# Gene Expression Profile of Multiple Myeloma

Subjects: Oncology

Contributor: Tadeusz Robak

Multiple myeloma (MM) is a genetically complex disease resulting from a multistep transformation of normal to malignant plasma cells in the bone marrow. Its precursors are believed to be monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.

Keywords: multiple myeloma ; biology ; gene expression profiling ; mRNA

## 1. Introduction

Multiple myeloma (MM) is a genetically complex disease resulting from a multistep transformation of normal to malignant plasma cells in the bone marrow [1]. Its precursors are believed to be monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. However, while both lack the clinical features of organ damage presence, such as hypercalcemia, renal insufficiency, anemia, and bone lesions, they share some genetic mutations of symptomatic MM [2][3]. Further progression of the disease may lead to the proliferation of clonal plasma cells at sites outside the bone marrow, manifesting as extramedullary myeloma and plasma cell leukemia (PCL), both known to be very aggressive malignancies with inferior outcomes [4].

As MM occurs mainly in older patients, its treatment has gained prominence in today's aging population. Its annual incidence in the United States in 2020 was estimated to be as high as 4–6 cases per 100,000, with 32,270 new cases and 12,830 deaths reported [4][5].

In the era of molecular cytogenetic methodologies such as G-band karyotyping, fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), as well as more advanced novel genetic techniques, such as single nucleotide polymorphism (SNP) arrays and next-generation sequencing (NGS), it has become possible to better understand the molecular background of myelomagenesis [6]. Multiple myeloma is a genetically heterogeneous disease. The genetic alterations present in MM can be categorized into translocations, copy number abnormalities (CNAs), and point mutations [7][8]. The most important molecular mechanism underlying MM pathogenesis is thought to be immunoglobulin heavy chain (IgH) translocation [9]. Although the molecular mechanisms responsible for the initiation and heterogeneous evolution of MM remain largely unknown to date, the identification of driver mutations is fundamental to understanding the oncogenesis of MM and its response to therapy. However, the genetic landscape of MM is very complex, and distinguishing driver from passenger mutations is challenging. The somatic mutation rate of patients with multiple myeloma was reported to be approximately 1.6 mutations per Mb [10]. Certain genes, including *KRAS, NRAS, TP53, FAM46C, DIS3*, and *BRAF* have been reported to demonstrate frequent mutations in myeloma patients [11][12][13].

The introduction of gene expression profiling (GEP) in MM was an important step in elucidating the molecular heterogeneity of MM and its clinical relevance. Initially array-based studies, and more recently, those based on RNA sequencing (RNASeq), provided information on the transcriptomic background of myeloma, its clinical course, and prognosis. Since some mutations in MM occur in non-coding regions [14], analytical approaches based on mRNA provide more comprehensive information on the oncogenic pathways and mechanisms relevant to MM biology.

## 2. Gene Expression Profile in Multiple Myeloma Biology and Prognosis

Multiple myeloma is a genetically complex and heterogeneous neoplasm in which the concurrency of multiple genomic events results in tumor development and progression. MM exists as hyperdiploid and nonhyperdiploid forms, with different karyotype [15][16]. Its most important oncogenic mechanisms are believed to be oncogene activation by IgH translocations and oncogene mutations [17]. IgH translocations are present in up to 50% of patients, and mainly involve five chromosomal loci, 11q13, 6p21, 4p16, 16q23, and 20q11, which contain the CCND1, CCND3, *FGFR3/NSD2, MAF*, and *MAFB* oncogenes [18].

The transcriptome of multiple myeloma has been evaluated in different patient cohorts [19][20][21][22]. Studies based on GEP have been widely used to better understand the biology of MM by identifying the genes involved in the molecular pathogenesis of the disease and their clinical significance, to predict survival in multiple myeloma, and to identify patients who will benefit from particular types of therapy. Some groups have even made an attempt to compare the transcriptome of MM and primary plasma cell leukemia: a more aggressive form of plasma cell dyscrasia [23]. Expression profiles of differentially expressed genes are of critical importance and have provided insights into MM biology. These genes may relate to cell cycle, cell death, autophagy, kinome, stemness, cytogenetic abnormalities, chromosome 1, homozygous deletions, and immune subnetworks [22][24][25][26][27][28][29][30][31].

GEP studies have led to the identification of Cyclin D family deregulation in MM and MGUS [19][32][33]. Deregulation of the cyclin D family (CCND1, CCND2, and CCND3) appears to be one of the key molecular events in the pathogenesis of MM [34]. It can result from the translocation of CCND1 or CCND3 with the *IgH* gene in the t(11;14) and the t(6;14), specific cyclin D amplification, trisomies, and other cytogenetic events. CCND2 is particularly overexpressed in t(4;14) and t(14;16) patients [19][20]. A proposed classification based on CCND1 gene expression status and 14q32 translocations divides MM patients into eight different subgroups [33].

Another attempt to use gene expression profiling in order to develop a prognostically relevant molecular classification of MM was made by Zhan et al. [21] The findings indicated the presence of seven disease subtypes that were strongly influenced by known genetic lesions including *c-MAF*– and *MAFB*-, CCND1- and CCND3-, *MMSET*-activating translocations and hyperdiploidy, these being CD1 [(t(11;14)], CD2 [t(11;14) and t(11;16)], MS [t(4;14)], MF [t(14;16) and t(14;20)], hyperdiploid cluster (HY), low bone disease (LB), and proliferation-associated genes (PR). Zhan et al. also identified myeloid gene expression signatures but excluded them from profiling analyses [21]. Broyl et al. confirmed the findings made by Zhan et al. and identified three novel subsets of MM: the nuclear factor kappa light chain-enhancer (NF-kB) subgroup, the cancer/testis antigen (CTA) subgroup characterized by high proliferation index, and the PRL3 subgroup characterized by up-regulation of protein tyrosine phosphatases PRL-3 and PTPRZ1 [20].

A review by Szalat et al. indicated the existence of 11 different molecular subgroups of MM based on transcriptomic studies [35]. A summary of this classification correlated with the clinical outcome is given in **Table 1**. Liu et al. combined data from whole-genome gene expression profiling microarrays and CytoScan HD high-resolution genomic arrays to integrate GEP with copy number variations (CNV); the findings highlighted certain molecular alterations in MM that were important for disease initiation, progression, and poor clinical outcome. In particular, eight cytogenetic driver lesions essential to the development and progression of myeloma were highlighted by the amplification of chromosome 1q: they suggest that 1q gains and the upregulated *ANP32E, DTL, IFI16, UBE2Q1,* and *UBE2T* gene expression could be responsible for MM aggressiveness [36]. These findings support those of Shaughnessy et al., who found that most of the up-regulated genes mapped to chromosome 1q, and the down-regulated genes mapped to chromosome 1p; this suggests that disease progression may be influenced by changes in the transcriptional regulation of genes mapping to chromosome 1 [29]. However, studies based on different molecular methods have yielded conflicting findings considering 1q gain as an adverse prognostic factor. Some early studies suggest it has no prognostic value [37][38], while some latest reports suggest it may be associated with an inferior outcome [39][40][41][42].

**Table 1.** The identification of 11 molecular subgroups of incorrectly expressed genes using gene expression profiling.

| Prognosis | Subgroup | Cytogenetics | Cyclin D Expression | Upregulated Genes | Downregulated Genes | Frequency |
|---|---|---|---|---|---|---|
| Low risk | CD1 | t(11;14) | CCND1 | *INHBE*<br>*ETV1*<br>*MACROD2* | *CD9*<br>*NOTCH2NL* | 4–9% |
| | CD2 | t(11;14)<br>t(6;14) | CCND1<br>CCND3 | *cd79a*<br>*cd20* | CCND2 | 11–17% |
| | LB | - | CCND1<br>CCND2 | *EDN1*<br>*IL6R*<br>*SMAD1* | *DKK1*<br>*STAT1*<br>*STAT2* | 12–17% |
| | HY | HD | CCND1 | *TRAIL*<br>*DKK1*<br>*CCR5* | CCND2<br>*CD52*<br>*TAGLN2*<br>*CKS1B*<br>*OPN3* | 26–32% |
| | NF-κB | HD | CCND1<br>CCND2 | *CD40*<br>*BCL10*<br>*IL8* | *TRAF3*<br>*CCR2*<br>*MAT2A* | 11% |
| | PRL3 | HD | CCND2 | *SOX3*<br>*PTP4A3*<br>*PTPRZ1* | *CD44*<br>*DUSP6* | 2–3% |
| | Myeloid | - | CCND1<br>CCND2 | *CD163*<br>*CA1*<br>*LIZ* | *PRMT1*<br>*DUSP5*<br>*SMAD7* | 12% |
| High risk | MF | t(14;16)<br>t(14;20) | CCND2 | *IL6R*<br>*c-MAF*<br>*MAFB* | *DKK1*<br>CCND1 | 6–10% |
| | MS | t(4;14)<br>1q gain | CCND2 | *MMSET*<br>*FGFR3*<br>*PBX1* | CCND1<br>*DUSP2*<br>*SYK PAX5* | 15–17% |
| | PR | 1q gain | CCND2<br>CCND1 | *CCNB1*<br>*MCM2*<br>*CDC2*<br>*BIRC5*<br>*CCNB2*<br>*AURKA* | *CXCR4*<br>*CD27* | 11% |
| | CTA | 1q gain | CCND1<br>CCND2 | Cancer testis antigen<br>*AURKA* | *MALAT1* | 7% |

Manasach et al. compared the value of retrospective GEP data with FISH criteria to identify high-risk (HR) patients. They conclude that GEP identified more HR patients than FISH. Patients reclassified from standard-risk FISH to HR GEP presented with 1q amplification of equal to or over four copies [43]. Elsewhere, a multi-tissue transcriptome-wide association study (TWAS) aimed at exploring MM biology by Went et al. [44] identified 108 genes at 13 independent regions associated with MM risk; all of these were within 1 Mb of known MM GWAS risk variants [45][46][47][48].

It should be noted that transcriptomic approaches have rarely been employed in assessments of the risk of multiple myeloma or progression from MGUS. A number of GWAS and SNP studies have been conducted in order to explore this field, including multiple studies by the International Multiple Myeloma Research (IMMEnSE) consortium [45][46][47][48][49][50][51].

## 3. Gene Expression Profile and Multiple Myeloma Prognosis

Many different transcriptomic models for prognostication have been identified; however, none of them have been introduced into routine clinical practice. So far, the revised International Staging System (R-ISS) is still the first choice in MM management [52], and the older Durie-Salmon staging system is still used in some places [53]. Zhan et al. performed a microarray analysis on tumor cells from 532 newly diagnosed patients with MM in order to identify high-risk disease [21]. They report that high-risk groups presented a similar gene expression profile to human MM cell lines, whereas low-risk MM groups exhibited patterns identical to MGUS and normal plasma cells. After evaluation of the 70-gene risk model in relapse samples of 51 out of 351 of the training cohort, high-risk scores associated with poor survival were found in 39 patients. Kuiper et al. identified a 92-gene signature (EMC-92) that proved to be an independent prognostic factor of

survival [54]. More recently Decaux et al. proposed a risk stratification model based on 15 different genes and note that patients with high-risk MM were characterized by the overexpression of genes involved in multiple phases of the entire cell cycle [22]. Dickens et al. limited the prognostication to six genes [30]. Similarly, Botta et al. proposed a prognostic risk score based on only six genes: *IFNG, IL2, LTA, CCL2, VEGFA,* and *CCL3* [31]. This list was acquired from a gene expression profiling dataset of MGUS, smoldering MM, and symptomatic-MM, and identified inflammatory and cytokine/chemokine pathways as the most progressively affected during disease evolution.

Hose et al. proposed that assessment of proliferation by GEP allows the selection of patients for risk-adapted anti-proliferative treatment [55]. Liu et al. [24] constructed a multiple myeloma molecular causal network (M3CN) based on gene expression, copy number variation, and clinical data to better understand MM tumorigenesis, progression, and drug responses. The M3CN-derived prognostic subnetwork achieved demonstrated satisfactory separation between different risk groups [24]. However, the most complex approach was proposed by Katiyar et al. [56], who identified unified potential signatures for MM based on a genome-wide meta-analysis of differentially expressed genes (DEGs) and miRNAs (DEMs) in MM cells and normal plasma cells. The authors identified the top five most functionally connected hub genes *(UBC, ITGA4, HSP90AB1, VCAM1, VCP*) using protein–protein interactions.

In addition, transcription factor regulatory networks were determined for five seed DEGs with four or more biomarker applications (*CDKN1A, CDKN2A, MMP9, IGF1, MKI67*) [56]. The above studies indicate, that DEGs may influence disease pathogenesis, clinical presentation, and drug sensitivities in MM patients.

In recent years, gene expression profiling has been used to establish classifiers for prognostication. Various studies have shown that that GEP classifiers are more robust than FISH markers in identifying risk. For instance, a multivariate analysis by Kuiper et al. found that combinations of GEP with ISS, particularly SKY92 + ISS, proved superior to other combinations for stratifying MM into high-risk and low-risk categories [57].

## References


1. Morgan, G.J.; Walker, B.A.; Davies, F.E. The genetic architecture of multiple myeloma. Nat. Rev. Cancer 2012, 12, 335–348.
2. Corral, L.L.; Gutierrez, N.; Vidriales, M.-B.; Mateos, M.V.; Rasillo, A.; Garcia-Sanz, R.; Paiva, B.D.L.; Miguel, J.S. The Progression from MGUS to Smoldering Myeloma and Eventually to Multiple Myeloma Involves a Clonal Expansion of Genetically Abnormal Plasma Cells. Clin. Cancer Res. 2011, 17, 1692–1700.
3. Rajkumar, S.V.; Dimopoulos, M.A.; Palumbo, A.; Blade, J.; Merlini, G.; Mateos, M.-V.; Kumar, S.; Hillengass, J.; Kastritis, E.; Richardson, P.; et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014, 15, e538–e548.
4. Palumbo, A.; Anderson, K. Multiple Myeloma. N. Engl. J. Med. 2011, 364, 1046–1060.
5. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30.
6. Cardona-Benavides, I.J.; de Ramón, C.; Gutiérrez, N.C. Genetic Abnormalities in Multiple Myeloma: Prognostic and Therapeutic Implications. Cells 2021, 10, 336.
7. Walker, B.A.; Mavrommatis, K.; Wardell, C.P.; Ashby, C.; Bauer, M.; Davies, F.; Rosenthal, A.; Wang, H.; Qu, P.; Hoering, A.; et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. Blood 2018, 132, 587–597.
8. Maura, F.; Bolli, N.; Angelopoulos, N.; Dawson, K.J.; Leongamornlert, D.; Martincorena, I.; Mitchell, T.J.; Fullam, A.; Gonzalez, S.; Szalat, R.; et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. Nat. Commun. 2019, 10, 3835.
9. Ross, F.M.; Avet-Loiseau, H.; Ameye, G.; Gutiérrez, N.C.; Liebisch, P.; O'Connor, S.; Dalva, K.; Fabris, S.; Testi, A.M.; Jarosova, M.; et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 2012, 97, 1272–1277.
10. Lawrence, M.S.; Stojanov, P.; Mermel, C.; Robinson, J.T.; Garraway, L.A.; Golub, T.R.; Meyerson, M.; Gabriel, S.B.; Lander, E.S.; Getz, G. Discovery and saturation analysis of cancer genes across 21 tumour types. Nat. Cell Biol. 2014, 505, 495–501.
11. Lohr, J.G.; Stojanov, P.; Carter, S.L.; Cruz-Gordillo, P.; Lawrence, M.S.; Auclair, D.; Sougnez, C.; Knoechel, B.; Gould, J.; Saksena, G.; et al. Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy. Cancer Cell 2014, 25, 91–101.

12. Bolli, N.; Avet-Loiseau, H.; Wedge, D.; Van Loo, P.; Alexandrov, L.; Martincorena, I.; Dawson, K.J.; Iorio, F.; Nik-Zainal, S.; Bignell, G.R.; et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Nat. Commun. 2014, 5, 2997.

13. Walker, B.; Boyle, E.M.; Wardell, C.; Murison, A.; Begum, D.B.; Dahir, N.M.; Proszek, P.Z.; Johnson, D.C.; Kaiser, M.F.; Melchor, L.; et al. Mutational Spectrum, Copy Number Changes, and Outcome: Results of a Sequencing Study of Patients With Newly Diagnosed Myeloma. J. Clin. Oncol. 2015, 33, 3911–3920.

14. Hoang, P.H.; Dobbins, S.E.; Cornish, A.J.; Chubb, D.; Law, P.; Kaiser, M.; Houlston, R.S. Whole-genome sequencing of multiple myeloma reveals oncogenic pathways are targeted somatically through multiple mechanisms. Leukemia 2018, 32, 2459–2470.

15. Du Pont, S.R.; Cleynen, A.; Fontan, C.; Attal, M.; Munshi, N.; Corre, J.; Avet-Loiseau, H. Genomics of Multiple Myeloma. J. Clin. Oncol. 2017, 35, 963–967.

16. Manier, S.; Salem, K.; Glavey, S.V.; Roccaro, A.M.; Ghobrial, I.M. Genomic Aberrations in Multiple Myeloma. Cancer Treat. Res. 2016, 169, 23–34.

17. Nishida, K.; Tamura, A.; Nakazawa, N.; Ueda, Y.; Abe, T.; Matsuda, F.; Kashima, K.; Taniwaki, M. The Ig Heavy chain gene is frequently involved in chromosomal translocations in multiple myeloma and plasma cell leu-kemia as detected by in situ hybridization. Blood 1997, 90, 526–534.

18. Chesi, M.; Bergsagel, P.L. Advances in the pathogenesis and diagnosis of multiple myeloma. Int. J. Lab. Hematol. 2015, 37, 108–114.

19. Bergsagel, P.L.; Kuehl, W.M.; Zhan, F.; Sawyer, J.; Barlogie, B.; Shaughnessy, J.J. Cyclin D dysregulation: An early and unifying pathogenic event in multiple myeloma. Blood 2005, 106, 296–303.

20. Broyl, A.; Hose, D.; Lokhorst, H.; de Knegt, Y.; Peeters, J.; Jauch, A.; Bertsch, U.; Buijs, A.; Stevens-Kroef, M.; Beverloo, H.B.; et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. Blood 2010, 116, 2543–2553.

21. Zhan, F.; Huang, Y.; Colla, S.; Stewart, J.P.; Hanamura, I.; Gupta, S.; Epstein, J.; Yaccoby, S.; Sawyer, J.; Burington, B.; et al. The molecular classification of multiple myeloma. Blood 2006, 108, 2020–2028.

22. Decaux, O.; Lodé, L.; Magrangeas, F.; Charbonnel, C.; Gouraud, W.; Jézéquel, P.; Attal, M.; Harousseau, J.-L.; Moreau, P.; Bataille, R.; et al. Prediction of Survival in Multiple Myeloma Based on Gene Expression Profiles Reveals Cell Cycle and Chromosomal Instability Signatures in High-Risk Patients and Hyperdiploid Signatures in Low-Risk Patients: A Study of the Intergroupe Francophone du Myélome. J. Clin. Oncol. 2008, 26, 4798–4805.

23. Rojas, E.A.; Corchete, L.A.; Mateos, M.V.; García-Sanz, R.; Misiewicz-Krzeminska, I.; Gutiérrez, N.C. Transcriptome analysis reveals significant differences between primary plasma cell leukemia and multiple myeloma even when sharing a similar genetic background. Blood Cancer J. 2019, 9, 1–13.

24. Liu, Y.; Yu, H.; Yoo, S.; Lee, E.; Laganà, A.; Parekh, S.; Schadt, E.E.; Wang, L.; Zhu, J. A Network Analysis of Multiple Myeloma Related Gene Signatures. Cancers 2019, 11, 1452.

25. De Boussac, H.; Bruyer, A.; Jourdan, M.; Maes, A.; Robert, N.; Gourzones, C.; Vincent, L.; Seckinger, A.; Cartron, G.; Hose, D.; et al. Kinome expression profiling to target new therapeutic avenues in multiple myeloma. Haematologica 2019, 105, 784–795.

26. Zhu, F.; Wang, X.; Zeng, H.; Yin, Z.; Ye, Z. A predicted risk score based on the expression of 16 autophagy-related genes for multiple myeloma survival. Oncol. Lett. 2019, 18, 5310–5324.

27. Bai, H.; Chen, B. A 5-Gene Stemness Score for Rapid Determination of Risk in Multiple Myeloma. OncoTargets Ther. 2020, ume 13, 4339–4348.

28. Zhou, Y.; Zhang, Q.; Stephens, O.; Heuck, C.J.; Tian, E.; Sawyer, J.R.; Cartron-Mizeracki, M.-A.; Qu, P.; Keller, J.; Epstein, J.; et al. Prediction of cytogenetic abnormalities with gene expression profiles. Blood 2012, 119, e148–e150.

29. Shaughnessy, J.D.; Zhan, F.; Burington, B.E.; Huang, Y.; Colla, S.; Hanamura, I.; Stewart, J.P.; Kordsmeier, B.; Randolph, C.; Williams, D.R.; et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 2007, 109, 2276–2284.

30. Dickens, N.; Walker, B.A.; Leone, P.E.; Johnson, D.C.; Brito, J.L.; Zeisig, A.; Jenner, M.; Boyd, K.; Gonzalez, D.; Gregory, W.M.; et al. Homozygous Deletion Mapping in Myeloma Samples Identifies Genes and an Expression Signature Relevant to Pathogenesis and Outcome. Clin. Cancer Res. 2010, 16, 1856–1864.

31. Botta, C.; DI Martino, M.T.; Ciliberto, D.; Cucè, M.; Correale, P.; Rossi, M.; Tagliaferri, P.; Tassone, P. A gene expression inflammatory signature specifically predicts multiple myeloma evolution and patients survival. Blood Cancer J. 2016, 6, e511.

32. Miura, K.; Lida, S.; Hanamura, I.; Kato, M.; Banno, S.; Ishida, T.; Kusumoto, S.; Takeuchi, G.; Miwa, H.; Nitta, M.; et al. Frequent occurrence of CCND1 deregulation in patients with early stages of plasma cell dyscrasia. Cancer Sci. 2003, 94, 350–354.

33. Bergsagel, P.L.; Kuehl, W.M. Molecular Pathogenesis and a Consequent Classification of Multiple Myeloma. J. Clin. Oncol. 2005, 23, 6333–6338.

34. Waheed, S.; Mitchell, A.; Usmani, S.; Epstein, J.; Yaccoby, S.; Nair, B.; Van Hemert, R.; Angtuaco, E.; Brown, T.; Bartel, T.; et al. Standard and novel imaging methods for multiple myeloma: Correlates with prognostic laboratory variables including gene expression profiling data. Haematologica 2012, 98, 71–78.

35. Szalat, R.; Avet-Loiseau, H.; Munshi, N.C. Gene Expression Profiles in Myeloma: Ready for the Real World? Clin. Cancer Res. 2016, 22, 5434–5442.

36. Li, C.; Wendlandt, E.; Darbro, B.; Xu, H.; Thomas, G.; Tricot, G.; Chen, F.; Shaughnessy, J.; Zhan, F. Genetic Analysis of Multiple Myeloma Identifies Cytogenetic Alterations Implicated in Disease Complexity and Progression. Cancers 2021, 13, 517.

37. Fonseca, R.; Van Wier, S.A.; Chng, W.J.; Ketterling, R.; Lacy, M.Q.; Dispenzieri, A.; Bergsagel, P.L.; Rajkumar, S.V.; Greipp, P.R.; Litzow, M.R.; et al. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. Leukemia 2006, 20, 2034–2040.

38. Avet-Loiseau, H.; Li, C.; Magrangeas, F.; Gouraud, W.; Charbonnel, C.; Harousseau, J.-L.; Attal, M.; Marit, G.; Mathiot, C.; Facon, T.; et al. Prognostic Significance of Copy-Number Alterations in Multiple Myeloma. J. Clin. Oncol. 2009, 27, 4585–4590.

39. Shah, V.; Csg, O.B.O.T.N.H.-O.; Sherborne, A.L.; Walker, B.A.; Johnson, D.C.; Boyle, E.M.; Ellis, S.; Begum, D.B.; Proszek, P.Z.; Jones, J.R.; et al. Prediction of outcome in newly diagnosed myeloma: A meta-analysis of the molecular profiles of 1905 trial patients. Leukemia 2018, 32, 102–110.

40. Shah, G.L.; Landau, H.; Londono, D.; Devlin, S.M.; Kosuri, S.; Lesokhin, A.M.; Lendvai, N.; Hassoun, H.; Chung, D.J.; Koehne, G.; et al. Gain of chromosome 1q portends worse prognosis in multiple myeloma despite novel agent-based induction regimens and autologous transplantation. Leuk. Lymphoma 2017, 58, 1823–1831.

41. Giri, S.; Huntington, S.F.; Wang, R.; Zeidan, A.M.; Podoltsev, N.A.; Gore, S.; Ma, X.; Gross, C.P.; Davidoff, A.J.; Neparidze, N. Chromosome 1 abnormalities and clinical outcomes in multiple myeloma in the era of novel agents. J. Clin. Oncol. 2019, 37, 8044.

42. Abdallah, N.; Greipp, P.; Kapoor, P.; Gertz, M.A.; Dispenzieri, A.; Baughn, L.B.; Lacy, M.Q.; Hayman, S.R.; Buadi, F.K.; Dingli, D.; et al. Clinical characteristics and treatment outcomes of newly diagnosed multiple myeloma with chromosome 1q abnormalities. Blood Adv. 2020, 4, 3509–3519.

43. Manasanch, E.E.; Berrios, D.; Fountain, E.; Claussen, C.M.; Chuang, T.; Kaufman, G.; Amini, B.; Bashir, Q.; Nieto, Y.; Qazilbash, M.; et al. Gene expression profiling predicts relapse-free and overall survival in newly diagnosed myeloma patients treated with novel therapies. Br. J. Haematol. 2021, 192, e115–e120.

44. Went, M.; Kinnersley, B.; Sud, A.; Johnson, D.C.; Weinhold, N.; Försti, A.; Van Duin, M.; Orlando, G.; Mitchell, J.S.; Kuiper, R.; et al. Transcriptome-wide association study of multiple myeloma identifies candidate susceptibility genes. Hum. Genom. 2019, 13, 1–8.

45. Went, M.; The PRACTICAL Consortium; Sud, A.; Försti, A.; Halvarsson, B.-M.; Weinhold, N.; Kimber, S.; Van Duin, M.; Thorleifsson, G.; Holroyd, A.; et al. Identification of multiple risk loci and regulatory mechanisms influencing susceptibility to multiple myeloma. Nat. Commun. 2018, 9, 3707.

46. Mitchell, J.S.; Li, N.; Weinhold, N.; Försti, A.; Ali, M.; Van Duin, M.; Thorleifsson, G.; Johnson, D.C.; Chen, B.; Halvarsson, B.-M.; et al. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nat. Commun. 2016, 7, 12050.

47. Chubb, D.; Weinhold, N.; Broderick, P.; Chen, B.; Johnson, D.C.; Försti, A.; Vijayakrishnan, J.; Migliorini, G.; Dobbins, S.E.; Holroyd, A.; et al. Common variation at 3q26.2, 6p21.33, 17p11.2 and 22q13.1 influences multiple myeloma risk. Nat. Genet. 2013, 45, 1221–1225.

48. Swaminathan, B.; Thorleifsson, G.; Jöud, M.; Ali, M.; Johnsson, E.; Ajore, R.; Sulem, P.; Halvarsson, B.-M.; Eyjolfsson, G.; Haraldsdottir, V.; et al. Variants in ELL2 influencing immunoglobulin levels associate with multiple myeloma. Nat. Commun. 2015, 6, 7213.

49. Broderick, P.; Chubb, D.; Johnson, D.C.; Weinhold, N.; Försti, A.; Lloyd, A.; Olver, B.; Ma, Y.P.; Dobbins, S.E.; Walker, B.; et al. Common variation at 3p22.1 and 7p15.3 influences multiple myeloma risk. Nat. Genet. 2011, 44, 58–61.

50. Giaccherini, M.; Macauda, A.; Orciuolo, E.; Rymko, M.; Gruenpeter, K.; Dumontet, C.; Raźny, M.; Moreno, V.; Buda, G.; Beider, K.; et al. Genetically determined telomere length and multiple myeloma risk and outcome. Blood Cancer J.

2021, 11, 1–10.

51. Pertesi, M.; Vallée, M.; Wei, X.; Revuelta, M.V.; Galia, P.; Demangel, D.; Oliver, J.; Foll, M.; Chen, S.; Perrial, E.; et al. Exome sequencing identifies germline variants in DIS3 in familial multiple myeloma. Leukemia 2019, 33, 2324–2330.
52. Palumbo, A.; Avet-Loiseau, H.; Oliva, S.; Lokhorst, H.M.; Goldschmidt, H.; Rosinol, L.; Richardson, P.; Caltagirone, S.; Lahuerta, J.J.; Facon, T.; et al. Revised International Stag-ing System for Multiple Myeloma: A Report from International Myeloma Working Group. J. Clin. Oncol. 2015, 33, 2863–2869.
53. Durie, B.G.; Salmon, S.E. A Clinical Staging System for Multiple Myeloma. Correlation of Measured Mye-loma Cell Mass with Presenting Clinical Features, Response to Treatment, and Survival. Cancer 1975, 36, 842–854.
54. Kuiper, R.; Broyl, A.; De Knegt, Y.; Van Vliet, M.H.; Van Beers, E.H.; Van Der Holt, B.; El Jarari, L.; Mulligan, G.; Gregory, W.; Morgan, G.; et al. A gene expression signature for high-risk multiple myeloma. Leukemia 2012, 26, 2406–2413.
55. Hose, D.; Rème, T.; Hielscher, T.; Moreaux, J.; Messner, T.; Seckinger, A.; Benner, A.; Shaughnessy, J.D.; Barlogie, B.; Zhou, Y.; et al. Proliferation is a central independent prognostic factor and target for personalized and risk-adapted treatment in multiple myeloma. Haematologica 2011, 96, 87–95.
56. Katiyar, A.; Kaur, G.; Rani, L.; Jena, L.; Singh, H.; Kumar, L.; Sharma, A.; Kaur, P.; Gupta, R. Genome-wide identification of potential biomarkers in multiple myeloma using meta-analysis of mRNA and miRNA expression data. Sci. Rep. 2021, 11, 1–15.
57. Kuiper, R.; van Duin, M.; van Vliet, M.H.; Broijl, A.; van der Holt, B.; el Jarari, L.; van Beers, E.H.; Mulligan, G.; Avet-Loiseau, H.; Gregory, W.M.; et al. Prediction of high- and low-risk multiple myeloma based on gene expression and the International Staging System. Blood 2015, 126, 1996–2004.

---