

Review Article**Molecular Markers in AML: Prognostic Implications and Impact on Treatment Decision-Making**

Patrizia Chiusolo^{1,2,*}, Roberto Maggi^{1,2,*}, Angela Alessi² and Simona Sica^{1,2}.

¹ Dipartimento di Scienze di Laboratorio ed Ematologiche, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Roma.

² Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma.

* These authors equally contributed to the article.

Competing interests: The authors declare no competing interest.

Abstract. Acute myeloid leukemia (AML) is a biologically heterogeneous hematologic malignancy in which recurrent cytogenetic and molecular abnormalities critically influence diagnostic classification, prognosis, therapeutic allocation, measurable residual disease (MRD) assessment, and relapse biology. Over the last decade, next-generation sequencing (NGS) has profoundly expanded AML molecular characterization, complementing morphology, immunophenotyping, and cytogenetics and enabling increasingly personalized therapeutic strategies. The European LeukemiaNet (ELN) 2022 recommendations established an integrated cytogenetic-molecular backbone for risk stratification. In contrast, subsequent refinements in the era of hypomethylating agents plus venetoclax demonstrated that molecular risk is increasingly treatment-dependent rather than universally fixed across therapeutic platforms. In parallel, targeted therapies against FLT3, IDH1/2, BCL2, CD33, and menin-dependent transcriptional programs have profoundly reshaped AML management in both fit and unfit patients. Emerging data further indicate that co-mutational architecture, clonal hierarchy, variant allele frequency, and MRD kinetics may refine prognostic assessment beyond traditional single-gene models. Consequently, modern AML management increasingly relies on dynamic molecular interpretation integrating baseline genomics with treatment response and longitudinal disease monitoring. This review discusses the current prognostic and predictive role of major molecular markers in AML, focusing on FLT3-mutated AML, IDH1/2-mutated AML, NPM1-mutated AML, TP53-mutated disease, KIT-mutated core-binding factor AML, and KMT2A/NUP98-driven leukemias, together with treatment-dependent risk stratification, co-mutational refinement, menin inhibitors, germline predisposition syndromes, and MRD-guided therapeutic adaptation. The central concept is that molecular abnormalities should no longer be considered static prognostic labels, but rather operational biomarkers capable of guiding time-sensitive clinical decisions from diagnosis through post-transplant surveillance and relapse management.

Keywords: Molecular Markers; Acute Myeloid leukemia; Targeted therapy.

Citation: Chiusolo P., Maggi R., Alessi A., Sica S. Molecular markers in AML: prognostic implications and impact on treatment decision-making. *Mediterr J Hematol Infect Dis* 2026, 18(1): e2026087, <http://dx.doi.org/10.4084/MJHID.2026.087>

Published: November 01, 2026

Received: September 29, 2026

Accepted: October 19, 2026

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Patrizia Chiusolo, MD, PhD. Sezione di Ematologia, Università Cattolica del Sacro Cuore, Largo Francesco

Introduction. AML remains a paradigmatic malignancy in which molecular medicine has rapidly moved from descriptive biology to clinical decision-making. The ELN 2022 recommendations formalized the need to integrate cytogenetics, mutation status, and response assessment when assigning risk and selecting therapy.¹ Contemporary reviews of AML management emphasize the same shift: AML is no longer approached as a single disease uniformly treated with cytarabine and anthracycline, but as a family of biologically distinct entities whose outcomes depend on age, disease ontogeny, genomic architecture, measurable residual disease, and access to targeted drugs.²

The first major conceptual leap came from genomic sequencing studies demonstrating that adult AML contains recurrent somatic lesions affecting epigenetic regulation, signaling, transcriptional control, tumor suppression, and RNA splicing.³ Sequencing a cytogenetically normal AML genome showed that apparently normal karyotype disease can conceal a complex molecular landscape with biologically meaningful driver and cooperating mutations.⁴ Shortly thereafter, researchers identified DNMT3A mutations as frequent early events associated with clonal hematopoiesis and poorer outcomes in several contexts.⁵ Large integrative studies then demonstrated that AML prognosis is best understood through genomic classes rather than through single-gene interpretation alone.⁶

This genomic revolution coincided with a therapeutic revolution. Venetoclax-based regimens changed outcomes in older or unfit patients and revealed distinct molecular patterns of response and resistance.⁷ The interaction between epigenetic lesions, IDH mutations, and BCL2 dependence suggested that biology could predict sensitivity to lower-intensity therapy.⁸ Venetoclax plus low-dose cytarabine and venetoclax plus azacitidine established new standards for patients ineligible for intensive chemotherapy.⁹⁻¹³ In parallel, targeted therapies moved from salvage settings to frontline combinations, challenging the traditional sequence of induction, consolidation, transplantation, and maintenance.¹⁴

The objective of this review is therefore not to provide an exhaustive catalog of the genomic landscape of AML, but to focus on molecular alterations directly relevant to risk stratification, treatment selection, MRD assessment, and longitudinal clinical decision-making. Molecular markers can be diagnostic, prognostic, predictive, and MRD-enabling. A diagnostic marker defines an AML entity or refines classification; a prognostic marker informs relapse and survival risk; a predictive marker identifies vulnerability to a specific therapy; and an MRD-enabling marker permits longitudinal monitoring. Many AML lesions occupy more than one category. FLT3 is prognostic and

predictive; NPM1 is diagnostic, prognostic, and MRD-enabling; IDH1/2 mutations are biologically informative and therapeutically actionable; TP53 defines high-risk biology but remains incompletely targetable. This multidimensional meaning of “marker” supports modern AML management.

From Genomic Discovery to a Decision Framework.

The clinical utility of molecular markers is clearest when they are placed along the AML timeline. At diagnosis, molecular profiling informs classification, induction strategy, eligibility for targeted agents, trial enrollment, and early transplant planning. After induction, the same genetic information is reinterpreted through MRD. Before transplantation, persistent molecular disease identifies patients at high relapse risk even when morphologic remission is achieved. After transplantation, serial molecular monitoring can anticipate hematologic relapse and support pre-emptive intervention. At relapse, repeat NGS may reveal clonal selection, acquisition of new actionable lesions, or loss of diagnostic targets.

This longitudinal model matters because AML is not genetically static. Molecular patterns of response and treatment failure after venetoclax-based therapy demonstrated that relapse may be driven by expansion of resistant clones, including signaling pathway mutations and TP53-altered disease.⁷ Studies of AML ontogeny showed that secondary AML and therapy-related AML are enriched for distinct mutation patterns, including splicing factor alterations, ASXL1, RUNX1, and TP53, which carry adverse implications independent of conventional morphology.^{15,16} Clonal evolution studies further showed that relapse may arise from either persistence of diagnostic clones or expansion of minor subclones that survive therapy.¹⁷

Consequently, a single baseline NGS report is not sufficient for complete disease governance. It provides the starting map, but clinical decisions must be updated as the disease responds, escapes, or evolves. This concept is especially relevant for signaling mutations such as FLT3 or RAS pathway lesions, which may be gained or lost at relapse. It also applies to preleukemic mutations such as DNMT3A, TET2, and ASXL1, which may persist in remission without necessarily representing active leukemia. Modern AML practice therefore requires careful separation of founder mutations, leukemic drivers, residual disease markers, and age-related clonal hematopoiesis.

Molecular lesions have a particularly strong prognostic impact in intermediate-risk cytogenetic AML. Integrated genetic profiling showed that combinations of mutations, rather than isolated lesions, better explain heterogeneity within cytogenetically normal AML.¹¹ The prognostic model proposed by Papaemmanuil and

ELN 2022 genetic risk classification in AML

For patients treated with intensive chemotherapy

Risk category	Genetic abnormalities
Favorable risk	<ul style="list-style-type: none"> t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 Mutated NPM1 without FLT3-ITD bZIP in-frame mutated CEBPA
Intermediate risk	<ul style="list-style-type: none"> FLT3-ITD, irrespective of allelic ratio or NPM1 mutation t(9;11)(p21.3;q23.3)/MLLT3::KMT2A Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse risk	<ul style="list-style-type: none"> t(6;9)(p23;q34.1)/DEK::NUP214 t(v;11q23.3)/KMT2A rearranged, excluding KMT2A-PTD t(9;22)(q34.1;q11.2)/BCR::ABL1 t(8;16)(p11;p13)/KAT6A::CREBBP inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) t(3q26.2;q21.3)/MECOM(EVI1)-rearranged −5 or del(5q); −7; −17/abn(17p) Complex karyotype; monosomal karyotype Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 Mutated TP53 with variant allele frequency ≥10%
Essential interpretation notes	
<ul style="list-style-type: none"> Concurrent KIT or FLT3 mutations do not alter risk in core-binding factor AML. AML with mutated NPM1 and adverse-risk cytogenetic abnormalities is classified as adverse risk. Only in-frame mutations affecting the CEBPA bZIP region, whether monoallelic or biallelic, are considered favorable. t(9;11)(p21.3;q23.3)/MLLT3::KMT2A takes precedence over rare concurrent adverse-risk gene mutations. Complex karyotype: ≥3 unrelated chromosomal abnormalities, excluding hyperdiploid karyotypes with ≥3 trisomies/polysomies without structural abnormalities. Monosomal karyotype: ≥2 distinct monosomies, or 1 autosomal monosomy plus ≥1 structural abnormality; excludes core-binding factor AML. MDS-related gene mutations should not currently be used as adverse markers when co-occurring with favorable-risk AML subtypes; in NPM1-mutated AML, these mutations do not currently alter risk category. 	

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; HMA, hypomethylating agent; ITD, internal tandem duplication; MRD, measurable residual disease; PTD, partial tandem duplication; VAF, variant allele frequency; wt, wild type.

Figure 1. ELN 2022 genetic risk classification in adult AML. Genetic risk classification for patients with AML treated with intensive chemotherapy according to the ELN 2022 recommendations. Risk assignment integrates recurrent molecular and cytogenetic abnormalities and should be interpreted together with treatment response, MRD, transplant eligibility, and patient-specific factors. Original graphical representation created by the authors based on the ELN 2022 recommendations.¹

colleagues further highlighted that genomic classes have distinct outcomes and biological trajectories.⁶

ELN 2022 as the Prognostic Backbone. The European LeukemiaNet (ELN) 2022 recommendations currently represent the primary prognostic framework for adult acute myeloid leukemia (AML), particularly for patients eligible for intensive chemotherapy.¹ ELN 2022's major conceptual strength is translating AML's extraordinary genomic complexity into clinically actionable therapeutic categories, establishing molecular profiling as the backbone of modern AML decision-making. Unlike historical classifications based primarily on morphology and cytogenetics, ELN 2022 formally integrates recurrent molecular abnormalities into risk stratification and recognizes measurable residual disease (MRD) as an increasingly relevant dynamic prognostic variable.

The ELN 2022 classification stratifies AML into favorable, intermediate, and adverse-risk categories according to cytogenetic and molecular characteristics. Favorable-risk AML includes core-binding factor (CBF) leukemias characterized by RUNX1::RUNX1T1 and CBFB::MYH11 rearrangements, AML with mutated NPM1 in the absence of FLT3-internal tandem duplication (FLT3-ITD), and AML harboring in-frame bZIP mutations of CEBPA.¹ These subgroups are generally associated with higher complete remission

rates, deeper molecular responses, and better long-term survival after intensive induction chemotherapy. Importantly, favorable-risk classification increasingly reflects not only baseline disease biology but also the expected sensitivity to cytarabine-based treatment approaches.

Intermediate-risk AML remains biologically heterogeneous and clinically challenging. This category includes NPM1-mutated AML associated with FLT3-ITD, cytogenetically normal AML lacking favorable or adverse features, and multiple molecular combinations with variable clinical behavior.¹ Growing evidence suggests this subgroup is not biologically homogeneous, since prognosis is strongly influenced by co-mutational architecture, MRD kinetics, disease ontogeny, and therapeutic context. Consequently, treatment decisions in intermediate-risk AML often require individualized interpretation integrating molecular complexity with patient-specific clinical variables.

The adverse-risk category includes AML with complex or monosomal karyotype, TP53 mutations, myelodysplasia-related gene mutations, and specific high-risk chromosomal rearrangements.¹ These leukemias are frequently characterized by chemotherapy resistance, genomic instability, clonal heterogeneity, and poor survival outcomes. In this setting, conventional induction chemotherapy alone is rarely curative, and allogeneic hematopoietic cell transplantation (allo-HCT),

ELN 2024 genetic risk classification in AML

For patients treated with less-intensive therapy

Risk category	Genetic abnormalities
Favorable risk	<ul style="list-style-type: none"> • Mutated NPM1 with FLT3-ITDwt, NRASwt, KRASwt, and TP53wt • Mutated IDH2 with FLT3-ITDwt, NRASwt, KRASwt, and TP53wt • Mutated IDH1 with TP53wt • Mutated DDX41 • Other cytogenetic and/or molecular abnormalities with FLT3-ITDwt, NRASwt, KRASwt, and TP53wt
Intermediate risk	<ul style="list-style-type: none"> • Other cytogenetic and/or molecular abnormalities with FLT3-ITDpos and/or NRASmut and/or KRASmut, with TP53wt
Adverse risk	<ul style="list-style-type: none"> • Mutated TP53
Essential interpretation notes <ul style="list-style-type: none"> • This classification is intended for AML treated with less-intensive therapy and does not apply after prior hypomethylating-agent exposure. • The IDH1 favorable-risk assignment applies specifically to patients treated with azacitidine plus ivosidenib, irrespective of activating signaling-gene mutations. • A DDX41 mutation at near-heterozygous frequency should prompt consideration of a germline DDX41 variant. • For many single or co-occurring cytogenetic/molecular abnormalities, data remain limited; provisional grouping depends on the absence or presence of activating signaling mutations. 	

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; HMA, hypomethylating agent; ITD, internal tandem duplication; MRD, measurable residual disease; PTD, partial tandem duplication; VAF, variant allele frequency; wt, wild type.

Figure 2. ELN 2024 genetic risk classification for AML treated with less-intensive therapy. Genetic risk classification according to molecular and cytogenetic features in patients with newly diagnosed AML receiving less-intensive therapy. The framework applies to HMA monotherapy, HMA plus venetoclax, and azacitidine plus ivosidenib in IDH1-mutated AML, with treatment-specific considerations as defined by the ELN recommendations. Original graphical representation created by the authors based on the ELN 2024 recommendations for less-intensive therapies.²⁰

clinical trials, or investigational targeted combinations should be considered according to disease response, molecular risk, transplant eligibility, and patient-specific factors.

One important limitation of ELN 2022 is that it was developed primarily in patients receiving intensive chemotherapy and may not fully discriminate outcomes with less-intensive regimens. The introduction of azacitidine plus venetoclax (HMA-VEN), established by VIALE-A as a standard treatment for older or unfit patients with newly diagnosed AML, highlighted the treatment-dependent prognostic impact of molecular abnormalities.^{7,12,18,19} In particular, NPM1 and IDH1/2 mutations are associated with high response rates and favorable outcomes with HMA-VEN, whereas TP53 and signaling-pathway mutations such as FLT3-ITD, NRAS, and KRAS identify subgroups with less durable responses and inferior survival.^{7,18,19} These observations demonstrate that the prognostic significance of individual genomic lesions may vary substantially according to therapeutic context and support the development of treatment-specific molecular risk models.

Importantly, these findings demonstrated that traditional ELN 2017 and ELN 2022 classifiers inadequately discriminate outcomes among patients treated with HMA-VEN regimens.¹⁹ In pooled analyses of treatment-naïve patients receiving venetoclax plus azacitidine, a 4-gene classifier incorporating TP53, FLT3-ITD, NRAS, and KRAS separated patients into groups with different survival outcomes.¹⁹

Figure 2 summarizes the ELN 2024 genetic risk classification for patients with AML receiving less-intensive therapy.

The formal ELN 2024 recommendations for patients receiving less-intensive therapies extend molecular risk stratification to treatment-specific settings and differ from the preceding venetoclax-azacitidine molecular analyses.²⁰ The framework recognizes that the prognostic weight of individual lesions may vary according to therapeutic context and applies to commonly used less-intensive approaches, including HMA monotherapy, HMA-VEN, and azacitidine plus ivosidenib in IDH1-mutated AML.²⁰ Further evidence supporting treatment-dependent molecular risk comes from the PRISM-AML prognostic model, developed for patients with newly diagnosed AML receiving frontline hypomethylating agent plus venetoclax (HMA-VEN). In a multinational cohort of 2,092 patients, PRISM integrated 17 clinical, cytogenetic, and molecular variables into an individualized prognostic model.²¹ The resulting PRISM-3 score identified low-, moderate-, and high-risk groups, with median overall survival ranging from 25.1–28.8, 12.5–14.7, and 5.8–6.7 months, respectively, across study cohorts. Compared with the 4-gene classifier, PRISM reclassified approximately 40% of patients overall and more than 50% of patients assigned to the 4-gene favorable-risk group, with higher prognostic discrimination (C-index 0.63–0.65 vs 0.59–0.61).²¹ These findings further support treatment-specific prognostic assessment integrating co-mutational architecture, cytogenetic features, and clinical variables rather than isolated molecular biomarkers. PRISM is a

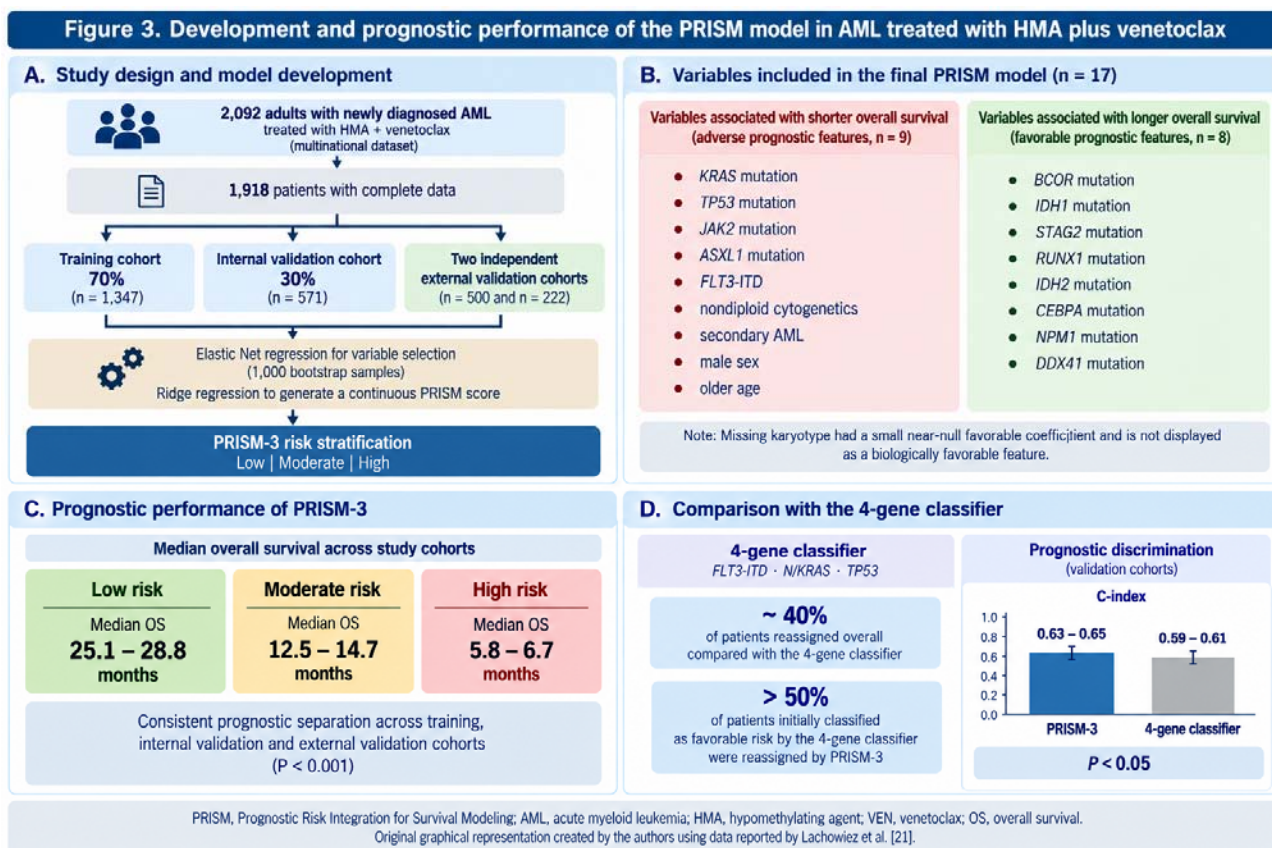


Figure 3. Development and prognostic performance of the PRISM model in AML treated with HMA plus venetoclax. PRISM integrates 17 clinical, cytogenetic, and molecular variables into a continuous prognostic score and stratifies patients into low-, moderate-, and high-risk groups (PRISM-3). Across the study cohorts, median OS ranged from 25.1–28.8, 12.5–14.7, and 5.8–6.7 months, respectively. Compared with the 4-gene classifier, PRISM-3 reclassified approximately 40% of patients overall and more than 50% of patients previously classified as favorable risk, with higher prognostic discrimination (C-index 0.63–0.65 vs 0.59–0.61). Original graphical representation created by the authors using data reported by Lachowicz et al.²¹

promising next-generation individualized prognostic model that complements current ELN frameworks in the HMA-VEN setting. However, broader prospective and real-world validation is needed before incorporating it into routine clinical risk classification.²¹ Integrated treatment-specific models such as PRISM-AML may further refine individualized risk assessment beyond categorical molecular classifications.

Molecular Work-Up at Diagnosis and Turnaround Time. Incorporating next-generation sequencing (NGS) into routine AML diagnostics has profoundly transformed risk stratification and therapeutic decision-making. Unlike traditional cytogenetic approaches, NGS simultaneously identifies multiple recurrent somatic mutations involved in leukemogenesis, clonal evolution, treatment resistance, and measurable residual disease (MRD) assessment.^{3,6,22} However, the increasing complexity of molecular profiling has also raised important practical questions about turnaround time (TAT), prioritizing urgent molecular results, and integrating genomic data into real-world clinical workflows. Current AML management increasingly

relies on a tiered molecular strategy integrating rapid targeted testing at diagnosis with broader NGS profiling during induction therapy. Rapid assessment of *FLT3* and *NPM1* mutations is considered particularly critical because these lesions directly influence frontline therapeutic allocation.¹ Identifying *FLT3* mutations may guide the addition of *FLT3* inhibitors such as midostaurin or quizartinib to intensive chemotherapy, whereas *NPM1* mutations strongly influence ELN risk classification and subsequent MRD monitoring strategies.

Consequently, current guidelines recommend that rapid *FLT3* and *NPM1* testing should ideally be available before treatment initiation or within the first few days after diagnosis.¹ In contrast, comprehensive NGS panels evaluating broader mutational landscapes do not necessarily need to be completed before induction therapy begins.

Therefore, contemporary molecular workflows increasingly prioritize clinically actionable mutations with immediate therapeutic implications while allowing broader genomic profiling to be finalized during induction therapy or by the end of the first induction

cycle.^{1,22} This approach allows timely therapy initiation without sacrificing the comprehensive biologic characterization needed for post-remission planning, transplant allocation, and longitudinal MRD interpretation.

The progressive expansion of NGS has also challenged the traditional distinction between diagnostic and monitoring biomarkers. Molecular profiling is no longer restricted to baseline disease classification but increasingly serves as a dynamic longitudinal tool integrated throughout the disease course. Baseline NGS establishes molecular architecture and co-mutational patterns, whereas sequential molecular assessment may identify clonal evolution, treatment-emergent resistance mutations, and persistence of residual leukemic clones.

In this context, NGS-based MRD assessment has emerged as an important complementary approach in modern AML management. NGS can potentially monitor multiple leukemia-associated mutations simultaneously; however, NGS-MRD should not be considered interchangeable with multiparameter flow cytometry (MFC) or validated target-specific molecular MRD assays, such as quantitative or digital PCR (qPCR/dPCR). Analytical sensitivity and clinical interpretability depend on the molecular target,

sequencing platform, depth of coverage, and assay characteristics.²³ Interpretation is particularly challenging for DNMT3A, TET2, and ASXL1 (DTA) mutations, which may persist during remission as part of clonal hematopoiesis rather than representing residual AML.^{1,23} Consequently, molecular persistence does not invariably indicate residual leukemia and should be interpreted according to the tracked mutation, baseline molecular architecture, variant allele frequency, and longitudinal kinetics. MRD assessment provides important prognostic information during and after treatment, although optimal timing and methodology depend on the molecular marker and therapeutic context.²³ Patients achieving deep molecular clearance generally demonstrate superior long-term outcomes compared with those with persistent MRD despite morphologic remission.^{1,24,25} However, MRD positivity should not be considered an isolated indication for treatment intensification or allogeneic transplantation; therapeutic decisions should integrate baseline genetic risk, MRD methodology and kinetics, treatment received, transplant eligibility, and patient-specific factors.

Table 1 summarizes the principal prognostic, predictive, MRD-related, and therapeutic implications of major molecular markers in AML.

TABLE 1. Clinical implications of major molecular markers in AML

Molecular marker	Prognostic role	Predictive role	MRD applicability	Therapeutic implications
 FLT3-ITD	Historically adverse ; now context-dependent in ELN 2022 due to FLT3 inhibitors	Predicts benefit from FLT3 inhibitors	Limited as standalone MRD marker; useful if tracked with broader molecular profile	Add midostaurin/quazartinib to intensive chemotherapy; gilteritinib in R/R AML; consider post-transplant FLT3 inhibitor maintenance
 FLT3-TKD	Less clearly adverse than FLT3-ITD	Predicts sensitivity to selected FLT3 inhibitors, particularly type I inhibitors	Limited	Relevant for gilteritinib/midostaurin sensitivity; resistance mutations may emerge under FLT3 inhibitor pressure
 NPM1	Favorable in absence of FLT3-ITD under ELN 2022, but modified by co-mutations	Associated with high sensitivity to intensive chemotherapy and HMA-VEN	Excellent ; qPCR-based MRD is highly informative	MRD-guided consolidation; transplant generally avoided in MRD-negative favorable-risk disease but considered if MRD persists
 NPM1 + FLT3-ITD / DNMT3A	Higher relapse risk than isolated NPM1 mutation	May modify response durability	NPM1 MRD remains highly useful	HARMONY data support co-mutational refinement; consider intensified consolidation or transplant if MRD-positive
 IDH1	Intermediate/context-dependent ; often associated with normal karyotype AML	Predicts benefit from ivosidenib	Limited	Ivosidenib monotherapy in R/R AML; ivosidenib + azacitidine in frontline unfit IDH1-mutated AML
 IDH2	Context-dependent; may be favorable in HMA-VEN-treated patients	Predicts response to enasidenib and venetoclax-based regimens	Limited ; interpretation complicated by clonal persistence	Enasidenib active in R/R AML but not EMA-approved; IDH2-mutated AML often sensitive to HMA-VEN
 TP53	Strongly adverse across treatment platforms	Poor response durability to chemotherapy and HMA-VEN	NGS-MRD possible but interpretation depends on clone size and cytogenetics	Clinical trial priority; transplant outcomes poor; TP53-directed strategies remain investigational
 CEBPA bZIP	Favorable when in-frame bZIP mutation	Predicts chemotherapy-sensitive biology	Not routinely used as MRD marker	Intensive chemotherapy followed by consolidation; transplant usually reserved for relapse or high-risk features
 KIT in CBF AML	May increase relapse risk , especially exon 17/D816 in t(8;21)	Potential TKI relevance but not standard	CBF fusion transcript MRD more informative than KIT alone	KIT status should be interpreted with MRD kinetics; not automatic indication for transplant
 RUNX1::RUNX1T1 / CBFβ::MYH11	Favorable-risk CBF AML	Sensitive to cytarabine-based chemotherapy; GO benefit in CBF AML	Excellent ; fusion transcript monitoring by qPCR	Intensive chemotherapy + consideration of gemtuzumab ozogamicin; transplant guided mainly by MRN persistence
 KMT2A rearrangement	Generally adverse/intermediate depending on partner and context	Predicts sensitivity to menin inhibition	Fusion-based MRD possible in selected cases	Menin inhibitors such as revumenib/ziftomenib in R/R or investigational frontline combinations
 NUP98 rearrangement	Adverse ; often HOX-driven biology	Potential sensitivity to menin inhibition	Molecular monitoring possible if fusion identifiable	Clinical trial priority; consider menin inhibitor strategies where available
 RUNX1 mutation	Adverse in ELN 2022 when not defining another entity	No approved direct targeted therapy	Not ideal as MRD marker alone	Supports adverse-risk allocation; transplant-oriented strategy if fit
 ASXL1 mutation	Adverse /MDS-related biology	No direct approved targeted therapy	Poor MRD marker due to CHIP/preleukemic persistence	Suggests secondary/ontogeny-related AML; consider transplant or clinical trial
 Spliceosome genes (SRSF2, SF3B1, U2AF1, ZRSR2)	Adverse /MDS-related biology	No established targeted therapy in AML	Poor MRD markers alone	Suggest adverse-risk biology; relevant for classification and transplant consideration
 DTA mutations (DNMT3A, TET2, ASXL1)	Often age-related/preleukemic; prognostic impact context-dependent	TET2/IDH/NPM1 patterns may influence venetoclax sensitivity	Not reliable alone for MRD (because of clonal hematopoiesis persistence)	Should not be overinterpreted as residual leukemia without accompanying AML-defining markers
 RAS pathway (NRAS, KRAS, PTPN11)	Variable; often associated with resistance in HMA-VEN settings	May predict inferior response duration to venetoclax-based therapy	Not standard MRD marker	Consider clinical trial or alternative combinations; may mediate resistance to targeted therapies
 WT1	Often adverse when persistent or co-mutated	No approved direct targeted therapy	Can be used for MRD in selected settings, but less specific than NPM1/fusions	Supports closer monitoring; may influence transplant consideration if persistent
 Germline mutations (DDX41, RUNX1, GATA2, CEBPA, TP53)	Prognostic impact varies by syndrome and AML biology	Predictive role indirect, mainly through treatment tolerance and donor selection	Not MRD markers	Crucial for genetic counseling, donor selection, family screening, and surveillance

AML, acute myeloid leukemia; CBF, core-binding factor; CHIP, clonal hematopoiesis of indeterminate potential; ELN, European LeukemiaNet; FLT3-ITD, FLT3 internal tandem duplication; GO, gemtuzumab ozogamicin; HMA-VEN, hypomethylating agent plus venetoclax; MRD, measurable residual disease; qPCR, quantitative polymerase chain reaction; R/R, relapsed/refractory; TKI, tyrosine kinase inhibitor.
Table created and adapted from Döhner et al. *Blood* 2022;142:1-11. Döhner et al. *Blood* 2024;144:2211-2222 [33], DiNardo et al. *Blood* 2020;135:791-803 [23], Battaller et al. *Blood Adv.* 2024;8:927-935 [32], Hernández-Sánchez et al. *Leukemia*. 2021;35:2845-2857 [56], and additional cited literature.

Table 1. Clinical implications of major molecular markers in AML. Summary of the diagnostic, prognostic, predictive, MRD-monitoring, and therapeutic implications of selected molecular abnormalities with immediate relevance to clinical decision-making in AML. The clinical significance of individual markers may vary according to treatment context, co-mutational architecture, clonal hierarchy, and response kinetics. Table created by the authors based on the literature cited in the text.^{1,7,18,19,20,55}

Figure 4. Co-mutational refinement of *NPM1*-mutated AML according to the HARMONY model

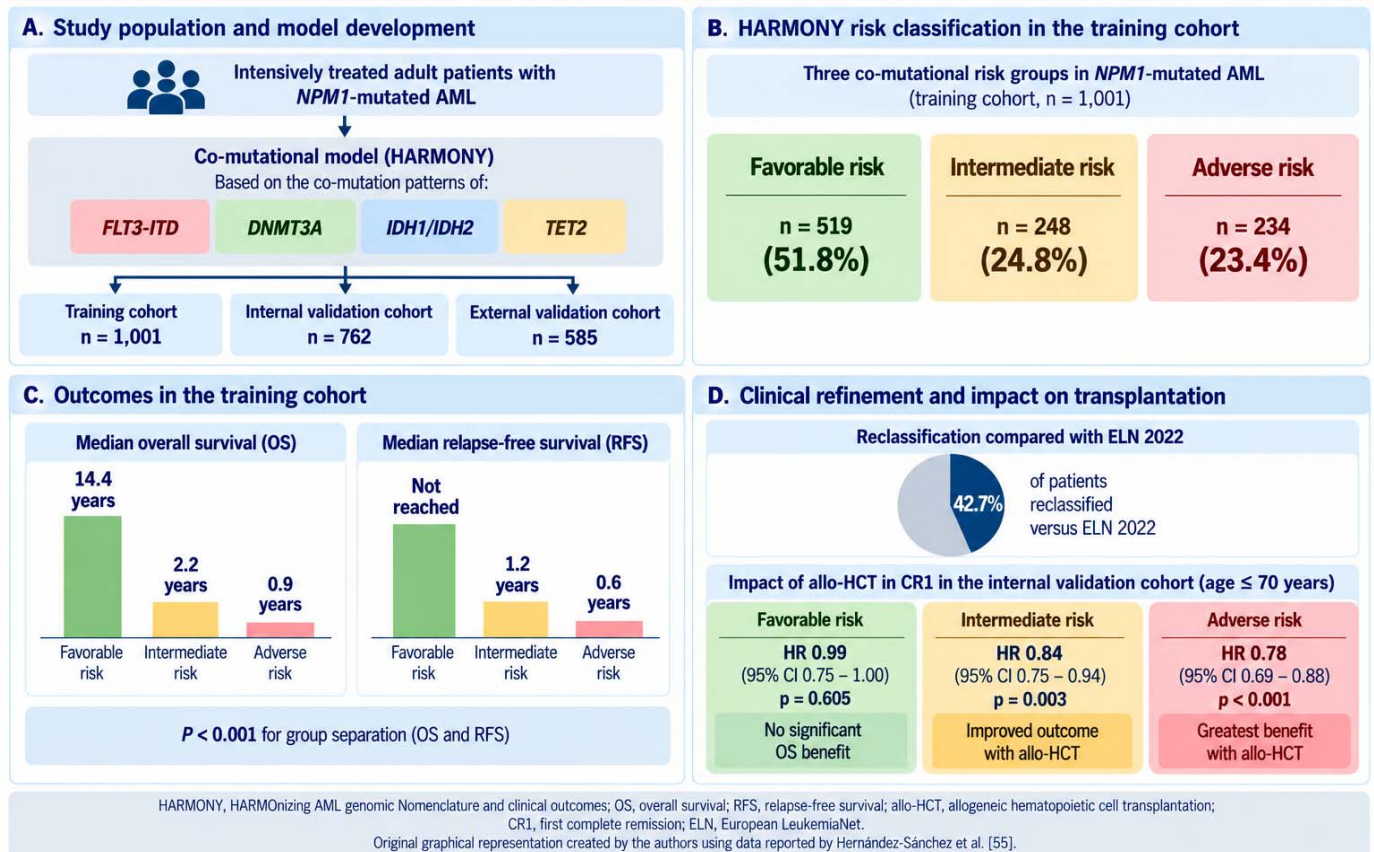


Figure 4. Co-mutational refinement of *NPM1*-mutated AML according to the HARMONY model. The HARMONY classification integrates co-mutational patterns involving FLT3-ITD, DNMT3A, IDH1/IDH2, and TET2 to stratify intensively treated *NPM1*-mutated AML into favorable-, intermediate-, and adverse-risk groups. In the training cohort, median OS was 14.4, 2.2, and 0.9 years, respectively, and 42.7% of patients were reclassified compared with ELN 2022. In the internal validation cohort, allo-HCT in CR1 was not associated with improved OS in favorable-risk patients but was associated with improved outcomes in intermediate- and adverse-risk patients, with the greatest benefit observed in the adverse-risk subgroup. Original graphical representation created by the authors using data reported by Hernández-Sánchez et al.⁵⁵

IDH1 and IDH2 Mutations: Biology, Prognosis, and Targeted Therapy. IDH1 and IDH2 mutations occur in approximately 15-20% of adult AML and represent a model of how metabolic alterations can drive epigenetic leukemogenesis. Mutant IDH enzymes acquire neomorphic activity that converts alpha-ketoglutarate to 2-hydroxyglutarate, an oncometabolite that inhibits alpha-ketoglutarate-dependent dioxygenases and alters DNA and histone methylation.²⁶⁻²⁸

Sequencing studies first identified recurrent IDH mutations in AML, revealing previously unrecognized metabolic drivers.²⁶ Subsequent analyses demonstrated that IDH1 and IDH2 mutations are frequent in cytogenetically normal AML and may define biologically distinct subgroups.^{29,30} However, their prognostic impact has remained controversial. Some studies suggested favorable outcomes in specific *NPM1*-mutated, FLT3-ITD-negative contexts, whereas others identified adverse effects depending on mutation type, co-mutations, and treatment.³¹⁻³⁴ IDH1 mutations most commonly involve R132, whereas IDH2 mutations involve R140 or R172. This distinction

matters clinically. IDH2 R140 appears more frequent and often coexists with *NPM1* mutations, whereas IDH2 R172 may have different biology and prognostic implications. IDH2 mutations are particularly relevant in older AML and in lower-intensity therapy settings, where responses to azacitidine-venetoclax can be substantial.^{7,19}

The development of mutant IDH inhibitors transformed IDH-mutated AML from a biologically interesting subgroup into a therapeutically actionable disease entity. Ivosidenib, an oral selective inhibitor of mutant IDH1, demonstrated durable clinical activity in relapsed/refractory (R/R) IDH1-mutated AML. In the pivotal phase I study by DiNardo et al., ivosidenib monotherapy achieved an overall response rate (ORR) of 41.6%, with complete remission (CR) rates of approximately 21.6% and a median overall survival (OS) of 8.8 months in R/R AML.³⁶ Importantly, several responding patients achieved transfusion independence and molecular clearance of IDH1-mutated clones, supporting the biologic activity of differentiation-directed therapy.

The AGILE trial expanded the therapeutic role of ivosidenib by evaluating azacitidine plus ivosidenib versus azacitidine plus placebo in newly diagnosed IDH1-mutated AML patients considered unfit for intensive chemotherapy.³⁵ The combination demonstrated significant improvements across multiple clinically relevant endpoints. Median event-free survival (EFS) improved from 7.9 months in the azacitidine-alone arm to 17.5 months in the ivosidenib-azacitidine arm, while median OS improved from 7.9 to 24.0 months, respectively.³⁵ Composite CR rates also increased substantially, reaching approximately 47% with the combination versus 15% with azacitidine alone.³⁵ These findings established ivosidenib plus azacitidine as one of the most effective molecularly targeted frontline strategies currently available for unfit AML patients.

In contrast, enasidenib, a selective inhibitor of mutant IDH2, followed a different regulatory trajectory. Enasidenib received FDA approval in 2017 for relapsed/refractory IDH2-mutated AML based on a multicenter phase I/II trial demonstrating clinically meaningful activity.³⁷ In this study, enasidenib achieved an overall response rate of 40.3%, with median OS of 9.3 months among patients with relapsed/refractory AML.³⁷

Enasidenib also demonstrated clinical activity in older patients with newly diagnosed IDH2-mutated AML who were not candidates for intensive chemotherapy. However, despite encouraging results, enasidenib has not received EMA approval for AML treatment, limiting its availability in Europe.³⁸

Multiple studies showed that HMA-VEN combinations frequently achieve CR/CRi rates exceeding 75% in IDH1- and IDH2-mutated AML, with median OS approaching or surpassing 20 months in selected cohorts.^{7,18,19} Consequently, the optimal integration of IDH inhibitors with venetoclax-based regimens remains an active area of clinical investigation, particularly regarding frontline triplet combinations and post-relapse therapeutic sequencing.

FLT3-Mutated AML. FLT3 mutations are among the most clinically important lesions in AML. FLT3 encodes a class III receptor tyrosine kinase that regulates hematopoietic progenitor proliferation and survival. Activating mutations produce constitutive signaling through STAT5, PI3K/AKT, and RAS/MAPK pathways. FLT3 internal tandem duplications occur in roughly one quarter of AML patients, whereas tyrosine kinase domain mutations are less frequent.^{39,40}

FLT3 alterations are detected in approximately 25–30% of adult AML cases and are broadly divided into internal tandem duplications (FLT3-ITD) and tyrosine kinase domain mutations (FLT3-TKD). FLT3-ITD mutations usually involve the juxtamembrane domain and are historically associated with hyperleukocytosis, high relapse risk, short remission duration, and inferior

overall survival. FLT3-TKD mutations, most frequently involving codon D835, generally have a less consistent adverse prognostic impact but remain therapeutically relevant because they influence sensitivity and resistance patterns to different FLT3 inhibitors.^{39,40} The increasing availability of FLT3 inhibitors and the variability of allelic ratio measurement across laboratories led ELN 2022 to remove FLT3-ITD allelic ratio from formal risk classification.¹

The first major therapeutic advance in FLT3-mutated AML was the RATIFY trial, which demonstrated that adding midostaurin to intensive induction and consolidation chemotherapy improved survival in newly diagnosed FLT3-mutated AML.⁴¹ In RATIFY, midostaurin combined with standard “7+3” induction and high-dose cytarabine consolidation reduced the risk of death compared with chemotherapy alone, with a median overall survival of 74.7 months versus 25.6 months, respectively.⁴¹ The benefit was observed across FLT3-ITD and FLT3-TKD subgroups, establishing FLT3 inhibition as a standard component of frontline intensive therapy in fit patients with FLT3-mutated AML. In relapsed or refractory FLT3-mutated AML, gilteritinib represented a second major step forward. The ADMIRAL trial compared gilteritinib with investigator-choice salvage chemotherapy in relapsed/refractory FLT3-mutated AML and demonstrated superior overall survival with gilteritinib.⁴² Median OS was 9.3 months with gilteritinib versus 5.6 months with salvage chemotherapy, and the composite complete remission rate was higher in the gilteritinib arm.⁴² These results established gilteritinib as a preferred targeted therapy in relapsed/refractory FLT3-mutated AML, reinforcing the importance of repeating FLT3 testing at relapse, given the dynamic acquisition or loss of FLT3 mutations during clonal evolution.^{43,44} Quizartinib, a potent type II FLT3 inhibitor with strong activity against FLT3-ITD, further expanded the therapeutic landscape. In the QuANTUM-First trial, adding quizartinib to intensive chemotherapy, followed by continuation therapy, improved survival in newly diagnosed FLT3-ITD-positive AML.⁴⁵ The trial demonstrated a median overall survival of 31.9 months with quizartinib versus 15.1 months with placebo, supporting the integration of quizartinib into frontline therapy for FLT3-ITD AML.⁴⁵ Unlike midostaurin and gilteritinib, quizartinib is more selective for FLT3-ITD and has limited activity against certain TKD resistance mutations, an important consideration when sequencing FLT3 inhibitors. The role of FLT3 inhibitors does not end with induction or salvage therapy. Post-transplant maintenance has emerged as a clinically relevant strategy to reduce relapse risk in FLT3-ITD AML. In the randomized phase II SORMAIN trial, sorafenib maintenance after allo-HCT significantly reduced the risk of relapse or death compared with placebo (HR, 0.39; 95% CI, 0.18–0.85;

$P=0.013$), with a 24-month RFS of 85.0% versus 53.3%, respectively.⁴⁶ Real-world data have also supported the effectiveness of FLT3 inhibition in the transplant pathway: in the Italian study by Cairoli et al., including 205 patients with relapsed/refractory FLT3-mutated AML treated with gilteritinib, median OS was 11.0 months; among 124 transplant-eligible patients, 52.4% achieved CR and 48% subsequently underwent allo-HCT.⁴⁷ Quizartinib has been approved as part of frontline therapy for newly diagnosed FLT3-ITD-mutated AML, including continuation maintenance after consolidation.⁴⁵ In contrast, gilteritinib narrowly failed to meet the primary RFS endpoint of the phase III MORPHO study in the overall post-transplant population (HR, 0.679; 95% CI, 0.459–1.005; $P=0.0518$).⁴⁷ However, patients with detectable peri-transplant FLT3-ITD MRD had a significant RFS benefit (HR, 0.515; 95% CI, 0.316–0.838; $P=0.0065$).⁴⁸ These findings suggest that maintenance FLT3 inhibition may be most effective in molecularly selected patients. Resistance to FLT3 inhibitors remains a major clinical challenge. Mechanisms include acquisition of secondary FLT3-TKD mutations, activation of parallel signaling pathways such as RAS/MAPK, persistence of FLT3-independent clones, and clonal evolution under therapeutic pressure.^{39,49,50} Type I FLT3 inhibitors, including gilteritinib and midostaurin, retain activity against both FLT3-ITD and FLT3-TKD mutations because they bind the receptor in its active conformation. In contrast, type II inhibitors such as quizartinib and sorafenib bind the inactive conformation of FLT3 and therefore lack activity against FLT3-TKD mutations, particularly D835 variants.

The interaction between FLT3 mutations and venetoclax-based lower-intensity regimens has become increasingly relevant. FLT3-mutated AML may achieve initial responses to HMA-VEN, but remission duration is often shorter than in NPM1- or IDH-mutated AML, likely due to persistent proliferative signaling and early clonal escape.^{7,19} This observation has provided the rationale for triplet regimens combining HMA-VEN with FLT3 inhibitors, particularly gilteritinib or quizartinib, in older/unfit or relapsed/refractory FLT3-mutated AML.

An emerging investigational concept is that of “FLT3-like” AML, referring to FLT3-ITD-negative leukemias that may nevertheless exhibit biologically relevant FLT3 pathway activation. Although FLT3-ITD remains the best-characterized mechanism of FLT3 signaling dysregulation, a substantial proportion of AML cases express high levels of wild-type FLT3, and increased FLT3 pathway activity has been documented even in the absence of canonical FLT3 mutations. While this remains a biologic hypothesis rather than a formally recognized AML subtype, these observations support therapeutic targeting of wild-type FLT3 signaling in

selected patients. This hypothesis underpins the ongoing QuANTUM-Wild trial, a global randomized phase III study evaluating quizartinib combined with intensive chemotherapy followed by maintenance therapy in newly diagnosed FLT3-ITD-negative AML. The study aims to determine whether pharmacologic inhibition of wild-type FLT3 signaling can improve outcomes in selected patients lacking canonical FLT3 mutations. Importantly, the trial incorporates induction, consolidation, and maintenance phases, with overall survival as the primary endpoint and measurable residual disease (MRD) negativity among key secondary endpoints.⁵¹

NPM1-Mutated AML and Co-Mutational Refinement. NPM1-mutated AML represents one of the most biologically distinctive and clinically relevant AML entities and accounts for approximately 25–30% of adult AML, with particular enrichment among patients with cytogenetically normal disease.⁵² Historically, NPM1-mutated AML without FLT3-ITD was considered a favorable-risk subtype according to ELN classification, reflecting high complete remission rates, chemosensitivity, and relatively favorable long-term survival after intensive chemotherapy.¹ However, increasing genomic resolution has demonstrated that NPM1-mutated AML is not a homogeneous favorable-risk entity. Instead, co-mutational architecture, clonal hierarchy, MRD kinetics, and treatment context substantially modify prognosis.^{54,55}

The HARMONY study represents one of the most important recent attempts to refine risk stratification within NPM1-mutated AML using large-scale co-mutational profiling.⁵⁵ The study analyzed intensively treated adults with NPM1-mutated AML and developed a co-mutational classification incorporating FLT3-ITD, DNMT3A, IDH1/IDH2, and TET2 alterations. The model was subsequently validated in independent cohorts, supporting its robustness and potential clinical applicability.⁵⁵

In the HARMONY study, co-mutational profiling identified clinically distinct prognostic groups within NPM1-mutated AML, demonstrating substantial heterogeneity beyond traditional ELN 2022 classification. Importantly, a large proportion of patients were reassigned to different risk categories, supporting the idea that co-mutational architecture provides clinically relevant prognostic information beyond NPM1 and FLT3-ITD status alone.⁵⁵

The adverse impact of co-mutational architecture was most evident in patients with combined NPM1, FLT3-ITD, and DNMT3A mutations. This “triple-mutated” genotype represents a clinically significant subgroup of NPM1-mutated AML and is associated with higher leukemic burden, increased relapse risk, and inferior survival.^{53,54} DNMT3A and FLT3 alterations frequently

co-occur in NPM1-mutated AML, supporting a biologic interaction between these lesions and potentially contributing to the adverse prognosis observed in triple-mutated disease.^{54,55}

Taken together, these observations highlight the transition from single-gene prognostication toward integrated molecular risk assessment in NPM1-mutated AML.

This refined classification has direct clinical relevance for transplant decision-making. In HARMONY, the benefit of allo-HCT in first complete remission was not uniform across molecular subgroups and appeared greatest among patients classified as adverse risk. These findings support a risk-adapted transplant strategy in NPM1-mutated AML rather than automatic reliance on ELN 2022 categories alone.⁵³

MRD kinetics further refine this decision-making process. NPM1 mutations are among the most reliable molecular MRD markers in AML because they are leukemia-specific, stable across disease evolution in most patients, and quantifiable with high sensitivity by RT-qPCR.^{24,25} The German-Austrian AML Study Group demonstrated that persistence of NPM1-mutated transcripts after chemotherapy strongly predicts relapse and inferior survival. In contrast, molecular clearance identifies patients with substantially better relapse-free and overall survival.^{24,25} Subsequent studies confirmed that post-induction and post-consolidation NPM1 MRD status can outperform baseline genetic risk in predicting relapse.²⁵

Therefore, the therapeutic implications of NPM1-mutated AML should be interpreted through a dual framework: baseline co-mutational risk and dynamic MRD response. Patients with favorable HARMONY classification and rapid NPM1 MRD clearance may be managed with chemotherapy consolidation or non-transplant strategies. In contrast, adverse co-mutational profiles, persistent NPM1 MRD, or delayed molecular clearance identify patients at higher relapse risk and may contribute to decisions regarding post-remission therapy, clinical trials, or allo-HCT in CR1.^{24,25}

The emergence of venetoclax-based lower-intensity regimens has further modified the clinical interpretation of NPM1-mutated AML. Multiple studies demonstrated that NPM1-mutated AML is highly sensitive to HMA-VEN therapy, frequently achieving CR/CRi rates above 80% and deep molecular responses.^{7,19} These findings suggest that NPM1 mutation functions not only as a favorable prognostic marker in intensive chemotherapy but also as a predictive marker of venetoclax sensitivity in older or unfit patients.

Overall, NPM1-mutated AML illustrates the transition from single-gene prognostication to integrated molecular decision-making. The HARMONY study demonstrates that co-mutational patterns involving DNMT3A, FLT3-ITD, IDH1/2, and TET2 can

meaningfully reclassify risk, predict OS and RFS, and guide transplant allocation. When combined with MRD kinetics, this refined genomic approach provides a more clinically actionable framework for individualized therapy than ELN classification alone.^{24,25,55}

Mechanistically, NPM1-mutated AML depends on HOX/MEIS transcriptional programs, creating vulnerability to menin inhibition. Therefore, NPM1 status is now relevant not only for prognosis and MRD, but also for emerging targeted therapy selection.

KIT Mutations in Core-Binding Factor AML. Core-binding factor AML (CBF-AML), defined by the presence of RUNX1::RUNX1T1 resulting from t(8;21)(q22;q22) or CBFB::MYH11 associated with inv(16)/t(16;16), has historically been considered a favorable-risk AML subtype because of its high sensitivity to cytarabine-based chemotherapy and relatively favorable long-term survival.¹ However, increasing molecular characterization demonstrated that CBF-AML is biologically heterogeneous and that co-occurring mutations may substantially influence relapse risk and therapeutic outcomes.

Among secondary molecular lesions, KIT mutations represent the most clinically relevant co-mutations in CBF-AML. KIT encodes a receptor tyrosine kinase involved in hematopoietic proliferation and survival, and activating KIT mutations occur in approximately 20–40% of CBF-AML cases, particularly in t(8;21) AML.^{56,57} Most mutations involve exon 17, including D816 substitutions, or less commonly exon 8 alterations. Constitutive KIT activation promotes downstream proliferative signaling through MAPK and PI3K/AKT pathways and may partially counterbalance the otherwise favorable biologic behavior of CBF leukemia.

Several studies demonstrated that KIT mutations, particularly exon 17 mutations in t(8;21) AML, are associated with increased relapse risk and inferior relapse-free survival.^{56,57} However, their prognostic impact appears less pronounced in inv(16) AML, suggesting biologic differences between CBF subtypes. Importantly, intensive cytarabine-based consolidation and achievement of deep molecular MRD clearance may partly mitigate the adverse effect of KIT mutations.

Integrating measurable residual disease monitoring has substantially refined risk stratification in CBF-AML. Quantitative PCR assessment of RUNX1::RUNX1T1 and CBFB::MYH11 transcripts allows highly sensitive MRD monitoring and frequently provides more clinically relevant prognostic information than KIT mutation status alone.¹ Consequently, current therapeutic decision-making increasingly integrates KIT mutational status with MRD kinetics rather than relying exclusively on baseline genomics.

Another major therapeutic development in CBF-AML has been the incorporation of gemtuzumab

ozogamicin (GO), an anti-CD33 antibody-drug conjugate linked to calicheamicin. Because most CBF-AML blasts strongly express CD33, this subtype appears particularly sensitive to GO-containing regimens. The ALFA-0701 trial showed that adding fractionated-dose GO to standard induction chemotherapy improved event-free survival in newly diagnosed AML.⁵⁸ Although the benefit was observed across several molecular groups, subgroup analyses and subsequent studies suggested that favorable-risk AML, particularly CBF-AML, derived some of the greatest benefit from GO-based therapy.

Importantly, an individual patient data meta-analysis by Hills et al. showed that GO significantly reduced relapse risk and improved survival, particularly in favorable-risk AML.⁵⁹ In this meta-analysis involving more than 3000 AML patients, the survival benefit associated with GO was most pronounced among patients with favorable cytogenetics, including CBF-AML.⁵⁹ These findings established GO as one of the few targeted agents that can improve outcomes in biologically favorable AML subsets.

Although KIT mutations increase relapse risk in CBF-AML, several studies suggest that intensified treatment strategies incorporating GO may partially overcome the adverse prognostic effect associated with KIT-mutated disease.^{56,59}

From a biologic perspective, CBF-AML represents an important example of how co-mutational architecture modifies prognosis within otherwise favorable genomic subtypes. While RUNX1::RUNX1T1 and CBFB::MYH11 define chemotherapy-sensitive leukemia, additional lesions such as KIT mutations may increase proliferative signaling, relapse risk, and MRD persistence. Nevertheless, integration of GO-containing regimens and MRD-guided therapeutic strategies has substantially improved risk adaptation in this setting.

KMT2A Rearrangement, NUP98-Rearranged AML and Menin Inhibition. KMT2A rearrangements generate fusion proteins that promote persistent activation of HOXA and MEIS1 transcriptional programs through interaction with menin, a critical chromatin-associated cofactor.⁶⁰ Importantly, NPM1-mutated AML also demonstrates dependency on HOXA/MEIS1 signaling despite lacking KMT2A rearrangements, providing the biologic rationale for menin inhibition in both AML subtypes.⁶⁰ NUP98-rearranged leukemias similarly activate HOX/MEIS1 transcriptional programs and may also depend on the menin-KMT2A interaction, extending the biologic rationale for menin-directed therapy beyond the two canonical molecular subgroups.⁶⁵ Accordingly, menin inhibition has evolved from an experimental epigenetic strategy into a clinically validated therapeutic approach in molecularly defined acute leukemias.

Revumenib was the first menin inhibitor to enter clinical practice. In the phase I/II AUGMENT-101 study, revumenib demonstrated clinically meaningful activity in heavily pretreated patients with relapsed/refractory (R/R) KMT2A-rearranged acute leukemia. In the phase II efficacy population, the CR/CRh rate was 22.8%, the overall response rate (ORR) was 63.2%, and approximately 70% of evaluable CR/CRh responders achieved MRD negativity.⁶² These results supported FDA approval in 2024 for adult and pediatric patients aged ≥ 1 year with R/R acute leukemia harboring a KMT2A translocation. Subsequent AUGMENT-101 results in NPM1-mutated R/R AML showed a CR/CRh rate of 23.4% and an ORR of 46.9%, including activity in patients previously exposed to venetoclax, leading to expansion of the FDA indication to this molecular subgroup in 2025.⁶³ Differentiation syndrome and QTc prolongation remain clinically relevant toxicities requiring appropriate monitoring.

Ziftomenib has similarly transitioned to an approved molecularly targeted therapy. In the phase II KOMET-001 study, ziftomenib 600 mg once daily achieved a CR/CRh rate of 22% and an ORR of 33% in R/R NPM1-mutated AML, with MRD negativity in 61% of evaluable CR/CRh responders.⁶⁴ These results supported FDA approval in 2025 for adults with R/R NPM1-mutated AML without satisfactory alternative treatment options. In contrast, activity in KMT2A-rearranged AML was lower, highlighting that molecular dependencies within menin-sensitive leukemias are not necessarily equivalent across agents. Thus, revumenib and ziftomenib provide clinical validation of menin dependency as an actionable vulnerability in molecularly selected R/R acute leukemia.

The therapeutic landscape is rapidly expanding beyond these first approved agents. Next-generation menin inhibitors, particularly enzomenib (DSP-5336) and bleximenib (JNJ-75276617), have demonstrated encouraging early single-agent activity in both KMT2A-rearranged and NPM1-mutated R/R AML.⁶⁵ These findings support the development of menin inhibition as a therapeutic class rather than an agent-specific strategy, although cross-trial comparisons remain inappropriate and these compounds require prospective validation.

A major direction is incorporating menin inhibitors into combination regimens and earlier treatment settings. Revumenib is being investigated with both venetoclax-based lower-intensity therapy and intensive chemotherapy. The all-oral SAVE regimen combining revumenib, decitabine/cedazuridine and venetoclax has demonstrated high response rates in NPM1-mutated, KMT2A-rearranged and NUP98-rearranged AML.⁶⁶ In fit patients with newly diagnosed NPM1-mutated AML, the phase III REVEAL-ND NPM1 trial is evaluating the addition of revumenib to standard intensive chemotherapy.⁶⁵ In patients aged ≥ 60 years with newly diagnosed NPM1-mutated or KMT2A-rearranged AML,

a phase I study of azacitidine, venetoclax, and revumenib reported an ORR of 88.4%, a composite CR rate of 81.4%, and MRD negativity by centralized flow cytometry in all 37 evaluable patients.⁶¹ Similarly, the KOMET clinical development program is evaluating ziftomenib with both intensive chemotherapy and azacitidine/venetoclax, following encouraging early combination data from KOMET-007.⁶⁵ These approaches remain investigational and require confirmation of response durability and survival benefit before routine frontline incorporation.

Importantly, the expanding menin-inhibitor class is also redefining molecular monitoring and resistance. Acquired somatic MEN1 mutations at the inhibitor-binding interface can impair drug binding while preserving menin function, thereby mediating therapeutic escape.⁶⁷ Resistance appears heterogeneous across individual inhibitors, with some MEN1 substitutions conferring cross-resistance and others producing agent-specific resistance patterns. In 2026, mutation-guided switching from revumenib to bleximenib was reported to eradicate an emergent MEN1^{M327I} resistant clone in a patient with KMT2A-rearranged AML, providing clinical proof-of-concept that resistance profiling may eventually guide sequencing within the menin-inhibitor class.⁶⁸ However, this observation derives from limited clinical experience and should be regarded as hypothesis-generating rather than an established therapeutic strategy. Sensitive detection of emergent MEN1 resistance mutations, including through circulating cell-free DNA, has also been demonstrated and could potentially identify molecular escape before overt hematologic progression, although the optimal assay, timing, and clinical consequences of such monitoring remain to be established.⁶⁹

Overall, menin inhibitors represent a paradigm shift from mutation-directed therapy toward dependency-directed precision medicine. KMT2A rearrangements and NPM1 mutations now identify clinically actionable menin dependence, whereas NUP98 rearrangements and other HOX/MEIS1-driven leukemias represent emerging investigational extensions of this framework. The development of multiple agents, combination strategies, and molecularly defined resistance mechanisms suggests that menin inhibition may ultimately require a longitudinal approach integrating molecular identification, response assessment, characterization of treatment-emergent resistance, and rational sequencing of targeted therapy.

TP53-Mutated AML: Persistent Adverse Risk and Therapeutic Challenges. TP53-mutated AML represents one of the most biologically distinct and therapeutically challenging AML subgroups and is frequently associated with therapy-related disease,

complex and monosomal karyotypes, chemoresistance, and poor survival. TP53 mutations identify adverse-risk disease within the ELN 2022 classification for intensively treated AML¹ and retain a major adverse prognostic role in patients receiving less-intensive therapy, although their prognostic impact is further influenced by cytogenetic context and allelic configuration.^{19,20} In particular, multihit TP53 alterations and their frequent association with complex cytogenetics identify patients with particularly unfavorable disease biology.

Contemporary therapies have not substantially overcome this adverse prognosis. Although hypomethylating agents and venetoclax-based combinations can induce remission in TP53-mutated AML, responses are frequently short-lived and have not translated into the survival improvements observed in other molecular subgroups.^{7,18} In the 2026 COMMAND registry study of 652 patients with newly diagnosed TP53-mutated AML, including 321 treated with HMA-based induction, decitabine was associated with a higher CR/CRi rate than azacitidine among response-evaluable patients (54% vs 39%), but no significant differences in EFS or OS were observed after propensity matching. Multihit TP53 status independently predicted inferior EFS and OS, further supporting the importance of allelic configuration beyond TP53 mutation status alone.⁷¹

Attempts to improve outcomes through novel targeted or immune-based strategies have also been disappointing. In the phase III ENHANCE-2 trial, magrolimab plus azacitidine failed to improve survival in previously untreated TP53-mutated AML. Among patients ineligible for intensive therapy, median OS was 4.4 months with magrolimab plus azacitidine versus 6.6 months with venetoclax plus azacitidine, while no survival advantage was observed over intensive chemotherapy in fit patients.⁷² These findings illustrate the difficulty of therapeutically overcoming TP53-driven biology and, together with the limited durability of responses to currently available regimens, reinforce the need for novel therapeutic approaches.

Allo-HCT occupies a distinct position in this setting. TP53 mutations remain associated with a high risk of post-transplant relapse and inferior survival, and allo-HCT should therefore not be regarded as overcoming the adverse prognostic effect of TP53. Nevertheless, it remains the only currently available treatment capable of providing durable disease control and potential cure in a minority of appropriately selected patients. A systematic review and meta-analysis including 297 patients with TP53-mutated AML undergoing allo-HCT reported a pooled 2-year OS of 29.7%, despite a relapse rate of 61.4%, supporting the concept that transplantation can provide meaningful long-term survival in a subset of patients despite the overall poor prognosis.⁷⁰ Outcomes after transplantation appear heterogeneous and may be

influenced by disease status, cytogenetic complexity, TP53 allelic burden, and depth of molecular response at transplantation. Consistent with this heterogeneity, a 2026 multicenter study showed that pre-transplant TP53 VAF >0.1% in AML/MDS-AML was associated with inferior 2-year OS (47.2% vs 77.2%), EFS (30.7% vs 70.5%), and a markedly higher cumulative incidence of relapse (62.3% vs 12.8%) compared with VAF ≤0.1%.⁷³ These findings suggest that quantitative TP53 molecular burden may help refine transplant prognostication, although prospective validation is required before specific molecular thresholds can guide transplant decisions.

Overall, TP53-mutated AML remains a major unmet therapeutic need across both intensive and less-intensive treatment settings. Available non-transplant therapies can achieve initial disease control but rarely provide durable remission, whereas allo-HCT, despite its substantial relapse risk and inability to eliminate the adverse prognostic impact of TP53, offers the possibility of long-term disease control in a selected minority of patients. Improved patient selection for transplantation, deeper pre-transplant disease control, and development of effective novel therapies therefore remain major priorities for this molecular subgroup.

Germline Predisposition and Inherited Myeloid Malignancies. Broad next-generation sequencing (NGS) panels increasingly identify germline variants associated with inherited predisposition to myeloid malignancies.^{74,75} Recognition of these syndromes is clinically relevant because germline genetics may influence donor selection, family counseling, surveillance strategies, and therapeutic decisions.

Among inherited predisposition syndromes, germline DDX41 mutations are among the most common causes of hereditary adult myeloid neoplasms and frequently present as apparently sporadic late-onset AML or MDS.⁷⁴ Germline RUNX1 and CEBPA mutations predispose to familial AML, whereas GATA2 deficiency syndrome is associated with immunodeficiency, bone marrow failure, and progression to MDS/AML.^{74,75} Germline TP53 alterations associated with Li-Fraumeni syndrome may predispose to therapy-related or de novo AML and complicate management because of increased susceptibility to secondary malignancies.

Importantly, clinically asymptomatic related donors may harbor the same pathogenic variants, making germline recognition particularly relevant before allogeneic transplantation. Suspicion should arise in patients with early-onset AML, family history of hematologic malignancies, unexplained cytopenias, recurrent infections, multiple primary tumors, or detection of potentially germline variants on tumor-based sequencing, particularly when variant allele frequencies are near 50% or the variant persists during

remission.^{74,75} However, a suspected germline variant identified by tumor-only NGS should be confirmed using an appropriate non-hematopoietic tissue source, preferably cultured skin fibroblasts, before definitive genetic counseling or exclusion of a related donor.^{74,75}

Integrated Decision-Making Across Disease Phases

Modern AML management increasingly relies on dynamic integration of molecular profiling, treatment response, and MRD assessment across different disease phases. At diagnosis, molecular testing should define four key elements: disease classification, baseline risk, actionable therapeutic targets, and MRD-trackable markers. In fit patients, these data guide induction strategy, incorporation of FLT3 inhibitors or gemtuzumab ozogamicin, transplant planning, and clinical trial eligibility. In older or unfit patients, molecular profiling increasingly influences selection of venetoclax-based regimens, IDH inhibitor combinations, or investigational targeted approaches.

After induction, therapeutic decisions become increasingly response-adapted rather than exclusively baseline-risk adapted. Patients achieving deep molecular remission may continue consolidation, whereas persistent MRD identifies patients at increased relapse risk and may inform post-remission decisions when considered alongside baseline genetics, prior treatment, and patient-specific factors.^{1,24,25} Conversely, TP53-mutated AML remains associated with poor outcomes despite transplant consolidation, emphasizing the limitations of current therapeutic strategies in this subgroup. At relapse, repeat molecular testing should be performed whenever feasible because clonal evolution may substantially modify disease biology and therapeutic vulnerability. FLT3 mutations may emerge at relapse, resistance mutations may develop after targeted therapy exposure, and persistent NPM1-mutated disease may become eligible for menin inhibitor strategies. Consequently, relapse should be interpreted as a new molecular decision point rather than simply recurrence of the diagnostic disease.

The future of AML management will likely depend on adaptive risk models integrating baseline genomics, treatment-specific risk, MRD kinetics, clonal evolution, and patient fitness. Longitudinal sequencing, single-cell approaches, and integrated molecular monitoring may progressively refine prediction of relapse and therapeutic resistance. However, increasing biologic complexity will be clinically useful only if molecular models remain interpretable and can directly inform therapeutic decisions.

Conclusions. Molecular profiling has profoundly transformed the diagnostic and therapeutic landscape of AML, complementing morphology, immunophenotyping, and cytogenetics with genomic information that increasingly influences disease

classification, prognosis, therapeutic allocation, and measurable residual disease (MRD) monitoring. ELN 2022 remains the principal framework for risk stratification in intensively treated AML. In contrast, emerging data from venetoclax-based regimens demonstrate that molecular risk is increasingly treatment-dependent rather than universally fixed.

FLT3, IDH1/2, NPM1, TP53, KIT, KMT2A rearrangements, and NUP98 fusions all carry important clinical implications, but their significance must be interpreted within the broader context of co-mutational architecture, clonal hierarchy, treatment backbone, and MRD kinetics. The HARMONY study further demonstrated that co-mutational refinement may substantially modify prognosis within apparently favorable molecular subgroups such as NPM1-mutated AML.

References:

- Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. <https://doi.org/10.1182/blood.2022016867> PMID:35797463
- Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet*. 2023;401(10374):872-890. [https://doi.org/10.1016/S0140-6736\(22\)02043-5](https://doi.org/10.1016/S0140-6736(22)02043-5) PMID:37496192
- Cancer Genome Atlas Research Network, Ley TJ, Miller C, Ding L, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059-2074. <https://doi.org/10.1056/NEJMoa1301689> PMID:23634996
- Ley TJ, Mardis ER, Ding L, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature*. 2008;456(7218):66-72. <https://doi.org/10.1038/nature07485>
- Ley TJ, Ding L, Walter MJ, et al. DNMT3A mutations in acute myeloid leukemia. *N Engl J Med*. 2010;363(25):2424-2433. <https://doi.org/10.1056/NEJMoa1005143>
- Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221. <https://doi.org/10.1056/NEJMoa1516192> PMID:27276561
- DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135(11):791-803. <https://doi.org/10.1182/blood.2019003988> PMID:31932844
- Im AP, Sehgal AR, Carroll MP, et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies. *Leukemia*. 2014;28(9):1774-1783. <https://doi.org/10.1038/leu.2014.124> PMID:24699305
- Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy. *Blood*. 2020;135(24):2137-2145. <https://doi.org/10.1182/blood.2020004856>
- Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in AML patients. *Nat Med*. 2018;24(12):1859-1866. <https://doi.org/10.1038/s41591-018-0233-1> PMID:30420752
- Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089. <https://doi.org/10.1056/NEJMoa1112304> PMID:22417203
- DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated AML. *N Engl J Med*. 2020;383(7):617-629. <https://doi.org/10.1056/NEJMoa2012971> PMID:32786187
- Wei AH, Strickland SA Jr, Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. *J Clin Oncol*. 2019;37(15):1277-1284. <https://doi.org/10.1200/JCO.18.01600>
- Perl AE. The role of targeted therapy in the management of patients with AML. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):54-65. <https://doi.org/10.1182/hematology.2021000228> PMID:34889407
- Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood*. 2015;125(9):1367-1376. <https://doi.org/10.1182/blood-2014-11-610543> PMID:25550361
- Medeiros BC, Isidori A, Pollyea DA. AML ontogeny and molecular classification. *Leukemia*. 2021;35(1):18-30. <https://doi.org/10.1038/s41375-020-01047-z> PMID:37880705
- McCormick SR, McCormick MJ, Grutkoski PS, et al. Clonal evolution in acute myeloid leukemia. *Leukemia*. 2010;24(10):1773-1780. <https://doi.org/10.1038/leu.2010.124>
- Battaller A, Bazinet A, DiNardo CD, et al. Prognostic risk signature in AML treated with hypomethylating agents and venetoclax. *Blood Adv*. 2024;8(4):927-935. <https://doi.org/10.1182/bloodadvances.2023011757> PMID:38113472
- Döhner H, Pratz KW, DiNardo CD, et al. Genetic risk stratification in AML treated with venetoclax and azacitidine. *Blood*. 2024;144(21):2211-2222. <https://doi.org/10.1182/blood.2024024944> PMID:39133921
- Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. *Blood*. 2024;144(21):2169-2173. <https://doi.org/10.1182/blood.2024025409>
- Lachowicz CA, Zeidner JF, Othman J, et al.; PRISM-AML Investigators. Risk Prognostication After Hypomethylating Agents Combined With Venetoclax in Acute Myeloid Leukemia: The PRISM Risk Model. *J Clin Oncol*. 2026;44(25):2422-2434. <https://doi.org/10.1200/JCO-26-00347> PMID:42391582
- Issa GC, DiNardo CD. Therapeutic implications of molecular profiling in AML. *J Clin Oncol*. 2023;41(8):1605-1617. <https://doi.org/10.1200/JCO.22.02118> PMID:42852411
- Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2021;138(26):2753-2767. <https://doi.org/10.1182/blood.2021013626> PMID:34724563
- Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374(5):422-433. <https://doi.org/10.1056/NEJMoa1507471>
- Balsat M, Renneville A, Thomas X, et al. Postinduction minimal residual disease predicts outcome in NPM1-mutated AML. *Blood*. 2017;129(11):1315-1323. <https://doi.org/10.1182/blood-2016-08-735928>
- Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-234. <https://doi.org/10.1016/j.ccr.2010.01.020> PMID:20171147

The most important practical implication is that molecular assessment must be rapid, longitudinal, and clinically interpretable. Baseline NGS should guide initial therapeutic allocation, whereas sequential MRD and molecular monitoring should support adaptive decision-making during remission, transplantation, and relapse. Precision AML management is increasingly shifting from static baseline risk assessment toward dynamic molecular decision-making. Future therapeutic strategies will likely integrate genomic architecture, measurable residual disease kinetics, treatment-specific risk, and clonal evolution into adaptive models capable of guiding therapy across the entire disease course, from diagnosis to post-transplant surveillance and relapse management.

27. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH mutations result in epigenetic dysregulation. *Cancer Cell*. 2010;18(6):553-567. <https://doi.org/10.1016/j.ccr.2010.11.015> PMID:21130701
28. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-KG-dependent dioxygenases. *Cancer Cell*. 2011;19(1):17-30. <https://doi.org/10.1016/j.ccr.2010.12.014>
29. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations in AML. *J Clin Oncol*. 2010;28(22):3636-3643. <https://doi.org/10.1200/JCO.2010.28.3762> PMID:20567020
30. Marcucci G, Maharry K, Wu YZ, et al. IDH mutations identify novel prognostic subgroups in AML. *J Clin Oncol*. 2010;28(14):2348-2355. <https://doi.org/10.1200/JCO.2009.27.3730> PMID:20368543
31. Chou WC, Lei WC, Ko BS, et al. Prognostic implication of IDH mutations in AML. *Leukemia*. 2011;25(2):246-253. <https://doi.org/10.1038/leu.2010.274> PMID:21116280
32. Green CL, Evans CM, Zhao L, et al. The prognostic significance of CEBPA, NPM1 and FLT3 mutations in AML. *Blood*. 2010;116(21):354-362. <https://doi.org/10.1182/blood.V116.21.354.354>
33. Ravandi F, Patel K, Luthra R, et al. Clinical relevance of IDH mutations in AML. *Cancer*. 2012;118(6):1591-1599. <https://doi.org/10.1002/cncr.26412> PMID:21800291
34. Boissel N, Nibourel O, Renneville A, et al. Prognostic impact of IDH mutations in AML. *J Clin Oncol*. 2015;33(15):1721-1728. <https://doi.org/10.1200/JCO.2014.59.8764>
35. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated AML. *N Engl J Med*. 2022;386(16):1519-1531. <https://doi.org/10.1056/NEJMoa2117344> PMID:35443108
36. DiNardo CD, Stein EM, Zhao L, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed AML. *N Engl J Med*. 2018;378(25):2386-2398. <https://doi.org/10.1056/NEJMoa1716984> PMID:29860938
37. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant-IDH2 relapsed or refractory AML. *Blood*. 2017;130(6):722-731. <https://doi.org/10.1182/blood-2017-04-779405> PMID:28588020
38. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. 2019;33(11):2575-2584. <https://doi.org/10.1038/s41375-019-0472-2> PMID:30967620
39. Daver N, Schlenk RF, Russell NH, et al. Targeting FLT3 mutations in AML. *Blood Cancer J*. 2019;9(7):60. <https://doi.org/10.1038/s41408-019-0218-8> PMID:37880705
40. Levis M. FLT3 tyrosine kinase domain mutations in AML. *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-226. <https://doi.org/10.1182/asheducation-2013.1.220> PMID:24319184
41. Stone RM, Mandrekas SJ, Sanford BL, et al. Midostaurin plus chemotherapy for AML with FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464. <https://doi.org/10.1056/NEJMoa1614359> PMID:28644114
42. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740. <https://doi.org/10.1056/NEJMoa1902688> PMID:31665578
43. Schmalbrock LK, Dolnik A, Cocciardi S, et al. Clonal evolution of acute myeloid leukemia with FLT3-ITD mutation under treatment with midostaurin. *Blood*. 2021;137(22):3093-3104. <https://doi.org/10.1182/blood.2020007626>
44. Cloos J, Goemans BF, Hess CJ, et al. Stability and prognostic influence of FLT3 mutations in paired initial and relapsed AML samples. *Leukemia*. 2006;20(7):1217-1220. <https://doi.org/10.1038/sj.leu.2404246>
45. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10388):1571-1583. [https://doi.org/10.1016/S0140-6736\(23\)00464-6](https://doi.org/10.1016/S0140-6736(23)00464-6) PMID:37116523
46. Burchert A, Bug G, Fritz LV, et al. Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). *J Clin Oncol*. 2020;38(26):2993-3002. <https://doi.org/10.1200/JCO.19.03345> PMID:32673171
47. Cairoli R, Del Castello L, Imbergamo S, et al. Gilteritinib in FLT3-mutated acute myeloid leukemia: A real-world Italian experience. *Cancer*. 2025;131(17):e70055. <https://doi.org/10.1002/cncr.70055> PMID:40839405
48. Levis MJ, Hamadani M, Logan B, et al. Gilteritinib as Post-Transplant Maintenance for AML With Internal Tandem Duplication Mutation of FLT3. *J Clin Oncol*. 2024;42(15):1766-1775. <https://doi.org/10.1200/JCO.23.02474>
49. Alotaibi AS, Yilmaz M, Kanagal-Shamanna R, et al. Resistance patterns in AML treated with type I versus type II FLT3 inhibitors. *Blood Cancer Discov*. 2021;2(2):125-134. <https://doi.org/10.1158/2643-3230.BCD-20-0143> PMID:33681815
50. Alotaibi AS, Yilmaz M, Loghavi S, et al. Emergence of BCR-ABL1 fusion in AML post-FLT3 inhibitor therapy. *Front Oncol*. 2020;10:588876. <https://doi.org/10.3389/fonc.2020.588876> PMID:33194747
51. Montesinos P, Cheong JW, Dayer N, et al. Trial in progress: the phase 3, randomized, double-blind, placebo-controlled QuANTUM-Wild study of quizartinib in combination with chemotherapy and as single-agent maintenance in newly diagnosed, FLT3-ITD-negative acute myeloid leukemia. *Blood*. 2024;144(Suppl 1):1504.3-1504.5. <https://doi.org/10.1182/blood-2024-205101>
52. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in AML with normal karyotype. *N Engl J Med*. 2005;352(3):254-266. <https://doi.org/10.1056/NEJMoa041974>
53. Loghavi S, Zuo Z, Ravandi F, et al. Clinical features of triple-mutated AML. *Blood Adv*. 2021;5(7):1837-1847. <https://doi.org/10.1182/bloodadvances.2020004021>
54. Ostronoff F, Othus M, Gerbing RB, et al. NPM1 combined with FLT3-ITD and DNMT3A in AML prognosis. *Leukemia*. 2015;29(4):897-904. <https://doi.org/10.1038/leu.2014.273> PMID:25227910
55. Hernández-Sánchez A, Villaverde Ramiro A, Sträng E, et al. Unravelling co-mutational patterns with prognostic implications in NPM1-mutated adult acute myeloid leukemia: a HARMONY study. *Leukemia*. 2026;40:418-428. <https://doi.org/10.1038/s41375-025-02851-9> PMID:41535568
56. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B study. *J Clin Oncol*. 2006;24(24):3904-3911. <https://doi.org/10.1200/JCO.2006.06.9500> PMID:16921041
57. Cairoli R, Beghini A, Grillo G, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. *Blood*. 2006;107(9):3463-3468. <https://doi.org/10.1182/blood-2005-09-3532>
58. Castaigne S, Pautas C, Terré C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de novo acute myeloid leukemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;379(9825):1508-1516. [https://doi.org/10.1016/S0140-6736\(12\)60485-1](https://doi.org/10.1016/S0140-6736(12)60485-1)
59. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;15(9):986-996. [https://doi.org/10.1016/S1470-2045\(14\)70281-5](https://doi.org/10.1016/S1470-2045(14)70281-5) PMID:25008258
60. Krivtsov AV, Evans K, Gadrey JY, et al. A menin-MLL inhibitor induces specific chromatin changes and eradicates disease in models of MLL-rearranged leukemia. *Cancer Cell*. 2019;36(6):660-673. <https://doi.org/10.1016/j.ccell.2019.11.001> PMID:31821784
61. Zeidner JF, Lin TL, Welkie RL, et al. Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed NPM1-Mutated or KMT2A-Rearranged AML. *J Clin Oncol*. 2025;43(23):2606-2615. <https://doi.org/10.1200/JCO.25-00914> PMID:40504618
62. Issa GC, Aldoss I, Thirman MJ, et al. Menin Inhibition With Revumenib for KMT2A-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101). *J Clin Oncol*. 2025;43(1):75-84. <https://doi.org/10.1200/JCO.24.00826>
63. De Botton S, Grove CS, Mannis GN, et al. Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study. *Blood*. 2025;146(9):1065-1077. <https://doi.org/10.1182/blood.2025028357>
64. Wang ES, Montesinos P, Foran J, et al.; KOMET-001. Ziftomenib in Relapsed or Refractory NPM1-Mutated AML. *J Clin Oncol*. 2025;43(31):3381-3390. <https://doi.org/10.1200/JCO.25-01694> PMID:40997296
65. Watts J, Madarang E, Cierpicki T, Grembecka J. Menin inhibitors as a treatment for acute leukemia: from bench to the clinic. *Blood Neoplasia*. 2026;3(3):100253. <https://doi.org/10.1016/j.bneo.2026.100253> PMID:42519171
66. Issa GC, et al. All-Oral Combination of Revumenib, Decitabine, and Venetoclax for Relapsed or Refractory AML (SAVE). *J Clin Oncol*.

- 2026;44(22):2110-2120.
<https://doi.org/10.1200/JCO-26-01159> PMID:42272166
67. Perner F, Armstrong SA. Menin inhibition in acute myeloid leukemia: emerging mechanisms of resistance and therapeutic strategies. *Cancer Discovery*. 2024;14(2):214-228.
<https://doi.org/10.1158/2159-8290.CD-23-0674>
 68. Chin KK, Abdul-Hay M, Shukla M, et al. Overcoming MEN1-mediated resistance with menin inhibitor switching in KMT2A-rearranged acute myeloid leukemia. *Leukemia*. 2026;40(6):1331-1334.
<https://doi.org/10.1038/s41375-026-02959-6> PMID:41963592
 69. Shukla N, Charalambous K, Li S, et al. Detection of MEN1 resistance mutations in cell-free DNA from acute leukemia patients treated with menin inhibitors. *Blood Cancer J*. 2026;16(1):94.
<https://doi.org/10.1038/s41408-026-01545-4> PMID:42303978
 70. Shahzad M, Tariq E, Chaudhary SG, et al. Outcomes with allogeneic hematopoietic stem cell transplantation in TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis. *Leuk Lymphoma*. 2022;63(14):3409-3417.
<https://doi.org/10.1080/10428194.2022.2123228> PMID:36107118
 71. Badar T, Foran J, Jamy O, et al. Choice of hypomethylating agent for newly diagnosed TP53-mutant acute myeloid leukemia: a COMMAND registry study. *Leukemia*. 2026.
<https://doi.org/10.1038/s41375-026-03119-6>
 72. Zeidner JF, Sallman DA, Récher C, et al. Magrolimab plus azacitidine vs physician's choice for untreated TP53-mutated acute myeloid leukemia: the ENHANCE-2 study. *Blood*. 2025;146(5):590-600.
<https://doi.org/10.1182/blood.2024027408>
 73. Zhao Y, Cao W, Shi J, et al. Peri-transplant TP53 molecular MRD as a prognostic biomarker of relapse in TP53-mutated AML/MDS undergoing allogeneic HCT. *Blood Cancer J*. 2026;16:103.
<https://doi.org/10.1038/s41408-026-01561-4> PMID:42362536
 74. Churpek JE, Godley LA. How I diagnose and manage individuals at risk for inherited myeloid malignancies. *Blood*. 2019;133(14):1422-1432. 75. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood*. 2017;130(4):424-432.
<https://doi.org/10.1182/blood-2018-09-844662>