Genomic Test Accurately Identifies Patients at High Risk of Worsening Multiple Myeloma

Researchers identify a series of molecular abnormalities associated with greater risk of myeloma progression

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A genomic test of bone marrow tissue can determine whether people with a common precursor of multiple myeloma have a high risk of developing the full-blown form of the disease, a study led by Dana-Farber Cancer Institute researchers shows. Individuals found to be at an increased risk could benefit from close monitoring of their condition or from clinical trials of therapies intended to halt the progression toward myeloma.

The study, published by the Journal of Clinical Oncology, found that patients with smoldering multiple myeloma – a symptomless condition that often precedes myeloma – were at higher risk for myeloma if the tumor cells contained certain genetic abnormalities. These abnormalities were independent predictors of myeloma progression and improved on the traditional criteria used in clinics, the researchers found.

Multiple myeloma is a cancer of a type of white blood cells known as plasma cells and occurs in the bone marrow. Smoldering multiple myeloma (SMM) is diagnosed in people whose blood or urine is found to contain a certain level of the M protein, but who don't have symptoms of myeloma. (The M protein is a fragment of an antibody produced in excessive amounts by myeloma cells.) Because not everyone with SMM develops outright myeloma, treatment doesn't begin until symptoms of myeloma – such as bone lesions or fractures, low blood counts, kidney problems, and increased calcium levels – appear.

"As a group, patients with smoldering myeloma have a 10% annual risk of developing myeloma, but it's difficult to determine which are at the greatest risk, so our goal was to understand the heterogeneity within SMM and explore which genetic alterations could predict the high-risk group," said study lead author Mark Bustoros, MD, of Dana-Farber and the Broad Institute of MIT and Harvard.

"The standard biomarkers for risk of progression are based on tumor burden – how many abnormal cells are within a bone marrow sample, M protein or free light chain levels. But the

traditional risk models are not as accurate as we would like and don't reflect the basic biology of the disease," said Irene Ghobrial, MD, Director of Center for Prevention of Disease progression (CPOP) at Dana-Farber and the senior author of the study.

The new study involved a genomic analysis of the largest number of smoldering multiple myeloma tissue to date. Investigators collected bone marrow samples from 214 patients at the time of diagnosis with smoldering multiple myeloma and sequenced the DNA within the tumor cells. This was a multicenter cohort encompassing multiple centers from the United States and Europe.

"We found that the genomic alterations with smoldering multiple myeloma are essentially the same as full-fledged myeloma," Romanos Sklavenitis-Pistofidis, MD, the study co-lead remarked. "This suggests that by the time smoldering multiple myeloma is diagnosed, most of the molecular abnormalities found in myeloma have already occurred."

The researchers followed a group of the patients for a median of 6.8 years to track which ones developed myeloma, then cross-linked the molecular and clinical data to explore whether certain genomic abnormalities raised the risk of progression toward myeloma. They found that smoldering myeloma was more likely to advance, and advance sooner, in patients whose tissue samples had:

- Mutations in certain genes in the MAPK pathway
- An amplification or translocation of MYC gene
- A mutation or deletion in the TP53 gene

To test the validity of these findings, researchers applied them to an outside group of 72 patients with smoldering myeloma whose tumor DNA had been previously sequenced. They found that patients with any of the high-risk genomic alterations also had a higher risk of progression.

"This was a big collaborative effort between Dana-Farber and the Broad Institute to understand the genomic landscape of SMM and how this could help in a better management of patients and development of appropriate interventions," said Gad Getz, PhD, co-senior author of the study and Director of Cancer Genome Computational Analysis Group at Broad Institute of MIT and Harvard and bioinformatics department at the Massachusetts General Hospital (MGH) Cancer Center.

"Ideally, our biological model could be combined with the traditional clinical models to get the best indication of a patient's risk of progression. Patients identified as being high-risk could then be closely monitored for signs of advancing disease or participate in clinical trials of agents that aim to slow or stop progression," the authors concluded.

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