TUMOR GENOMICS AS A ROUTE TO CLARIFYING INHERITED GENETICS IN MULTIPLE MYELOMA

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Multiple Myeloma (MM) affects specialized white blood cells, called plasma cells, found in bone marrow. The diseased plasma cells affect the body by producing flawed antibodies that are unable to perform normally. As the MM malignant cells continue to divide, the bone marrow can become saturated with malignant cells. Though MM is fairly rare (6.3/100,000 per year), the incidence of this type of cancer is increasing by about 0.8% every year. Even with improving treatments, only about 52.2% of patients surpass 5 years of life after diagnosis.

It is currently unclear why certain people get MM, although genetic risk factors have been proposed and a few discovered. The molecular make-up of the malignant MM cells is also highly variable from patient to patient, thus making it difficult to model and difficult to treat. This research illustrates a novel characterization method for malignant MM cells that could help better characterize the malignant cells and hopefully lead to improved or more personalized treatments, better life expectancy and overall quality of life for patients with MM.

This study requires the acquisition of MM malignant cells. The process for acquisition begins when a patient is enrolled and consented into our study. At enrollment, several samples are collected from the patient including: bone marrow and whole blood or saliva. Bone marrow and whole blood are the essential biological samples and first undergo fluorescent activated cell sorting (FACS). This sorting process separates normal cells (CD138-) from malignant cells (CD138+). These cells are then used for RNA and DNA extraction. The extracted RNA is used for whole transcriptome sequencing (gene expression in malignant cells) and thereafter to characterize a patients MM.

Transcriptome sequencing provides expression for about 58,000 genes. Multi-dimensional reduction was used on the 58,000 genes, resulting in 30 variables or principal components (PC) necessary to describe the complexity of each tumor. Values for each PC vary across patients allowing us to better characterize the patient's MM. Example bar graphs representing the 30 PCs for 6 patients are shown in Figure 1.

Initial analyses show that the principal components can be used to predict patient prognosis. This is illustrated in Figures 2 and 3. In Figure 2 each line on the waterfall plot represents a patient's score based on 12 significant PCs, red represent patients with poor prognosis using current clinical methods and blue represents standard prognosis. The nonrandom grouping of the red shows that prognosis can be predicted using PCs. Figure 3 shows 4 PCs can predict intermediate prognosis (based on a known DNA aberration, translation between chromosomes 4 and 14).

Although still in the early stages, this novel characterization method shows excellent potential as a way to predict prognosis, useful for clinical management. In the future we will consider response to treatment, in the hopes that this characterization of tumors will help tailor treatments to patients. Before translation into the clinic, however, further research will be needed to replicate our findings and determine the full scope for this novel technique.
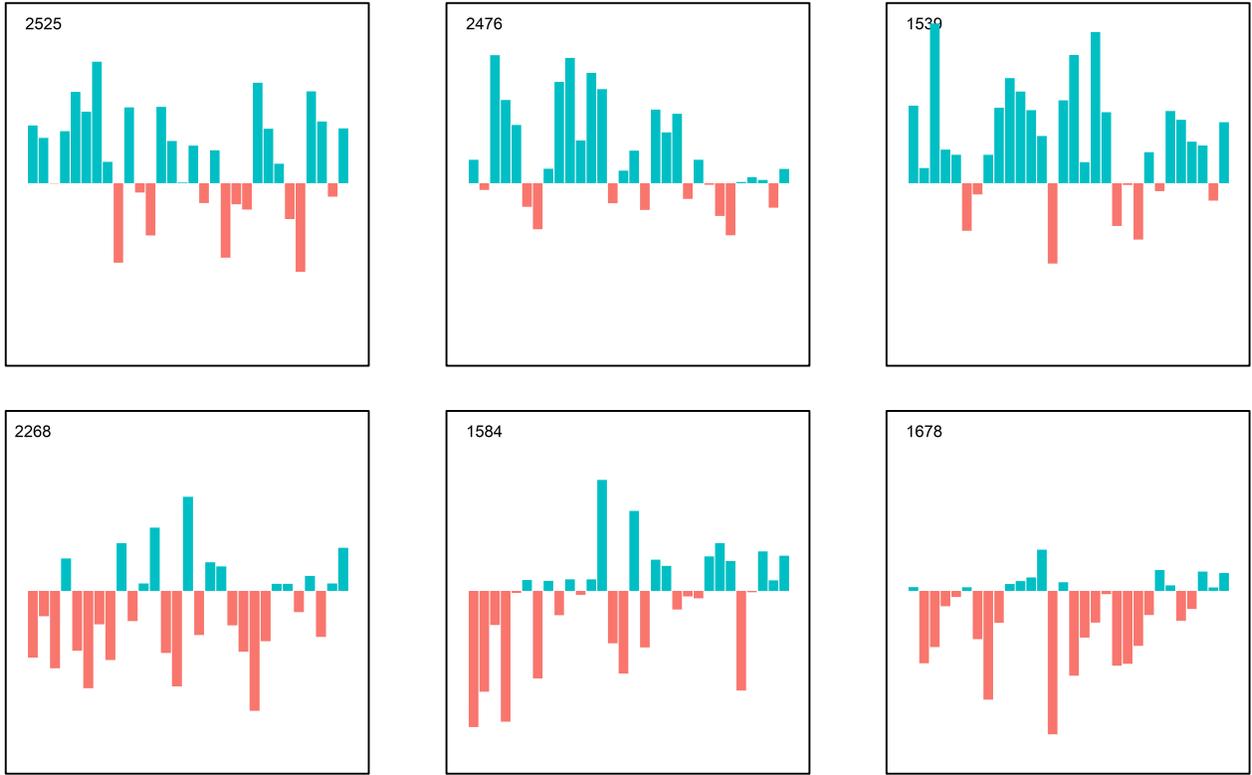
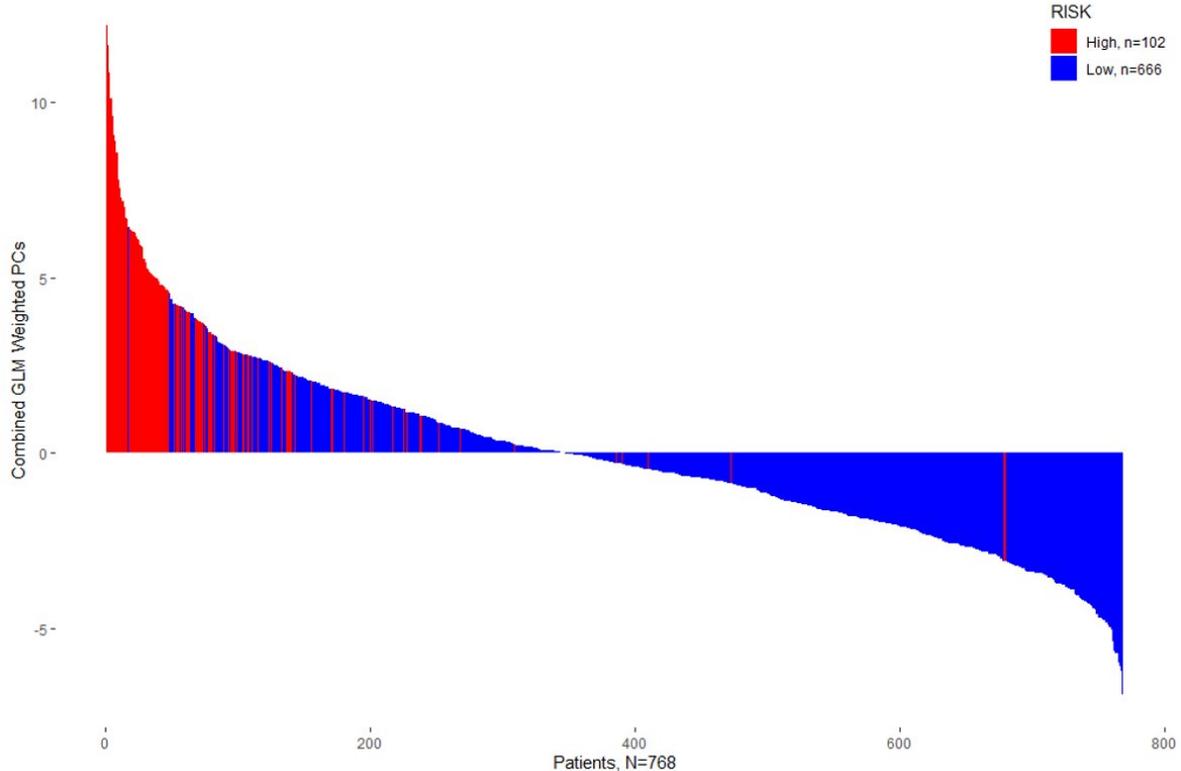**Figure 1.** Multi-dimension signatures for 6 patients.

Figure 2. Waterfall plot: 12 significant PCs and associated with predetermined prognosis.
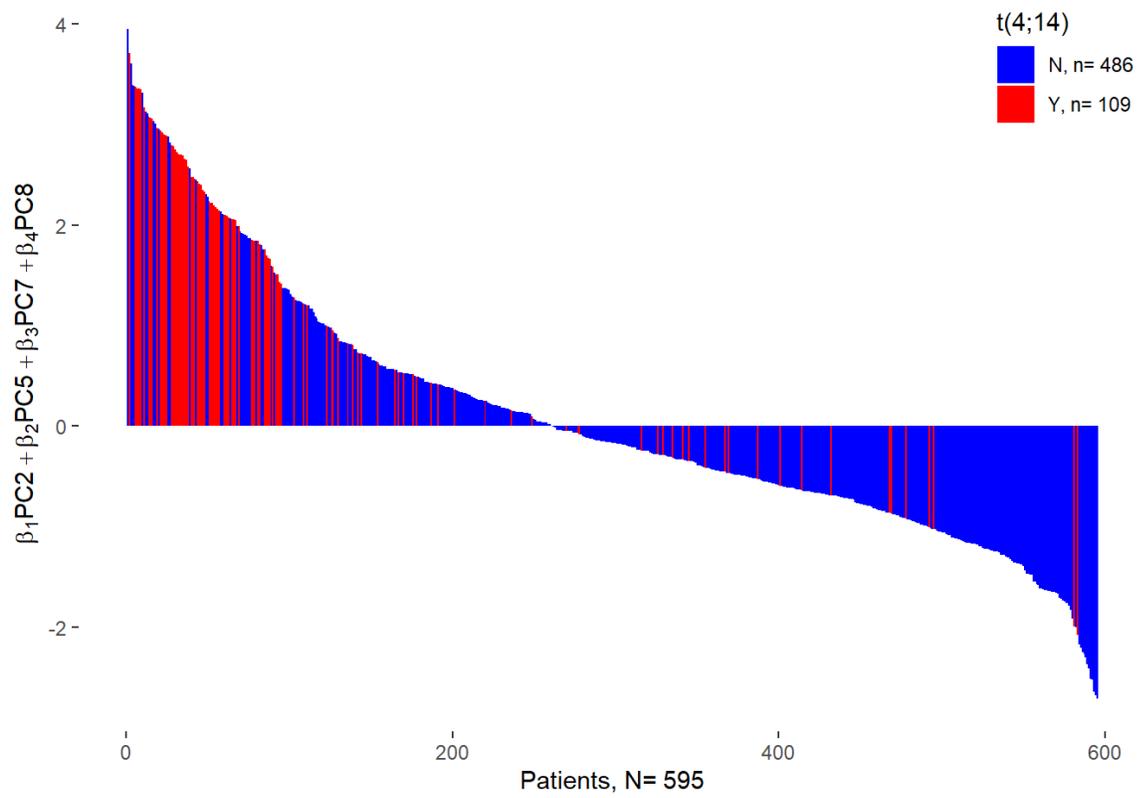
Figure 3. Waterfall plot: 4 PCs and associated with predetermined intermediate risk.