thrombocytopenic purpura. *N Engl J Med.* 2019;380(4):335-346.

4. Terrell DR, Vesely SK, Kremer Hovinga JA, Lämmle B, George JN. Different disparities of gender and race among the thrombotic thrombocytopenic purpura and hemolytic-uremic syndromes. *Am J Hematol.* 2010; 85(11):844-847.

5. Martino S, Jamme M, Deligny C, et al; French Reference Center for Thrombotic Microangiopathies. Thrombotic thrombocytopenic purpura in black people: impact of ethnicity on survival and genetic risk factors. *PLoS One.* 2016;11(7): e0156679.

6. Longo DM, Louie B, Mathi K, et al. Racial differences in B cell receptor signaling pathway activation. *J Transl Med.* 2012; 10(1):113.

7. Morsy L, Rothstein R. Toxic Stress and Children's Outcomes: African American Children Growing up Poor Are at Greater Risk of Disrupted Physiological Functioning and Depressed Academic Achievement. Economic Policy Institute; 2019.

8. McEwen BS. Neurobiological and systemic effects of chronic stress. *Chronic Stress (Thousand Oaks).* 2017;1:247054701769328.

9. Ma Q, Jacobi PM, Emmer BT, et al. Genetic variants in *ADAMTS13* as well as smoking are major determinants of plasma ADAMTS13 levels. *Blood Adv.* 2017;1(15): 1037-1046.

10. Zhou Z, Yu F, Buchanan A, et al. Possible race and gender divergence in association of genetic variations with plasma von Willebrand factor: a study of ARIC and 1000 genome cohorts. *PLoS One.* 2014;9(1): e84810.

MYELOID NEOPLASIA

Comment on Döhner et al, page 1345

How thinly can one slice the AML diagnostic pie?

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In this issue of *Blood*, Döhner et al,[1] on behalf of the European LeukemiaNet (ELN), present an update of their guidelines for the diagnosis and management of acute myeloid leukemia (AML). The authors revised their criteria for response and recommendations for treatment 5 years after their most recent report.[2]

During those 5 years, at least 2 regimens were approved for managing patients otherwise ineligible for intensive cytotoxic therapy. Clinical practitioners must now weigh which of their patients, based on the features of their disease, could benefit from the prolonged pancytopenia and hospitalization associated with cytarabine-based induction chemotherapy and postremission allogeneic hematopoietic cell transplantation.[3] One method for making that determination, in the absence of results from randomized clinical trials, could be based on frequently identified genetic markers of leukemia that predict for prognosis.

The clinical and biologic variants of AML encompass the interactions of molecular markers, the occurrence of co-mutations, and the presence of measurable residual disease (MRD) after induction therapy that collectively modify risk and may warrant a change in the classification of the disease.[4,5] Based on the power of molecular studies, and assuming that the techniques used to characterize changes are broadly available, the new ELN guidelines join the recent International Consensus Classification[6] that jettisons the histopathologic diagnoses of AML with myelodysplasia-related changes and therapy-related AML and revises the percentage of marrow blasts required for diagnosis. Of particular interest to those on the clinical front lines is the change in the definition of favorable-risk AML characterized by core-binding factor mutations to include in-frame mutations that affect the basic leucine zipper region of *CEBPA* rather than the previous definition of biallelic *CEBPA* mutation. The new classification guidelines emphasize monitoring MRD by using real-time polymerase chain reaction (RT-PCR) for all patients at diagnosis and during follow-up.

Several questions arise when considering the changes in a new, complex, and still evolving classification system for a disease characterized by molecular heterogeneity and, more importantly, varied clinical outcome. The first is, How does a change in the threshold of blast percentage affect management? There is a continuum among patients with high-risk myelodysplasia and AML. Will a more inclusive blast percentage allow patients to enroll in AML trials if they had previously been diagnosed with myelodysplastic syndrome (MDS)? Will entry onto clinical trials or treatment with approved AML agents earlier in the course of clonal hematopoiesis improve outcome? Or will they merely subject some patients with more indolent clinical features to earlier complications of therapy? Will a new risk-stratification system accelerate the transition of patients to allogeneic cell therapy? Or will patients with AML in first remission (good-risk AML, according to American Society for Blood and Marrow Transplantation [ASBMT] criteria),[7] but with adverse cytogenetic and molecular disease features that predict for relapse, be referred to centers that can absorb a high statistical risk of treatment failure even after allogeneic transplantation? Will assessment for inherited molecular features that may constitute risk also be applied to screen healthy donors? And how will assessment of allogeneic donors for inherited risk of germ line variants like *DDX41* and *CHEK2* be standardized?

Finally, the authors provide a detailed discussion on therapeutic options and clinical management. They also advocate for systematic monitoring of measurable leukemia by quantitative RT-PCR for all patients with AML, regardless of risk. Are tools available outside academic centers so that the clinicians' preference for using PCR can be made operational for observing patients in remission? And what interventions are available, outside clinical investigation, for managing MRD?

Unfortunately, at least half of all patients with AML are older than age 60 years, and many of these patients in developed countries are offered intensive induction

Treatment options based on dominant AML mutations

Dominant mutation	Available target agent	Available therapeutic regimens	Therapeutic impact
FLT3-ITD or TKD	Midostaurin	In combination with "7 + 3"	Incremental improvement in survival
	Gilteritinib	Single-agent therapy in relapse	Single-agent response rate of 34%[8]
		In combination with higher doses of cytarabine	Higher response rate in combination[9]
		In combination with hypomethylating agents	
	Quizartinib	Single-agent maintenance; single-agent therapy in relapse; combination therapy at diagnosis	
IDH1	Ivosidenib	Single agent OR in combination with "7 + 3" OR in combination with hypomethylating agents at diagnosis	Response rate with hypomethylating agents in newly diagnosed AML was 47%, and 1-y event-free survival was 37%[10]
IDH2	Enasidenib	Single agent in relapse	Median overall survival in relapsed setting was 6.5 mo[11]

therapy and allogeneic transplantation, which has led to long-term leukemia-free survival in younger patients. Among these otherwise vigorous older patients, adverse molecular and/or cytogenetic features of leukemia are common, and patients often present with a history of antecedent hematologic disorder (typically longstanding anemia, myelodysplasia, or myeloproliferative neoplasm), or previous cytotoxic chemotherapy or radiotherapy that confer poor prognosis. Despite selection at centers that are graded on outcomes, life-threatening toxicities of therapy still occur among those who had no previous comorbid conditions. Even without nonrelapse morbidity and mortality, sustained survival is less likely among those whose leukemia is characterized by high molecular risk. The question for leukemia doctors and clinical researchers is not whether these patients should be excluded from treatment, but whether identifying those at high risk of relapse can lead to unique investigational approaches that ameliorate risk.

A classification system that relies on distinct genomic profiling of neoplasia, including periodic assessment for MRD, attempts to impose order on an inherently disordered clonal neoplasm and suggests that targeting dominant molecular events might prove to be an effective management strategy. Although this concept is certainly valid for management of acute promyelocytic leukemia, it is less certain at present that targeting common mutations such as F*LT3* or *IDH1/2* can have a significant impact on

outcome (see table). How challenging for those of us treating AML and, more importantly for our patients, that nearly 40 years after identifying cytogenetic risk factors for recurrence after conventional therapy, we continue to classify disease based on outcomes after cytotoxic therapy and allogeneic transplantation. We continue to direct diagnosis and therapy at narrow slices of disease, defining a bewildering number of mutations, co-mutations, and other biologic features, uncertain as to whether we have made any major long-term impact on AML as a whole.

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REFERENCES

1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of acute myeloid leukemia in adults: 2022 recommendations from an international expert panel on behalf of the European LeukemiaNet. *Blood.* 2022; 140(12):1345-1377.

2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017; 129(4):424-447.

3. Cherry EM, Abbott D, Amaya M, et al. Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia. *Blood Adv.* 2021;5(24):5565-5573.

4. Itzykson R, Fournier E, Berthon C, et al. Genetic identification of patients with AML older than 60 years achieving long-term

survival with intensive chemotherapy. *Blood.* 2021;138(7):507-519.

5. Reville PK, Sasaki K, Kantarjian HM, et al. Improved outcomes among newly diagnosed patients with FMS-like tyrosine kinase 3 internal tandem duplication mutated acute myeloid leukemia treated with contemporary therapy: Revisiting the European LeukemiaNet adverse risk classification. *Am J Hematol.* 2022;97(3):329-337.

6. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: Integrating morphological, clinical, and genomic data [published online ahead of print 29 June 2022]. *Blood.* doi:10.1182/blood.2022015850

7. Patel H, Molina A, Nikanjam M, Schiller GJ. A comparison between two risk stratification schemes for allogeneic transplant for acute myeloid leukemia – implications for defining expected outcomes. *Blood.* 2017; 130(suppl 1):5547.

8. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML [published correction appears in N Engl J Med. 2022;386(19):1868]. *N Engl J Med.* 2019; 381(18):1728-1740.

9. Kantarjian H, Short NJ, DiNardo C, et al. Harnessing the benefits of available targeted therapies in acute myeloid leukaemia. *Lancet Haematol.* 2021;8(12): e922-e933.

10. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in *IDH1*-mutated acute myeloid leukemia. *N Engl J Med.* 2022;386(16):1519-1531.

11. Botton SD, Montesinos P, Schuh A, et al. Enasidenib vs conventional care in older patients with late-stage mutant-IDH2 relapsed/refractory AML: a randomized phase 3 trial [published online ahead of print 17 June 2022]. *Blood.*