Josh Baxt
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Whole Genome Sequencing Offers New Diagnostic Insights for Multiple Myeloma Precursor Conditions

In a study published in *Nature Communications*, researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine have shown that whole genome sequencing can help determine which patients with a multiple myeloma precursor condition, called MGUS or smoldering myeloma, progress to full-blown cancer. With further validation, these findings could revolutionize how these patients are diagnosed and treated.

“Most patients with MGUS will never progress, but some will,” said Ola Landgren, M.D., professor of medicine, chief of the Myeloma Service, and PI of the Myeloma Genomic Laboratory. “In this study, for the first time, we were able to use a novel low-input whole genome sequencing technology – partnered with our most advanced bioinformatics pipelines – to identify the progressors and the non-progressors. Using modern genomic assays and analytical algorithms, we are able to split the older terminology of MGUS – monoclonal gammopathies of undetermined significance – and define progressors *versus* non-progressors.”

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Multiple myeloma is the second most common hematologic malignancy in the United States, with about 35,000 patients being diagnosed each year. There are more than 130,000 people living with multiple myeloma in the U.S. Currently, there is no established curative therapy for multiple myeloma. Unlike most cancers, multiple myeloma has asymptomatic precursor conditions, which may or may not indicate a patient will develop the cancer.

Clinicians use a variety of tests to detect an abnormal protein associated with the disease. Patients with high protein levels are at higher risk of developing multiple myeloma and are diagnosed with smoldering myeloma. Those with lower levels have MGUS.

The key phrase in that description is “undetermined significance.” Many of the diagnostic technologies for multiple myeloma are relics from the 1980s and fail to delineate which MGUS patients are at greatest risk. This can be a major issue, as people must undergo repetitive and sometimes painful diagnostic tests to track progression, such as bone marrow biopsies and PET/CT exams. Also, recurrent blood monitoring can have adverse impact on quality of life, often driven by uncertainty and anxiety.

Dr. Landgren and Francesco Maura, M.D., assistant professor and co-PI of the Myeloma Genomic Laboratory, together with

their colleagues felt whole genome sequencing (WGS) could provide more specific answers to help clarify each patient's risk and potentially lead to better treatments.

In the study, the team used WGS to assess 18 MGUS patients, as well as 14 with smoldering myeloma and 80 with multiple myeloma, following these cohorts for more than a year. The researchers looked at a variety of genetic variations, including insertions, deletions, driver gene mutations and others. They found that patients with lighter mutational loads were less likely to develop multiple myeloma.

In addition to identifying a genomic signature that could delineate progressors from non-progressors, the team also developed crucial methods to produce robust results with only a few cells, building on a technique developed at the Sanger Institute.

"We successfully applied this technology in cancer for patients with a myeloma precursor where the disease burden is extremely low," said Dr. Maura. "The quality was incredibly good, allowing us to be the first to characterize the whole genome sequencing landscape in MGUS."

Prior to this study, scientists believed disease progression was linear from MGUS to smoldering myeloma to multiple myeloma. Now, it's unclear whether smoldering myeloma is a distinct condition at all or simply an earlier stage of multiple myeloma.

"The bigger picture is that there are several genomic defining events involved in the progression of multiple myeloma," said Dr. Maura. "So far, whole genome sequencing is the only technology that captures all these changes."

Dr. Landgren notes that further study is needed to both validate and clarify these findings. The researchers are not entirely certain that patients classified as non-progressors will definitely never progress.

However, with further validation, this approach could have a tremendous impact on the field. Non-progressors would no longer need to worry about their risk of developing multiple myeloma or wait anxiously for test results. In addition, better clarity on who will develop the disease could drive more efficient clinical trials.

“We are about to launch a large prospective study to take advantage of WGS and validate these findings,” said Dr. Landgren. “In 2021, we are planning on opening a new large study at the Myeloma Service in Sylvester Comprehensive Cancer Center. The plan is to offer individuals diagnosed with MGUS or smoldering myeloma to come to us here in Miami for a bone marrow biopsy which will include our new WGS test. This study also creates new opportunities to develop early treatment studies, which we are about to start. If we could prevent multiple myeloma from happening, that would be a huge contribution.”