Artificial Intelligence Individualized Risk Classifier in Multiple Myeloma

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Advancements in comprehending the biogenesis, dependencies, and mutational landscape of multiple myeloma dramatically expanded over the past two decades. This knowledge progress was paralleled by similar surge in novel therapeutics discovery, including the unveiling of new targets and classes of drugs. These advancements presented us, however, with novel challenges to prognosticate the disease with greater precision accounting for its individual biologic, genomic, and therapeutic features.

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How Did We End Up Here?

Since the coining of the term multiple myeloma by von Rustizky in 1873,[2] it became clearly evident over the years that indeed patients with multiple myeloma differ in their disease biology and have variable outcomes. But it was not until nearly a century after, in 1975, that Durie and Salmon introduced a method for measuring myeloma cell mass that helped prognosticate the diverse disease outcomes.[3] The Durie-Salmon (DS) classification was derived by analyzing clinical and biochemical covariates from 71 patients with newly diagnosed multiple myeloma (MM), where through multivariate regression analyses, they demonstrated that myeloma cell mass can be predicted on the basis of the extent of bone disease, degree of anemia (hemoglobin), the presence of hypercalcemia, and the quantification of the monoclonal protein in the serum and urine. This DS classification remained widely in use until 1995 when the International Myeloma Working Group (IMWG) adopted the International Staging System (ISS)[4,5] as a simplified prognostic classification for multiple myeloma. The ISS only required two readily available measurements of serum β2-microglobulin and albumin and hence was rapidly adopted as a simplified classification of this disease. However, the IMWG also recognized the shortcomings of the ISS staging system with its inability to identify all high-risk patients and the lack of integration of clonal plasma cells' cytogenetic and molecular genetics. A consensus by the International Myeloma Workshop in 2003 summarized a decade of variable genomic aberrations identified in multiple myeloma, recognizing their role not only in the disease biogenesis and classification but also in their clonal evolution and progression.[6] These discoveries led to the proposed translocations and cyclin D dysregulation-based classification (also referred to as translocation and cyclin D [TC] classification) by Bergsagel and Kuehl,[7,8] a classification of patients with myeloma into eight genetic subgroups. This TC classification provided a unified model of postgerminal center initiating events in multiple myeloma and afforded disease prognostication on the basis of genetic events with suboptimal outcomes correlated with hypodiploid disease.[7,8] Shortly after, the Arkansas University group proposed the gene expression molecular classification of multiple myeloma with a high-risk signature of 70 genes mostly mapping to chromosome 1.[9,10] Other gene array–based prognostic classifiers on the basis of the Affymetrix array platform followed suit, including, among others, IFM15 and SKY92.[11,12]

With this wealth of cytogenetic and gene expression profile (GEP) signatures, two decades after the release of the ISS, the IMWG introduced in 2015 the revised ISS classification (R-ISS),[13] integrating cytogenetics with fluorescence in situ hybridization (FISH) probes for the detection of deletion chr17p and translocations involving the immunoglobulin heavy chain gene locus on chromosome 14q32 with oncogenic partners mapping to chromosomes 4p16 (*NSD2*, *FGFR3*) or 16q23 (*MAF*). Along with high-risk cytogenetics, the R-ISS also included the presence of elevated serum lactate dehydrogenase as markers for high-risk disease to refine the ISS stage III definition. The reign of the R-ISS was short-lived with a second revision of the ISS (R2-ISS) recently introduced to account for the prognostic impact of the chromosome 1q gain or amplifications.[14]

THE TAKEAWAY

In the article that accompanies this editorial, Maura et al,[1] assisted by artificial intelligence and deep neuronal networks, have introduced the first individualized risk-prediction model for newly diagnosed multiple myeloma. This risk-prediction approach is the way forward for the dynamic integration of an ever-widening array of complex genomic, biologic, and soon immunologic features and will permit us to offer patients with myeloma a comprehensive individualized risk prediction adapted to the therapy they will receive.

Are We There Yet?

It is clear that the R2-ISS is not the last risk prediction algorithm we will have in multiple myeloma. As recognized by the authors of the R2-ISS, their revised classifier does not include numerous recently validated prognostic cytogenetic features such as chromosome 1p32 deletion or trisomy 21,[15] nor does it account for the co-occurrence of chromosomal events now recognized as double-hit myelomas,[16] lambda light chain,[17] and *MYC* translocations.[18] In addition, it does not incorporate other noncytogenetic prognostic features such as circulating tumor cells[19,20] and extramedullary disease.[21] Furthermore, transcriptome, exome, and whole-genome tumoral sequencing studies unraveled previously unrecognized genomic events and signatures. Analysis of the CoMMpass study identified novel molecular subgroups on the basis of their transcriptional profiles. It demonstrated the evolutionary dynamics of these signatures with nearly a quarter of patients transitioning to high-risk subgroups at first relapse.[22] Walker et al[23] also combined single-nucleotide mutations (SNVs) and APOBEC signatures, with ISS demonstrating the prognostic impact of SNVs. Finally, whole-genome sequencing studies revealed the role of mutational signatures and structural variants, particularly APOBEC and chromothripsis, not only in myeloma pathogenesis but also in disease survival outcomes.[24,25]

These complex genomic events in multiple myeloma, their interplay, weighted prognostic features, and their modulation by administered therapies at the individual patient level must be accounted for in any future individualized disease risk classifier. Such a classifier also needs to be scalable and adaptable to account for the rapidly expanding novel therapies, particularly immune-based adaptive T-cell therapies. While the R-ISS and R2-ISS have served us well in the pregenomic (in particular whole-genome studies) and large data era to prognosticate and predict myeloma disease outcomes, it is clear that we now need to integrate all the clinical, biologic, genomic, and immune features into one classifier that can be contextualized on the basis of the therapy received or to be administered.

How Do We Get There?

Mining complex cancer data sets exponentially expanding with the adoption of whole-genome and single-cell sequencing studies will only be effectively accomplished through artificial intelligence (AI). AI tools such as artificial neural networks (ANNs) can incorporate complex data and discern associations among variable features into adaptable classifiers.[26] Maura et al[1] apply such tools integrating clinical, genomic, and treatment variables to build a model that accurately predicts individualized risk in MM (IRMMa). To this end, they collected clinical, genomic, and therapeutic data from 1933 patients with newly diagnosed myeloma. Accounting for 20 genomic features, including chr.1q21 gain or amplifications, deletion chr.1p32, TP53 loss, NSD2 translocations, APOBEC mutational signatures, and copy number signatures such as chromothripsis, the authors reclustered previously defined FISH-TC or GEP subgroups into 12 molecular subgroups. Importantly, these newly defined molecular subgroups added valuable insights to the impact of co-occurring genomic aberrations on the survival of FISH-TC– or GEP-defined subgroups. In particular, the TC1 group harboring t(11;14) was divided into two: CCND1_Complex (9.4%) and CCND1_Simple (8.9%). In the CCND1_Complex, t(11;14) co-occurred with several deletions, 1q gain/amp, and chromothripsis signatures, while the CCND1_Simple lacked these features. Importantly, the CCND1_Complex had poorer survival compared with those in CCND1_Simple. Similarly, the hyperdiploid group was divided into three subgroups, including an HRD_Complex group enriched for aneuploidy and chromothripsis signatures and associated with poor outcomes. Providing such increased resolution to the currently defined molecular subgroups allows us to explain the unexpected poor outcomes encountered in some patients who until now would be classified as good or standard risk. Figure 1 summarizes the features included in IRMMa and the overlap with ISS, R-ISS, and R2-ISS.

This comprehensive integration of complex clinical, biologic, and genomic features afforded the herein-proposed IRMMa model accuracy for predicting survival outcomes significantly higher than all previous comparator prognostic models such as ISS, R-ISS, and R2-ISS. Of note, despite the comprehensive genomic data integration into this classifier, clinical features such as age and ISS retained their relevance for the model accuracy. Notably, the authors also noted that while the genomic features were key determinants of disease progression during induction therapy, the choice of first-line treatment significantly affected the risk weighted by poor clinical and genomic variables.

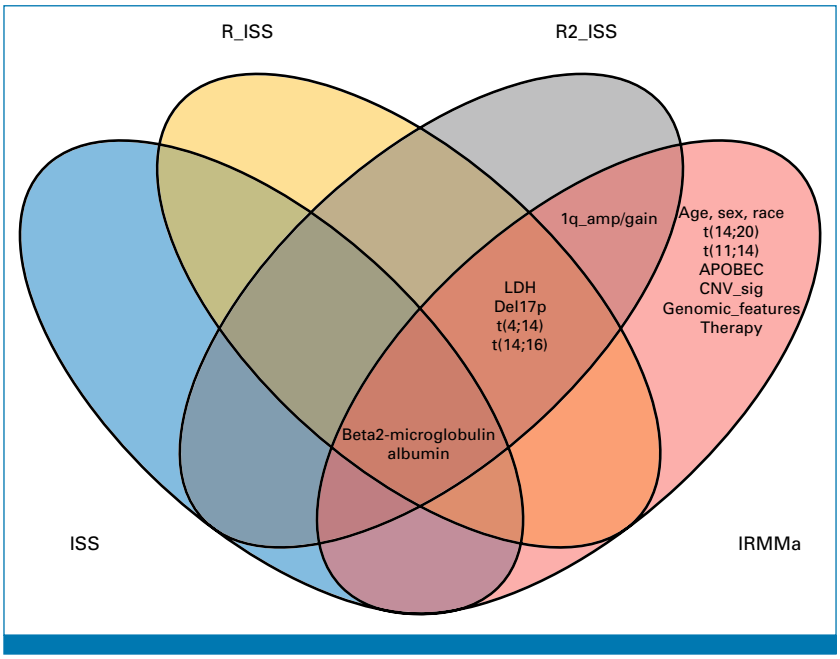

FIG 1. Venn diagram depicting the features included in the ISS, R-ISS, R2-ISS, and IRMMa risk-prediction models. 1q_amp/gain = chr 1q amplification (≥four copies) or gain (three copies), CNV_sig = copy number variation signatures (including chromothripsis), Genomic_features include SNVs in SAMHD1or PIK3CA, wild-type versus monoallelic versus biallelic deletion/mutations in TP53, RB1, FUBP1, TGDS, DNMT3a, BTG1, RPL5, and other structural variants: chr9gain, Del 2q37.3, Del 7p22.2, Del 10q26.3, Del 12p13.2, and Del 20q13.12.2. Therapy refers to the induction regimen (includes lenalidomide, thalidomide, bortezomib, carfilzomib, cyclophosphamide, low-dose melphalan, or any platinum-based chemotherapy) and postinduction (includes AHCT after high-dose melphalan and/or maintenance therapy). The IRMMa tool is available online.[27] AHCT, autologous hematopoietic cell transplantation; IRMMa, individualized risk in MM; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised ISS classification; R2-ISS, second revision of the ISS; SNVs, single-nucleotide mutations.

Finally, since the IRMMa is a multistate model, it does permit individual patient risk prediction on the basis of not only the molecular risk classifier but also the therapy patients receive as far as the type of induction regimen, upfront or deferred autologous hematopoietic cell transplantation, and whether consolidation or maintenance were administered. As such, the authors identified significant differences in the treatment variance among the 12 genomic groups they defined, each having predictable sensitivity to different therapies. Hence, the novelty and relevance of this new classifier are that it not only affords us a higher genomic resolution of the complex clinical and genomic features but also predicts individualized patient risks within the context of selected therapeutic strategies.

Big Data and AI-Assisted Classifiers

While AI-assisted tools such as ANN are very useful for complex data integration and risk prediction model generation, it is crucial to recognize their limitations and validate their usefulness in current clinical practice. In particular, the models constructed by ANN largely rely on big data and the quality of the data sets used for their model prediction. In multiple myeloma, the discovery and adoption of novel therapeutics (including immune-based therapeutics) are expanding at a pace that is not always permissive for big data generation. Hence, some limitations of the current work and proposed classifier include the relatively small data set used (despite being the largest genomic data set to date) and the lack of integration of training data sets with regimens containing immune-based therapies such as anti-CD38 antibodies.

Overall, to our knowledge, the herein-proposed risk classifier by Maura et al[1] is the most comprehensive to date, integrating established disease clinical variables with 20 genomics features, providing an accurate, individualized risk prediction of treatment outcomes vastly superior to that afforded by currently adopted risk scores and classifiers. However, further validation will be required before the full adoption of this new classifier, especially to account for the introduction of monoclonal antibodies and adaptive immune therapies to the disease treatment armamentarium.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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