

Dana-Farber Genomic Score Predicts Progression to Multiple Myeloma

The MM-like score focuses on the presence and progressive evolution of genetic abnormalities to assess the state of the disease.

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A new risk assessment score developed by researchers at [Dana-Farber Cancer Institute](#) and the Broad Institute of MIT and Harvard reveals how multiple myeloma, a form of blood cancer, begins and progresses from precancerous to malignant states by tracing DNA mutations.

The score, called an MM-like score, assesses the severity of disease and risk of progression to active cancer, with higher scores indicating faster progression. In the future, the MM-like score could be used in clinical practice to inform decisions about early intervention.

“In patients with a precursor condition for multiple myeloma, the multiple myeloma-like score helps to predict who is at a higher risk of progressing to active cancer,” says co-senior author Jean-Baptiste Alberge, PhD, an instructor in Medicine at Dana-Farber. “This study brings us closer to more personalized care for patients with a precursor stage of cancer and could better inform early intervention strategies in the future.”

The study was published in [Nature Genetics](#).

Multiple myeloma is a cancer in plasma cells that affects 32,000 individuals in the United States each year. Prior to developing multiple myeloma, patients go through precursor stages of the disease called monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM). Approximately 1 to 10 percent of patients with these conditions progress to active multiple myeloma per year, with 50-percent of high-risk SMM cases progressing within two years.

“There has been an urgent need to identify genomic risk factors that predict disease progression in smoldering myeloma,” says [Dr. Irene Ghobrial](#), Director of the Center for Early Detection and Interception of Blood Cancers at Dana-Farber. “This is especially true as we start early therapeutic interception for high risk SMM. Our data provides a simple genomic score that can help predict progression and can improve on our clinical markers to help stratify risk for our patients.”

Existing risk stratification models for multiple myeloma characterize patients as “high” or “low” risk based on measures of tumor burden. These models do not include genetic factors. The MM-like score defined in this study focuses on the presence and progressive evolution of genetic abnormalities to assess the state of the disease. The MM-like score increases over time with the accumulation of mutations that drive the disease.

“Treating risk as simply ‘high’ or ‘low’ fails to capture the complexity of tumor timing and evolution, and we saw an opportunity to redefine it through whole-genome sequencing,” says Alberge.

Along with co-first authors Ankit Dutta, PhD, a postdoctoral fellow in the Ghobrial lab, Andrea Poletti, PhD, a post-doctoral fellow at the University of Bologna, Italy, and collaborators from the UK, Germany, and Greece, Alberge compiled mostly whole genome sequencing data from over 1,000 individuals with multiple myeloma and precursor conditions, including 218 patients with MGUS or SMM. The study provides one of the largest analyses of whole genome data for multiple myeloma and its precursor conditions to date.

“This study greatly improves our ability to discover both potentially clinically-actionable cancer-driving mutations in MM and the timing of when these events occur across disease states,” says Gad Getz, PhD director of Cancer Genome Computational Analysis at the Broad Institute of MIT and Harvard and director of bioinformatics in the Krantz Family Center for Cancer Research and Department of Pathology at Massachusetts General Hospital. “These insights wouldn’t be possible without access to deeply sequenced whole genomes from a large number of patients and across different disease stages.”

By comparing mutations that were more commonly found in active disease than in asymptomatic precursor forms, they were able to identify genes that are likely linked to the transformation to active disease. The study also revealed the likely order and timing of genetic mutations.

To validate the score, the team evaluated 47 tumor samples from 20 patients at various points in the progression of disease. They found that the MM-like scores in individual patients reflected the course of their disease in multiple cases. For example, 11 of 13 patients who did not progress during the period of observation had stable MM-like scores, and 5 of 7 patients who did progress had MM-scores that increased at the time of progression.

The study also uncovered surprising findings about the origins of multiple myeloma. The team estimates based on this study that the earliest genomic changes related to the disease may appear very early in life, in the patient’s 20s or 30s, even though multiple myeloma is typically not diagnosed until much later.

To make the MM-like score more clinically accessible, the team is developing a test based on liquid biopsies instead of bone marrow biopsies to collect DNA. This change would potentially enable more frequent monitoring of the evolution of the condition. In addition, the team aims to continue to validate and improve the score by studying more patients over longer periods of time.

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