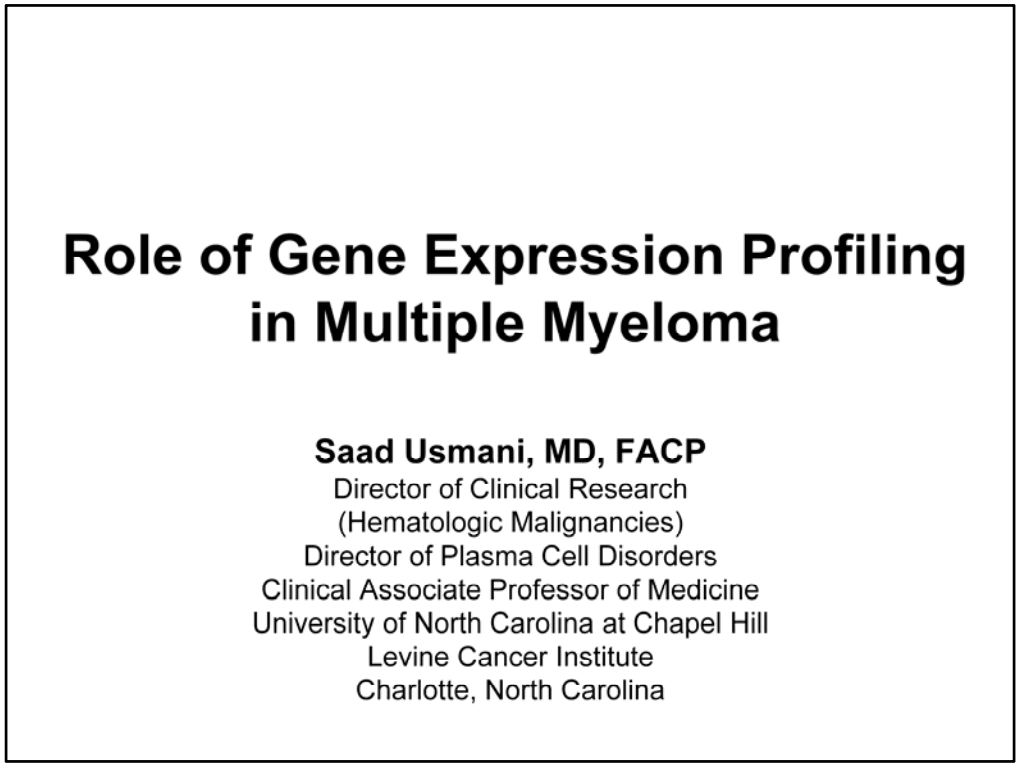
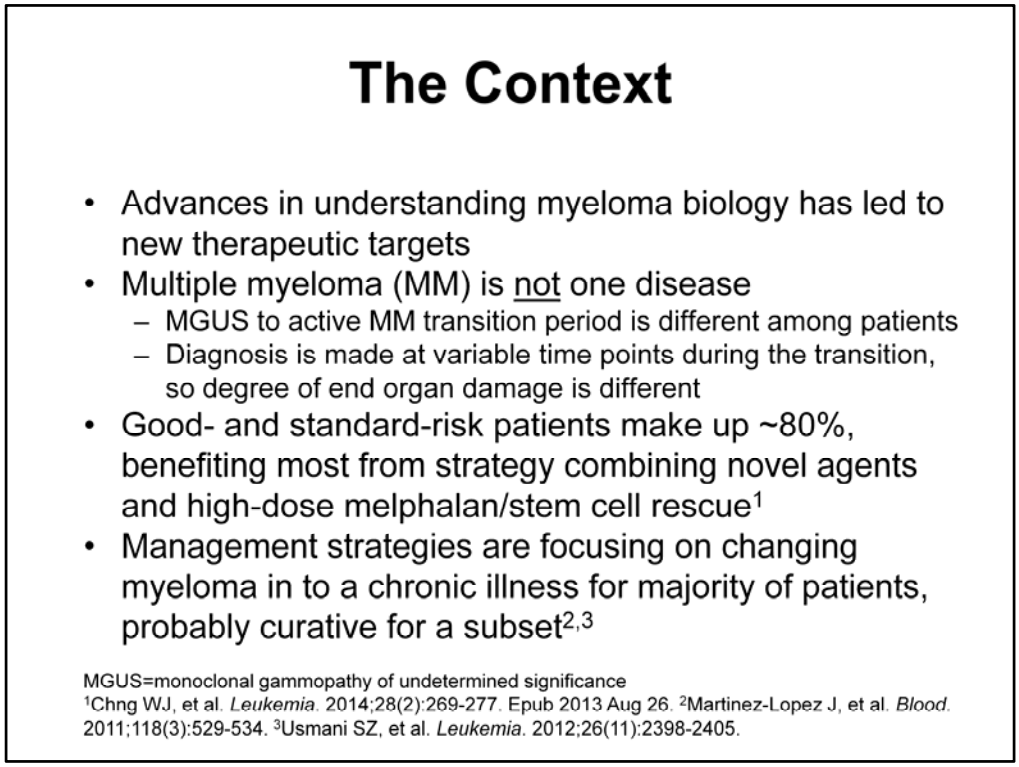
Role of Gene Expression Profiling in Multiple Myeloma



Welcome to *Managing Myeloma*. My name is Saad Usmani. I am the director of clinical research for hematologic malignancies and the director of plasma cell disorders program at the Levine Cancer Institute in Charlotte, North Carolina. I am frequently asked the question, "What is the role of gene expression profiling in multiple myeloma? How can it help in taking care of myeloma patients in a better way?"



To answer that question, it is important to understand the context of myeloma as a disease. We understand the biology of myeloma in a much better way than we did 15 or 20 years ago, and that understanding of disease biology has led to new therapeutic targets. We appreciate the fact that myeloma is not one disease, that the MGUS to active myeloma transition period is different amongst patients, and that diagnosis is made at variable time points during that transition so that the degree of end-organ damage is also different. We do appreciate that myeloma can be divided into good-, standard-, and high-risk disease; and good- and standard-risk patients are the ones that make up about 80% of newly diagnosed myeloma, and they are the ones who have benefited the most from the current strategies of combining novel agents and using high-dose melphalan with stem cell rescue. The current management strategies are focusing on changing myeloma into a chronic illness for the majority of myeloma patients and probably curative for a very small subset of patients, but the high-risk myeloma remains a major challenge.

We do appreciate the fact that MGUS to myeloma progression is not a linear process, it is a Darwinian process. Over time, the same mother clone in a given myeloma patient continues to divide and accumulate more genetic and genomic abnormalities. It will do it during the smoldering myeloma phase as well as under duress from chemotherapy while the myeloma patient is being treated. So there is a selective clonal expansion based on drug resistance in any given patient undergoing myeloma therapy. So that is extremely important to appreciate that the disease biology is different in different patients.

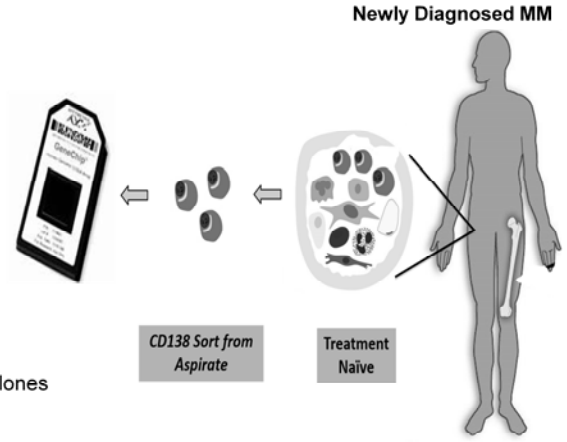
GEP Signatures in MM

Advantages:

- Provides a global snapshot of CD138+ve plasma cell (PC) gene expression
- Utility to identify a broad group biologic group of MM patients with high risk of relapse
- Help identify the dominant clone in a given patient responsible for initial clinical presentation

Disadvantages

- What about the CD138-ve PCs?
- What about the other dominant clones that remain below the waterline (iceberg analogy)?
- No info on driver pathways, mutations
- ? technically a legacy technology

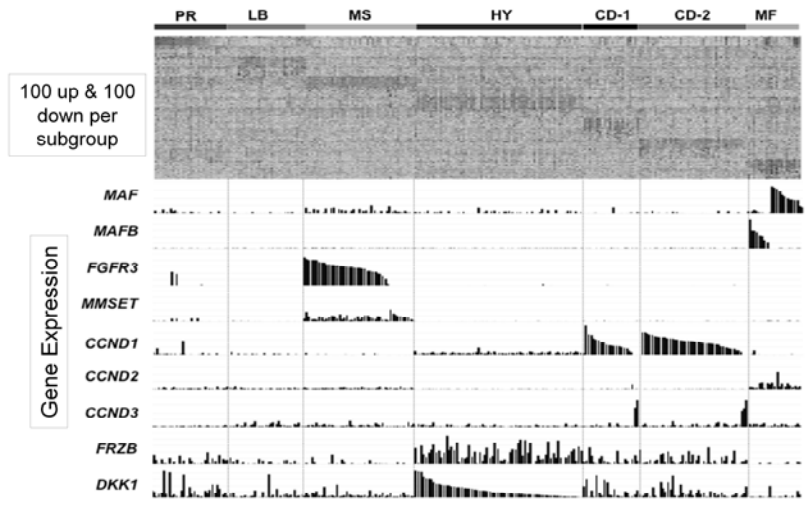


GEP=gene expression profile

Gene expression profiling (GEP) is a very unique tool which helps us look at the disease biology in a very broad sense in a given myeloma patient. That technology is based on the fact that we can collect bone marrow aspirate from a given patient, separate out CD138 selected cells from that bone marrow aspirate. CD138 is a surface marker that is highly expressed on plasma cells. RNA is extracted from all those CD138 positive plasma cells, and all the 30,000 genes present in a given human cell are probed on a GeneChip. So we have gene expression for all those 30,000 genes being evaluated through gene expression profiling. The advantages of doing the gene expression profiling on these malignant plasma cells is that it can provide you a global snapshot of disease biology. It can be utilized to identify a broad group of biologic patients with high risk of relapse. It can help identify the dominant clone in any given patient for the initial clinical presentation.

The disadvantages of gene expression profiling are that we are selecting CD138 cells, but there are a small subset of CD138 negative plasma cells as well. We do not get information about other non-dominant clones by gene expression profiling. We also do not get a lot of information about driver mutations on pathways, although some pathway information can be gained by utilizing software. Some would argue that gene expression profiling may be becoming a legacy technology with availability of RNA sequencing or whole exome sequencing, but one can also counter argue that gene expression profiling will be becoming a cheaper technology with easy availability on site for a majority of clinics and hospitals taking care of myeloma patients.

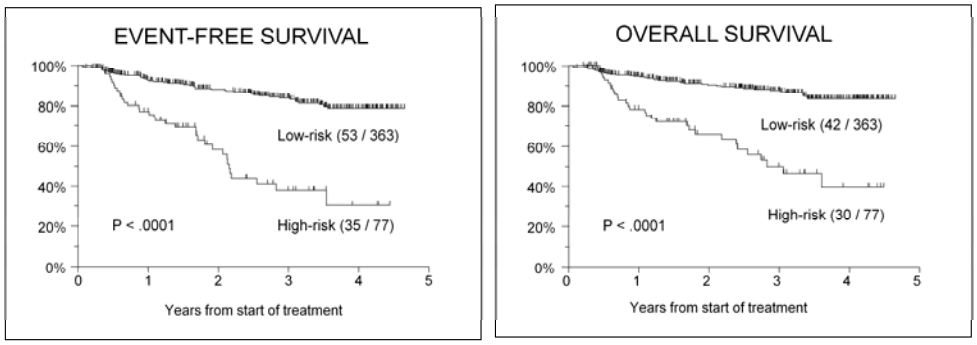
GEP in CD138 +ve PC Defines 7 MM Subtypes



Zhan F, et al. *Blood*. 2006;108(6):2020-2028.

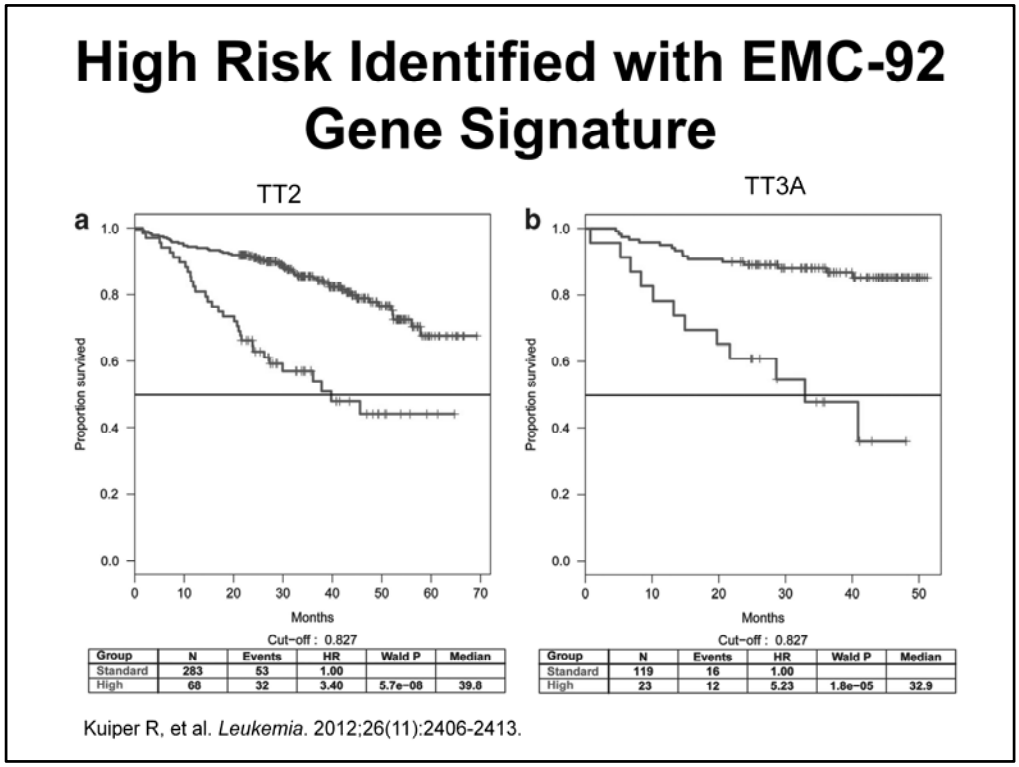
Gene expression profiling can distinguish myeloma into seven different molecular subgroups, and these molecular subgroups behave different clinically as well. There are some subsets which are more sensitive to proteasome inhibitors, for example the MS molecular subgroup, and there are some very indolent kinds of myeloma such as CD2 patients. High-risk patients within PR and MF subtypes still remain a challenge. So it may be important to identify these molecular subgroups as we get more drug classes that may have more activity in one subgroup of patients versus the other, and these questions are being explored in prospective clinical trials.

Treatment Outcomes By UAMS-70 Signature



PROGNOSTIC POWER OF GEP-DEFINED RISK VALIDATED IN TOTAL THERAPY 3A

This table highlights the risk of relapse within each specific subgroup that you can look into. It is important to recognize that gene expression profiling can identify a very high-risk group of patients who will be relapsing quickly. The University of Arkansas developed the UAMS-70 gene signature and showed their data and their total therapy program.



Similarly, the HOVON Group in Europe identified a 92-gene signature which has broader implications not just within total therapy trials, but also within the HOVON clinical trial experience in hundreds and hundreds of patients. Both of these gene signatures are now commercially available in the United States.

The IMWG consensus on risk stratification identifies GEP as a high-risk feature with a median overall survival of those patients being two years, and that subgroup of patients is now being identified for focused clinical trials for high-risk patients.

The NCI Myeloma Steering Committee also identifies gene expression profiling as a high-risk feature and the HOVON gene signature is also being utilized to identify poor-risk score for patients in that subgroup as well.

In summary, gene expression profiling is becoming a very important tool in identifying high-risk patients. It is going to be utilized to develop a biomarker-driven therapeutic approach where we can identify patients who are sensitive to a proteasome inhibitor-based therapy versus an immunomodulatory drug-based therapy and will be utilized in clinic more frequently than it is. I think the major challenge is understanding the technology and how it can be utilized.

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