mds foundation
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PRESS RELEASE

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FOR IMMEDIATE RELEASE
June 12, 2022

MOLECULAR INTERNATIONAL PROGNOSTIC SCORING SYSTEM DEVELOPED FOR MYELODYSPLASTIC SYNDROMES

Efficient, Accurate Risk Stratification Will Transform Patient Care

YARDVILLE, NJ, JUNE 12, 2022 — Today, the MDS Foundation announced the development of a new prognostic scoring system, the IPSS-Molecular, that will significantly improve risk stratification upon diagnosis to better inform the way treatment plans are built for patients with Myelodysplastic Syndromes.

> **"By considering each patient's genetic make up in the IPSS-M we can now truly deliver patient tailored risk stratification," says Dr. Elli Papaemmanuil of the Memorial Sloan Kettering Cancer Center. "This will enable optimized treatment decisions tailored to those most in need of intervention, and sets a biological framework for the design of future clinical trials."**

For more than two decades, MDS patient risk stratification at diagnosis was based on diagnostic blood counts, morphology, and cytogenetics through the International Prognostic Scoring System. In recent years, a complete catalog of the genes mutated in MDS has been discovered. However, even though patients increasingly receive panel gene testing at diagnosis, there were no guidelines as to how this information could be used clinically to guide risk stratification and treatment decisions.

The creation of an effective set of prognostic guidelines was especially important for MDS because current clinical courses are very heterogeneous. In this absence of targeted therapies, risk stratification at diagnosis is critical in guiding treatment decisions. For example, supportive care with less toxic treatments would be considered for low risk patients, while patients with high-risk disease need higher intensity treatments to mitigate the risk of leukemia progression and death.

AN INTERNATIONAL COLLABORATION TO IMPROVE RISK STRATIFICATION

Through the efforts of the International Working Group for the Prognosis of MDS—a consortium of expert clinicians, pathologists, computational biologists, and statisticians—and under the auspices of the MDS Foundation, a total of 2,957 patient blood and marrow samples were collected from 24 centers within 13 countries. Those samples were all sequenced uniformly by a panel test at Memorial Sloan Kettering Cancer Center and analyzed in the Papaemmanuil laboratory. Each sample was profiled for mutations in 152 genes and clinical and molecular variables were evaluated for associations with leukemia-free survival, leukemic transformation, and overall survival. In order to validate the IPSS-M, the study used another 754 samples derived from the Japanese MDS consortium. The results of this investigation, led by Drs Elsa Bernard, Elli Papaemmanuil and IWG colleagues, 'Molecular International Prognostic Scoring System for MDS (IPSS-M)', have just been published in the June 12, 2022 issue of the *New England Journal of Medicine Evidence*.

DETERMINING THE IPSS-M RISK SCORE AND RISK CATEGORIES

The study found at least one driver genomic alteration in 94% of patients (41% of patients with cytogenetic alterations and 90% of patients with gene mutations). On average, the higher the number of alterations, the worse the outcomes.

Using this data, researchers developed the IPSS-Molecular which incorporates information from 31 gene mutations as well as diagnostic and clinical parameters to deliver a personalized, patient-specific risk score. The IPSS-M risk score indicates the continuum of prognostic risk observed across patients with MDS and produces six risk categories (Very Low, Low, Moderate Low, Moderate High, High, Very High) that can be used for determining clinical trial eligibility criteria, correlative studies, and treatment recommendations.

In addition to its effective prognostic categorization of primary MDS, the IPSS-M efficiently stratifies patients with therapy-related MDS, a diagnostic subtype that was considered to be uniformly high risk and therefore lacked an applicable prognostic system. Compared to the

previous IPSS-R system, 46% (roughly 1 in 2) of patients were reassigned to a different risk category in the IPSS-M which led to improved prognostic discrimination. Importantly, 7% of patients were reassigned by more than one strata (e.g IPSS-R Low to IPSS-M High or vice versa).

THE FUTURE OF MDS RISK STRATIFICATION

The IPSS-Molecular is set to become a new international standard for risk stratification of MDS patients at diagnosis. The IPSS-M score is personalized, interpretable, reproducible, and provides a flexible and transparent strategy to account for missing values. It also provides a list of the 31 genes that must be considered in diagnostic assay design.

To support widespread adoption and use, the research team developed a web-based calculator where clinicians can enter patient clinical and molecular data to deliver a personalized prediction of risk, outcomes, and likelihood of leukemia transformation in order to guide cost-benefit analysis on treatment decisions.

> "It has been a privilege to work closely with expert MDS clinicians, pathologists, biologists, statisticians, and the broader IWG community to develop the IPSS-M, aiming to better guide and ultimately improve the care of patients with MDS," says Dr. Elsa Bernard of the Memorial Sloan Kettering Cancer Center. "While the IPSS-M can be calculated using a relatively simple formula, we built a web calculator and an R package to facilitate its application, which we hope will prove useful for the community."

EXPLORE THE WEB-BASED IPSS-M CALCULATOR:
https://www.mds-foundation.org/mds-iwg-pm/

READ THE IPSS-M STUDY:
https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200008

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