Dana-Farber Team Develops Open-Access Predictive Tool to Improve Monitoring of Smoldering Multiple Myeloma

PANGEA-SMM outperforms existing predictive tools by determining when smoldering multiple myeloma is progressing and requires treatment.

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Dana-Farber Cancer Institute investigators have developed an online, easy-to-use tool that more accurately predicts when a precursor blood condition called smoldering multiple myeloma is likely to turn into active cancer than existing predictive models. It identifies patients who are at a high risk of developing multiple myeloma and would benefit from treatment and enables doctors to spare those at low risk of progression from unnecessary treatment.

Current predictive tools use a static "snapshot" of a patient's lab results to make an assessment. This new tool, called PANGEA-SMM, adds new lab results to the assessment and dynamically tracks how the results change over time. The biomarkers leveraged by PANGEA-SMM are routine measures that are already used widely in standard smoldering multiple myeloma follow-up, making the tool accessible to patients around the world.

The study was published in Nature Medicine.

"By watching the speed and direction of the disease's trajectory, the tool can more accurately identify patients at high risk who need early treatment, while sparing those with stable disease from unnecessary interventions," says Dr. Irene Ghobrial, Director of the Center for Early Detection and Interception of Blood Cancers, who is co-senior author of the study along with Dana-Farber computational biologist Lorenzo Trippa. "A unified, straightforward, and precise risk stratification model incorporating dynamic biomarkers is essential to facilitate the implementation of therapeutic strategies and improve patient outcomes in smoldering multiple myeloma."

Multiple myeloma is a challenging bone marrow cancer, often preceded by precursor conditions such as smoldering multiple myeloma (SMM). Some patients with smoldering multiple myeloma are at a high risk of developing active cancer in the near term, while others have stable disease

and are at a low risk. The U.S. Food and Drug administration recently approved treatment with daratumumab for high-risk smoldering myeloma based on data showing its clinical benefit.

To develop and validate PANGEA-SMM, the team analyzed one of the largest cohorts studied to date, which was a cohort of 2,344 patients with smoldering multiple myeloma assembled from seven international centers. The study identified four dynamic biomarkers that are routinely collected for patients with precursor conditions and are indicative of progression.

Specific changes in these biomarkers – M-protein (an abnormal antibody produced by the disease), light chains (small proteins associated with the disease), kidney function, and blood counts – are "red flags" that signal an imminent risk of progression to active disease. For example, one "red flag" is an M-protein increase of as little as .2 grams per deciliter or more over 18 months.

Using these four dynamic biomarkers, PANGEA-SMM can predict a high risk of progression or a low risk of progression more accurately than the existing tools, such as the 20/2/20 and IMWG models, which use static, one-time measurements. PANGEA-SMM predictions also remain highly accurate even when doctors don't have a patient's full medical history or access to invasive bone marrow biopsies.

"Remarkably, PANGEA-SMM performs with similar accuracy whether or not recent bone marrow biopsy data is available," says Dana-Farber's Floris Chabrun, PhD, PharmD, a co-first author of the study along with Daniel E. Schwartz, PhD, a Dana-Farber biostatistician, Susanna Gentile, PhD, a Dana-Farber data scientist, and Dr. Elias K Mai, of Heidelberg University Hospital and Heidelberg Faculty of Medicine at Heidelberg University. "This allows for continuous risk assessment throughout routine follow-up without the need for frequent invasive sampling, which typically requires specialized expertise and can be burdensome for patients."

The free, online PANGEA-SMM calculator (https://pangeamodels.org) can be used immediately to monitor patients during routine follow-ups. It also can be used to compare PANGEA-SMM to established models in other cohorts of patients to identify areas for further improvement.

Future research includes continued refinement of the tool to improve predictive accuracy and research to determine the ideal monitoring frequency for patients.

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