19% blasts. This subgroup largely overlaps with MDS with excess blasts 2 and MDS with increased blasts 2, according to the 4th and 5th WHO editions, respectively, and may represent a continuum with AML-MR. The new MDS/AML group also makes these patients eligible for both MDS and AML trials.

However, AML-MR should not be regarded as a uniform adverse-risk disease category. Rather, it should be viewed as a biologically heterogeneous condition whose clinical behavior depends on genomic context, clonal architecture, disease dynamics, and host-related factors. MRG mutations define AML-MR as a genetically recognizable entity, but their prognostic impact is heterogeneous (**Table 3**). Large genomic studies have shown that MRG mutations identify biologically distinct AML subsets.[8–13]

However, outcomes are modulated by variant allele frequency (VAF), co-mutations, patient age, and the broader genomic context. The context-dependent prognostic role of MRG mutations is illustrated in **Figure 2**. Additionally, MDS mutations, which span functional categories including RNA splicing, transcription factors, and epigenetic regulation, have variable prognostic impact,[8-13] which is also influenced by the VAF level (**Table 3**).[8,12,13] In the European LeukemiaNet (ELN) 2022 recommendations, myelodysplasia-related (MR) gene mutations were classified as a novel adverse prognostic category for intensively treated acute myeloid leukemia (AML). To assess the prognostic impact of individual MR genes within the ELN, clinical, cytogenetic, and molecular data from 4,978 intensively treated AML patients were analyzed.[13] Remission rates and survival outcomes were evaluated. For analysis in the context of ELN2022 classification, patients carrying at least one MRG mutation (1698 patients, 34.1%) were excluded from the adverse group and analyzed separately; those with co-occurring favorable or intermediate features remained in their respective groups. MRG-mutated cases showed lower complete remission rates (65.7% vs 77.7%; $p < 0.001$), and shorter event-free (HR 1.45; $p < 0.001$), relapse-free (HR 1.33; $p < 0.001$), and overall survival (HR 1.45; $p < 0.001$). *ASXL1*, *RUNX1*, *SF3B1*, and *U2AF1* mutations were associated with adverse-risk outcomes, while *SRSF2* and *STAG2* mutations were linked to an intermediate-risk prognosis. In contrast,

Table 3. Myelodysplasia-related gene mutations and context-dependent prognostic impact. This table summarizes representative MRG mutations, biological function, and major interpretive caveats.

Gene	Functional category	Typical prognostic association	Contextual considerations
ASXL1	Epigenetic regulation	Often adverse	Frequently early/clonal; effect modulated by co-mutations and age
RUNX1	Transcription factor	Often adverse	Included in ICC AML-MR; not included in WHO 2022 MRG list
SRSF2	RNA splicing	Intermediate to adverse depending on context	Common in older patients and secondary AML biology
SF3B1	RNA splicing	Variable	May be influenced by co-mutations and ontogeny
U2AF1	RNA splicing	Often adverse	Frequently co-mutated; prognostic effect requires genomic context
STAG2	Cohesin complex	Intermediate in some cohorts	Clonal size and co-mutation pattern influence risk
BCOR	Transcriptional regulation	Variable	Less consistent adverse effects across cohorts
EZH2	Epigenetic regulation	Variable to adverse	Often reflects secondary-type biology
ZRSR2	RNA splicing	Uncertain/variable	Less frequent; limited gene-specific evidence

BCOR, *EZH2*, and *ZRSR2* mutations did not significantly differ from either the intermediate- or adverse-risk categories. Overall, these findings highlight the marked prognostic heterogeneity among MRG mutations, indicating that their clinical impact is gene-specific rather than uniformly adverse (**Table 3**).[13]

Myeloid neoplasms with "mutated TP53" warrant special mention because they carry an overall unfavorable prognosis. TP53 mutations occur in 5–13% of de novo myelodysplastic syndrome and are more common in the elderly. TP53mut is associated with extremely poor survival and limited therapeutic options.[5,6] While the ICC recognizes TP53mut AML as a distinct entity, the WHO-5 does not. Both classifications acknowledge the poor prognosis associated with MDS with TP53 biallelic inactivation; however, they differ in their emphasis on blast percentage. The ICC prioritizes allelic status and blast percentage in risk stratification, whereas WHO-5 defines allelic TP53 inactivation as a homogeneous category with poor survival regardless of blast percentage (0–19%). However, monoallelic TP53 MDS are excluded from the WHO-5 category of TP53mut MDS, as their survival is considered comparable to that of TP53wt.[14] In contrast to WHO-5, the ICC considers a monogenic TP53 mutation with a VAF >10% to be a disease-defining hallmark. In cases with a single TP53mut with VAF < 50% and a blast count <10%, the ICC defines "MDS with mutated TP53" if there is TP53 locus LOH or a complex karyotype (CK), often involving loss of the 17p chromosome.[5,6] Subsequent validation studies have also confirmed the prognostic role of TP53 monoallelic status vs. TP53wt in MDS/AML, raising questions about the need to refine current classification systems.[6,15,16]

Distinct groups[10,17] have conducted comparative analyses of the ICC and the WHO 2022 classification. A molecular and clinical convergence between AML-MR and MDS/AML has been observed; however, they also noted points favoring the ICC classification, highlighting the unique role of *TP53* and the importance of including *RUNX1* among mutations typical of MDS. Both the WHO 2022 and ICC classifications prioritize disease biology over clinical ontogeny, although the latter remains an important, yet debated, diagnostic qualifier. Validation studies have yielded conflicting results regarding the prognostic impact of antecedent MDS: while one study reported inferior overall survival in patients with clinically defined secondary AML arising from MDS compared with those with molecularly defined AML, [18] another found no significant survival differences between these groups, supporting the ICC approach of considering antecedent MDS primarily as a diagnostic qualifier rather than an independent biological entity.[19]

Furthermore, the use of a fixed blast percentage to distinguish MDS/AML from AML has been questioned, as patients in these categories often exhibit comparable overall survival. [20] However, validation studies of the ICC have demonstrated that the clinical relevance of the 20% blast threshold varies according to the underlying biological subgroup. In the MDS/AML with myelodysplasia-related gene mutations and NOS categories, where next-generation sequencing plays a central role in disease classification, the 20% blast cutoff continues to delineate two biologically and clinically distinct entities. In contrast, patients with TP53-mutated or myelodysplasia-related cytogenetic abnormality-defined disease show similar molecular profiles and clinical outcomes irrespective of blast count, supporting the concept that MDS/AML and AML represent a single biological entity in these subgroups.[14]

Removing dysplasia as a standalone criterion improves reproducibility, but it may also underrepresent phenotypic information that reflects disease ontogeny. Similarly, the ICC introduction of MDS/AML underscores persistent ambiguity in the biological boundary between advanced MDS and AML. Thus, classification has improved, but diagnostic labels alone do not fully capture clonal evolution, treatment vulnerability, or transplant risk. Current classifications

improve diagnostic reproducibility but remain insufficient for individualized therapeutic decision-making unless integrated with dynamic biomarkers such as MRD

Molecular Landscape: Beyond the Presence of MRG Mutations. Classical AML-associated mutations, which primarily determine prognosis in de novo AML, are also be frequently identified in secondary myeloid neoplasms and MDS-related AML, where their biological and prognostic significance may differ according to the underlying disease context (**Figure 3**). A particularly important unresolved issue is the interaction between *NPM1* and MRG mutations. The ICC has partially addressed this by adopting a hierarchical classification in which disease-defining AML genetic abnormalities, such as *NPM1* mutations, take precedence over MRG-defined biology (**Figure 3**).[21-31]

The presence of the *FLT3*-ITD mutation in the context of MDS/AML predicts a very poor outcome;[21,22] however, one study revealed that MRG mutations are particularly rare in the *FLT3*-ITD/*NPM1* co-mutant subgroup (9%), and they did not reveal any prognostic impact.[23] Conversely, in *FLT3*-ITD/*NPM1* wild- type AML, MRG mutations were predictive of shorter relapse-free survival (RFS, HR 1. 37, 95% CI 1. 01 - 1. 88, p = 0. 046) and OS (HR 1. 34, 95% CI 1. 02-1. 74, p = 0. 032). Several studies previously suggested that MRG mutations do not consistently erase the favorable biology of *NPM1*- mutated AML, especially in younger patients or in those achieving MRD negativity. Conversely, in older patients or when MRG mutations are highly clonal or associated with additional adverse features, the outcome may be worse (**Figure 3**).[23–27] Conversely, some other studies indicated that mutations highly specific to secondary AML are associated with poor outcomes in ELN-favorable-risk *NPM1*-mutant AML.[28-30] A recent systematic review and meta-analysis including 4,363 patients demonstrated that co-occurring myelodysplasia-related gene (MRG) mutations, present in approximately 15% of *NPM1*-mutated AML cases, were associated with significantly inferior OS (HR 1.30) and EFS (HR 1.43). These findings challenge the uniformly favorable prognosis of *NPM1*-mutated AML and suggest that MRG status should be incorporated into future risk stratification models.[32]

Evaluation of the Risk in AML-MR and in MDS/AML with ELN Parameters. AML disease classification systems directly influence prognostic stratification and, consequently, clinical management and patient outcomes.[1] European LeukemiaNet (ELN) genetic risk stratifications have been widely used in clinical practice and clinical trials.[33-35] The ELN 2017 and 2022 recommendations for the diagnosis and management of AML are designed for those patients who received intensive chemotherapy, and both include 3 prognostic groups (favorable, intermediate, and adverse) based on cytogenetic and molecular disease characteristics (**Table 4**).[33,34] Recent attempts to validate

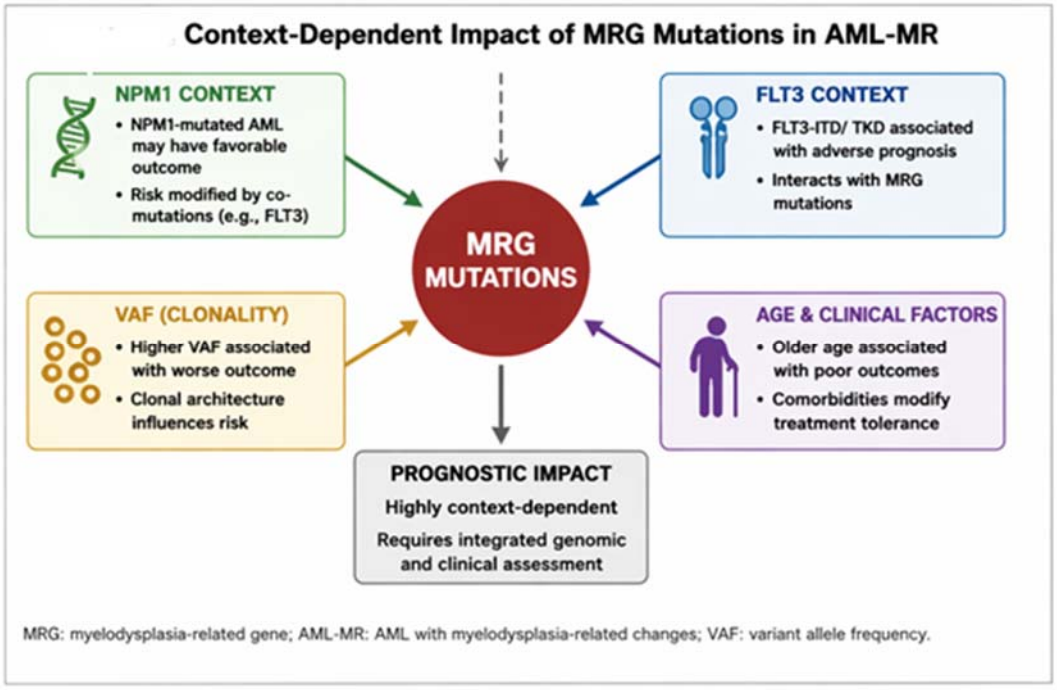

Figure 3. Context-dependent prognostic impact of MRG mutations in AML-MR. The figure illustrates how MRG mutations interact with NPM1 and FLT3 status, clonal dominance as reflected by VAF, and age/clinical factors. These variables explain why MRG mutations should not be interpreted as uniformly adverse in all patients. MRG: myelodysplasia-related gene; AML-MR: acute myeloid leukemia, myelodysplasia-related; VAF: variant allele frequency.[1,8–13, 22–29]

Table 4. 2022 ELN risk classification by genetics at initial diagnosis, Dohner, Blood 2022.[33]

Risk category	Genetic abnormalities
Favorable	t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11†,‡ Mutated NPM1†,§ without FLT3-ITD bZIP in-frame mutated CEBPAk
Intermediate	Mutated NPM1†,§ with FLT3-ITD Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23.3;q34.1)/DEK::NUP214 t(v;11q23.3)/KMT2A-rearranged# t(9;22)(q34.1;q11.2)/BCR::ABL1 t(8;16)(p11.2;p13.3)/KAT6A::CREBBP inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1) t(3q26.2;v)/MECOM(EVI1)-rearranged 25 or del(5q); 27; 217/abn(17p) Complex karyotype,** monosomal karyotype†† Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡ Mutated TP53a

the 2017 and 2022 ELN risk stratifications in older patients treated with less-intensive regimens have proven suboptimal, with most individuals classified as adverse risk.[3,4,9,10,35,36] This supported the need for a new stratification system (ELN 2024) tailored to patients receiving hypomethylating agent (HMA)-based regimens alone or in combination with either the B-cell leukemia/lymphoma 2 (BCL2) inhibitor venetoclax (VEN) or azacitidine (AZA) with the IDH1 inhibitor ivosidenib (IVO) for *IDH1*-mutated acute myeloid leukemia (AML) (**Table 5**).[35-37] The current stratification systems also has limited relevance to patients with prior myeloproliferative neoplasm or prior exposure to HMA therapies, including AML after an antecedent myelodysplastic syndrome, because such patients were generally excluded from clinical trials of VEN-AZA in AML..[36,37] The clinical presence of a previous MDS remains a risk factor not included in the ELN 2022 parameters,[10,38] like age and performance status. Furthermore, it is important to specify whether the ELN risk evaluation is applied to AML/MDS-related classes classified by WHO-5 or by ICC. TP53-mutated AML represents a notable example in which disease classification and prognostic stratification converge. The ICC recognizes it as a distinct biological entity, while

Table 5. ELN risk classification for patients receiving less-intensive therapies (ELN 2024 Less-Intensive) Dohner, Blood 2024.[37]

Risk Category	Genetic abnormality
Favorable	Mutated NPM1 (FLT3-ITDneg, NRASwt, KRASwt, TP53wt) Mutated IDH2 (FLT3-ITDneg, NRASwt, KRASwt, TP53wt) Mutated IDH1* (TP53wt) Mutated DDX41† Other cytogenetic and/or molecular abnormalities‡ (FLT3-ITDneg, NRASwt, KRASwt, TP53wt)
Intermediate	Other cytogenetic and molecular abnormalities‡ (FLT3-ITDpos and/or NRASmut and/or KRASmut; TP53wt)
Adverse	Mutated TP53

both ELN 2022 and ELN 2024 consistently classify these patients as adverse risk, reflecting the uniformly poor clinical outcomes associated with *TP53*-mutated AML.

The incorporation of MRG mutations into the ELN 2022 classification resulted in the reclassification of a substantial proportion of patients previously assigned to the intermediate-risk group into the adverse-risk category, reflecting their adverse biological features. In the validation study by Attardi *et al.*, approximately 21.8% of patients classified as intermediate risk according to ELN 2017 were reclassified as adverse risk in ELN 2022, predominantly because of the presence of MDS-related gene mutations.[39] However, despite this improved biological characterization, the overall prognostic performance of ELN 2022 was comparable to that of ELN 2017, suggesting that the revised classification primarily refined risk allocation without substantially enhancing its discriminatory capacity.

In conclusion, the ELN 22 risk classification for AML-MR, unlike other forms of AML, is not superior to ELN 17 and requires adjustments in elderly patients receiving new drugs.

Clinical Management and Therapy of AML-MR. AML-MR has historically been considered relatively resistant to conventional chemotherapy. More recent data supports a more nuanced interpretation. Appropriate, tailored therapy requires a broad, accurate molecular profile derived from NGS and cytogenetics, along with evaluation of the patient's clinical condition (**Figure 4** and **Table 6**). Current treatment strategies should integrate ELN recommendations, patient fitness,

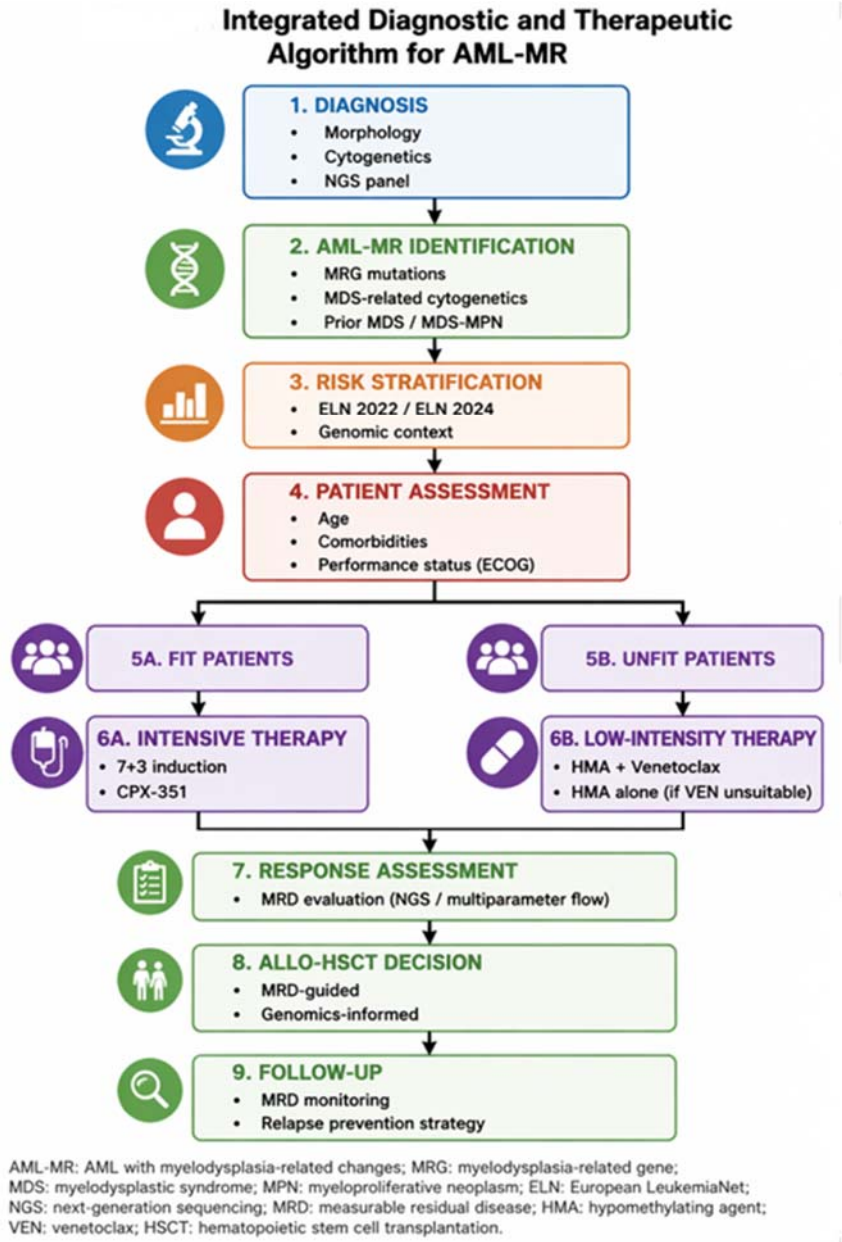

Figure 4. Integrated diagnostic and therapeutic algorithm for AML-MR. The algorithm integrates initial diagnostic work-up, AML-MR identification, risk stratification, patient fitness assessment, treatment selection, MRD evaluation, and allo-HSCT decision-making. AML-MR: acute myeloid leukemia, myelodysplasia-related; MRG: myelodysplasia-related gene; MDS: myelodysplastic syndrome; MDS-MPN: myelodysplastic/myeloproliferative neoplasm; NGS: next-generation sequencing; MRD: measurable residual disease; HMA: hypomethylating agent; VEN: venetoclax; HSCT: hematopoietic stem cell transplantation.[4,5,31–34]

molecular profile, and the expected probability of achieving MRD-negative remission.[4,5,31–35] A practical decision algorithm is provided in Figure 3. In the paper by Shimony et al.,[40] a cohort of 314 newly diagnosed AML patients received VEN in addition to HMAs. In secondary ontogeny (n = 115), median OS (14.1 vs. 6.9 months, P = 0.0054), composite complete remission (cCR 61% vs. 18%, P < 0.001), and allogeneic hematopoietic stem cell transplant (alloHCT) (24% vs. 6%, P = 0.02) rates were better in patients treated with HMA + VEN vs. HMA. In contrast, in TP53 AML (n = 111), median OS (5.7 vs. 6.1, p = 0.93), cCR (33% vs. 37%, P = 0.82), and alloHCT rates (15% vs. 8%, p = 0.38) did not differ between HMA + VEN and HMA. The benefit of adding VEN in the secondary group was preserved after adjustment for significant clinicopathologic variables (HR 0.59 [95% CI 0.38–0.94], p = 0.025). The OS benefit of HMA + VEN in secondary ontogeny was similar in those with vs. those without splicing mutations (p = 0.92). Secondary ontogeny AML highlights a group of patients whose disease is selectively responsive to VEN added to HMA, whereas the addition of VEN has no clinical benefit in *TP53*-mutated AML. Similar results were obtained by Dohner et al.,[37] confirming the advantage of combining azacitidine and venetoclax.

VEN-AZA has changed the therapeutic landscape for older or unfit patients and appears particularly relevant for subsets with secondary-type biology.[37,40,41]

Table 6. Therapeutic strategies for AML-MR based on patient profile and disease biology. The table summarizes practical therapeutic options and key decision points for AML-MR.

Clinical scenario	Preferred strategy	Alternative/adjunctive approach	Key decision point
Fit younger patients	Intensive induction chemotherapy	CPX-351 in selected secondary-type biology	Genetics, cytogenetics, and transplant eligibility
Fit patient with secondary AML biology.	CPX-351 or intensive chemotherapy	Clinical trial, when available	Depth of response and bridge to all-HSCT
Older/unfit patient	HMA plus venetoclax	HMA alone if venetoclax is unsuitable	Tolerability, cytopenias, infection risk
NPM1-mutated AML with MRG mutations	Individualized risk-adapted therapy	MRD-guided transplant consideration	MRD status may outweigh static genetic labels
FLT3-mutated AML with MRG mutations	FLT3 inhibitor-containing strategy when appropriate	HMA+VEN-based or intensive approach, depending on fitness	Interaction between FLT3, NPM1, and MRG burden
TP53-mutated AML-MR-like disease	Clinical trial preferred	HMA-based or investigational combinations	Very high-risk biology; standard approaches often inadequate
Post-remission setting	Allo-HSCT in appropriate candidates	Maintenance/clinical trial in selected cases	MRD, genomics, fitness, donor availability

Ikoma et al. confirmed the favorable results of this combination and demonstrated that the presence of MDS-related mutations, which are adverse factors in the ELN 2022, predicted favorable survival. Prior AZA, *TP53* mutation with variant allele frequency ≥0.10, and RAS-pathway mutations predicted shorter overall survival (OS), while *BCORL1* mutation predicted longer survival.[41]

Fit patients had previously received the typical 3+7 therapy (Cytarabine + Daunorubicin). However, in August 2017, CPX-351 (Vyxeos™ Jazz Pharmaceutcals), a liposomal formulation of cytarabine and daunorubicin, received Food and Drug Administration (FDA) and EMA approval for the treatment of newly diagnosed secondary acute myeloid leukemia (AML), including therapy-related AML (t-AML) and AML-MRC.[42] Since then, many papers have confirmed the benefit of CPX351 over typical 3+7 therapy.[43-50] However, compared with 7+3, CPX-351 improves OS in patients with AML-MR gene mutations who meet the enrollment criteria of the pivotal trial. There is no OS benefit of CPX-351 among enrolled patients with TP53 mutations, irrespective of allelic state.[51] CPX-351 showed its advantage over standard aggressive chemotherapy more frequently in patients over sixty; however, in a recent randomized trial versus daunorubicin, cytarabine, and gemtuzumab ozogamicin in older adults with non-adverse risk AML, CPX-351 did not provide a survival benefit in patients with MRG mutations and was associated with poorer survival in patients with *NPM1* (HR, 2.83) and *FLT3* mutations (HR, 2.14).[52] Overall, 37% of patients underwent transplantation in first remission, with no difference in transplantation frequency or survival after transplant between randomization groups. Among patients entering the course 2 randomization (n = 107), survival was equivalent between standard and intensified CPX doses (p = 0.565). In conclusion, in this population of older patients with AML without known adverse-risk cytogenetics, DAGO2 resulted in superior survival compared with CPX. CPX did not benefit patients with MDS-related mutations over DAGO2.[53] There has also been a phase Ib/II trial, conducted at The University of Texas MD Anderson Cancer Center, to evaluate the safety and efficacy of CPX + VEN. Eighteen patients with a new diagnosis of AML, a median age of 59 years (range, 43–69), were enrolled and treated between November 2018 and January 2022. Of them, 17 were evaluable, and 10 of them had MDS mutations. Patients with MR gene mutations had an ORR of 100% (95% CI, 69–100), including 90% (95% CI, 55–100) CRc and 70% (95% CI, 35–93) with undetectable MRD. Patients with de novo AML had a CRc rate of 100% (95% CI, 54–100) and an undetectable MRD rate of 50% (95% CI, 12–88). Those with wild-type TP53 had a CRc rate of 92% (95% CI, 62–100) and an undetectable MRD rate of 67% (95% CI, 35–90). Eight patients (47%) with ts-AML had prior HMA exposure; these patients had a CRc rate of 63% (95% CI, 24–91). The three non-responding patients in the study had highly adverse disease features: all three had ts-AML with previous HMA failure, were TP53 mutated, and had complex cytogenetics. Of course, the cases are few and the follow-up is short, but the results are exceptionally good, and the study deserves to be continued. There are no prospective, randomized studies comparing patients treated with VEN-AZA with those treated with CPX-351. However, two large retrospective studies[53,54] demonstrated comparable outcomes between patients treated with VEN-AZA and those treated with CPX-351, across all patients with secondary leukemia, with response rates differing by the type of sAML and MDS mutations.[54] The outcome of AML-MR treated with VEN-AZA was better, with an OS of 12 months versus 7, P=0.02.[54]

The optimal choice among intensive therapy, CPX-351, and HMA plus venetoclax should be individualized rather than dictated solely by the AML-MR label. Patients with negative MRD or minimally positive MRD after chemotherapy at allogeneic hematopoietic stem cell

transplantation could reduce relapse with continuous administration of azacitidine.[55]

New Therapies. Mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) occur in multiple tumors, including approximately 20% of AMLs. This mutation induces DNA hypermethylation, suggesting the combination of the mutant IDH1 inhibitor ivosidenib with the hypomethylating agent azacitidine in patients with newly diagnosed IDH1-mutant AML who were ineligible for intensive induction chemotherapy.[56] The overall response rate was 78.3% (18/23 patients; 95% CI, 56.3% to 92.5%), and the complete remission rate was 60.9% (14/23 patients; 95% CI, 38.5% to 80.3%). With a median follow-up of 16 months, the median duration of response in responders had not been reached. The 12-month survival estimate was 82.0% (95% CI, 58.8% to 92.8%). mIDH1 clearance in bone marrow mononuclear cells by BEAMing (beads, emulsion, amplification, magnetics) digital polymerase chain reaction was observed in 10/14 patients (71.4%) who achieved complete remission.

In a long-term follow-up, ivosidenib-azacitidine, with a median OS of 29.3 months, sustained survival and hematologic benefits in mutant IDH1 AML. Among patients with mutant IDH1 AML in complete remission receiving ivosidenib-azacitidine, 30% achieved deep molecular clearance during treatment.[57]

TP53-mutated MDS and AML are among the most aggressive and chemotherapy-refractory myeloid neoplasms, with a median overall survival of <6 months. There remains an enormous unmet need to develop novel therapeutic strategies and to understand resistance mechanisms to suboptimal existing therapies for this disease. In 2 parallel phase 2 clinical trials combining eprenetapopt with azacitidine in TP53-mutant MDS/AML, complete remission rates of 40%-50% and a molecular remission rate of 38%. Were observed. However, unless an allogeneic stem cell transplant was performed, relapse inevitably occurred and the Phase III trial did not meet its primary endpoint.[58] Continuous azacitidine administration to patients in remission, both MRD-negative and MRD-positive, has reduced relapse.[55]

Transplant Decision-Making and MRD. The evolving biological classification of AML myelodysplasia-related has direct implications for treatment strategies, with allogeneic hematopoietic stem cell transplantation (allo-HSCT) remaining the cornerstone of post-remission therapy for eligible high-risk patients. Indeed, allo-HSCT remains the preferred consolidation strategy for medically fit patients with adverse-risk AML according to the ELN 2022 recommendations. However, accumulating evidence indicates that transplant outcomes are not uniform across this risk category but are strongly influenced by the underlying disease biology. Although ELN 2022 groups AML with MRG mutations among adverse-risk diseases, patients harboring MR gene mutations exhibit substantially better post-transplant outcomes than those with complex karyotype, other adverse cytogenetic abnormalities, or *TP53* mutations, highlighting the biological heterogeneity within the adverse-risk category.[59] This concept is consistent with the earlier observations in AML with MRC, where cytogenetic abnormalities, rather than history of antecedent MDS or myelodysplasia alone, represented the major determinants of post-HSCT survival.[60] More recently, the ICC genetic hierarchy has further refined prognostic stratification after allo-HSCT, with progressively inferior RFS (46.9%, 39.5%, 31.9%, and 13.2% at 2 years) and OS (65.7%, 60.1%, 47.1%, and 24.5% at 2 years) observed from AML with MRG mutations to MR cytogenetic abnormalities, *TP53*-mutated non-complex karyotype AML, and *TP53*-mutated complex karyotype AML, respectively, confirming the dominant role of genetic classification in predicting transplant outcomes.[6] Conditioning intensity also influences outcomes in this setting. In transplant-eligible patients, myeloablative conditioning (MAC) has been associated with superior long-term OS compared with reduced-intensity conditioning (RIC), primarily through a lower risk of relapse despite a higher incidence of treatment-related mortality, supporting the use of MAC whenever clinically feasible.[61]

MRD assessment has become a central determinant of post-remission strategy and should be interpreted alongside the genomic profile, treatment response, comorbidities, and transplant feasibility. Overall, transplant outcomes in AML-MR show a pronounced dependence on genetic subtype.[54,62] AML-MR, characterized predominantly by myelodysplasia-related gene mutations, is associated with relatively favorable transplant efficacy, with prognostic outcomes approaching those observed in intermediate-risk AML. Conversely, TP53mut AML-MR with a complex karyotype is the subgroup with the poorest prognosis, for which allo-HSCT confers minimal survival benefit.[62] Several favorable prognostic factors for PFS include the absence of complex cytogenetics/5q or 7q deletion, a lower variant allele frequency (VAF), mono-hit status, and the use of a matched-related donor. Using classification and regression tree analysis, VAF and cytogenetics were identified as the 2 most important prognostic factors. Patients with TP53mut VAF ≥ 50% had a 2-year PFS of 3%, and patients with TP53mut VAF < 50% and complex/5q/7q cytogenetic abnormalities had a 2-year PFS of 22%. Patients with TP53mut VAF < 50% and without complex/5q/7q cytogenetic abnormalities had a 2-year PFS of 60%. These data inform clinical practice and help patients decide whether to pursue HSCT.[62] Patients with AML-related MDS undergo

allogeneic HSCT after achieving CR with CPX-351 or cytarabine plus venetoclax. Both treatments show reduced toxicity, so the proportion of patients in RC who are fit for transplantation is high. In the paper,[63] which reports the experience of the Italian Centers, 340 of 513 patients (66%) obtained CR, and 230 (48,5%) received an allogeneic HSCT. Median follow-up was 23.66 months, and median overall survival (OS) was 16.23 months. Patients with mutated NPM1 or with ELN 2017 favorable risk ($p<0.05$). In a landmark analysis, receiving allo-HSCT was associated with longer survival (median OS not reached vs. 16.3 months ($p<0.05$). Patients who underwent CR with VEN-AZA or with CPX-351 and then underwent transplantation showed the same OS.[54] A further demonstration of the importance of gene mutations and cytogenetics in predicting transplant outcome also comes from the large EBMT study.[64] Outcomes differed markedly among genetic categories, with an increasing relapse incidence (20.2%, 29.2%, 44.6%, and 57.6% at 2 years), OS (65.7%, 60.1%, 47.1%, and 24.5% at 2 years in MR-GM, MR-CG, TP53-mut non-CK, and TP53-mut CK AML, respectively.

These observations underscore the importance of integrating molecular genetic stratification into transplant decision-making and highlight the need to explore post-transplant maintenance strategies to reduce relapse risk. Continuous administration of azacitidine after transplant, with or without venetoclax, could reduce relapses.[55,65]

Conclusions. The 2022 classifications have shifted the formal subclassification of AML-MR toward genetically reproducible criteria; however, this should not be interpreted as diminishing the clinical significance of disease ontogeny. In older patients, particularly those with a documented history of MDS/MDS-MPN, the duration and evolution of cytopenias, prior therapies, comorbidities, functional status, and treatment tolerance remain integral to therapeutic decision-making. Molecular and cytogenetic abnormalities refine disease classification and prognosis but should complement, rather than replace, longitudinal clinical assessment.

Future studies should refine genomic risk models, prospectively test AML-MR-specific treatment strategies, and determine how MRD and co-mutation patterns should guide transplantation. A static diagnostic label is no longer sufficient: AML-MR requires integrated, dynamic, and individualized clinical decision-making. To improve therapy, prospective genotype- and MRD-stratified trials, individualized transplant strategies e treatment-specific risk models should be done. Furthermore, studies on the association of effective drugs such as Venetoclax with CPX-351 should be increased.

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