haematologica
Journal of the Ferrata Storti Foundation

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Received: November 6, 2025.
Accepted: November 21, 2025.

Citation: Michael Sandhu and Marina Konopleva. The LSC17 score: a prognostic biomarker now validated for real-world clinical application in acute myeloid leukemia.
Haematologica. 2025 Dec 4. doi: 10.3324/haematol.2025.288928 [Epub ahead of print]

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The LSC17 score: a prognostic biomarker now validated for real-world clinical application in acute myeloid leukemia

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An ongoing challenge in acute myeloid leukemia (AML) is the reliable identification of patients who may have resistant disease when treated with standard induction chemotherapy, or who may relapse early after remission. In this article titled “Real-world validation study of the LSC17 score for risk prediction in patients with newly diagnosed acute myeloid leukemia”, the authors present the first prospective, multicenter study aiming to evaluate the prognostic value of the Leukemic Stem Cell 17-gene (LSC17) score in patients with newly diagnosed AML[1].

The European LeukemiaNet (ELN 2022) remains the current standard clinical guidelines for risk stratification, using cytogenetic and molecular profiling data to broadly define risk categories and guide treatment. However, ELN 2022 does not fully account for resistance mechanisms to chemotherapy and predictors of relapse, which are often driven by leukemic stem cells (LSCs)[2]. In 2016, Ng and colleagues developed the LSC17 score: a panel which includes 17 genes associated with LSC biology[2], specifically with a focus on identifying prognostic biomarkers to predict resistance to standard induction therapy or predict relapse after therapy in patients lacking conventionally defined adverse risk factors[2,3]. The LSC17 score has been validated in retrospective cohorts[4,5], with a prognostic impact found in both younger (<60 years) and older (>60 years) patients[4]. Patients with a high LSC17 score were shown to have lower rates of complete response, shorter overall survival, and higher rates of positive MRD status[5].

In the ALFA-0702 trial, LSC17 score independently predicted outcomes in NPM1-mutated adult patients receiving intensive therapy, and added prognostic value when used in combination with NPM1-MRD[5]. LSC-based MRD testing was also shown to predict relapse after aSCT earlier than traditional MRD testing[6].

In the first prospective cohort utilizing the LSC17 score, 276 AML patients were recruited, of which 190 were treated with curative-intent intensive chemotherapy. Importantly, the cohort included patients of various ages, treatment intensities and mutational backgrounds. Samples from bone marrow aspiration or peripheral blood

were obtained at time of suspected diagnosis, and both patients and physicians were blinded to the LSC17 score. Patients with a high LSC17 score had lower complete remission (CR) rate, higher measurable residual disease (MRD) after induction, and shorter overall survival[1]. The LSC17 score was the best predictor of MRD over ELN 2022 adverse risk, and remained an independent predictor in multivariable models that included age, WBC count, and ELN risk.

Through this work, the LSC17 score was prospectively validated as a clinical tool with benefit in upfront risk assessment, and to guide therapy in patients with AML. Although the ELN classification system has improved prognostication, it does not comprehensively account for the biological complexity of the LSC in AML. The data presented in this study reinforces the concept of LSC stemness as a fundamental driver of treatment response in AML. With conventional risk stratification systems, there are challenges in certain risk categories of patients, specifically in the ELN 2022 intermediate risk group. In this study, the LSC17 score showed a significant advantage in predicting survival outcomes in patients deemed intermediate risk, being able to better predict relapse in patients with a high LSC17 score. The LSC17 score was also the best predictor in predicting presence of MRD following induction chemotherapy. Patients in the high LSC17 score group benefited from allogeneic stem cell transplant (aSCT) whereas patients in the low score group did not, suggesting LSC17 could also help to guide transplant decisions.

Another advantage of the LSC17 score is its feasibility and ease of integration into the real-world clinical setting for patients with AML. Samples were collected without additional procedural burden to the patient. Standardized, reproducible determination of the LSC17 score from diagnostic RNA was performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory using a NanoString-based assay[1], with a rapid turnaround time. These factors demonstrate the therapeutic implications of incorporating the LSC17 score into molecular modeling, alongside MRD and mutational testing.

The majority of the patients in the study received intensive induction chemotherapy, either with 7+3 or FLAG-Ida. However, the landscape of treatment in AML is evolving, with new treatment options including targeted agents, combinations with venetoclax, and the use of maintenance therapies. The utility of the LSC17 score to predict outcomes in this subset of patients, who may be frailer and receive less intensive regimens is not yet defined.

In addition to its clinical relevance, the LSC17 score reinforces the importance of understanding the biology of the LSC and the need for superior biomarkers in the management of AML. A set of LSC death genes were identified based on the expression of the programmed cell death gene[7]. These genes were used to develop a

LSCD score that, when high, could predict sensitivity to drugs used in the management of AML[7]. Venetoclax + hypomethylating agent combinations have been shown to target LSC[8], and the use of these biomarkers will aid in identifying patients who may benefit from alternative regimens.

In summary, in this landmark study, Murphy and colleagues have shown that the LSC17 score adds independent prognostic value in AML, and testing at diagnosis is feasible in the clinical setting. Looking forward, the incorporation of the LSC17 score in prospective clinical trials will be essential to further refine the utility of this score, and help to identify the selection of targeted therapies and indications for aSCT.

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Figure 1: Integration of the leukemic stem cell 17 gene expression score into AML risk stratification helps to refine risk assessment, including risk of relapse and MRD, and to inform post-remission therapy.

Integrating the LSC17 Score into AML Risk Stratification