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Are all risk factors created equal in multiple myeloma?

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Contributions

MFK and SAB wrote this editorial. SAB created the figure.

Editorial

In this issue of Haematologica, Chung et al [1] assessed whether additional molecular markers could improve on the 2025 IMS/IMWG high-risk multiple myeloma (MM) criteria, using an integrated mutational and transcriptional analysis of the CoMMpass dataset.

The 2025 International Myeloma Society (IMS) – International Myeloma Working Group (IMWG) updated definition of high-risk MM provided an important improvement for pre-emptively identifying patients at high-risk of early relapse. High-risk cytogenetic aberrations (HRCA) recommended to be tested in all patients at diagnosis now include gain(1q), del(1p), del(17p) and high-risk immunoglobulin translocations (t(4;14), t(14;16), t(14;20)), enabling the detection of disease harboring two or more HRCA - a well-established ultra-high-risk group [2,3]. In addition to HRCA, testing for *TP53* single nucleotide variants (SNV), preferentially by next-generation sequencing (NGS), is now required as well. Operationally, this means myeloma diagnostic laboratories need workflows that enable DNA extraction from highly purified CD138-positive tumour cells, either alongside traditional FISH or as part of an NGS-based tumour genetic analysis. As a consequence, myeloma diagnostics are finally getting integrated into modern molecular diagnostic workflows, which have accelerated and expanded vastly for solid oncology over the past decade. Large oncology diagnostic laboratories such as the UK National Health Service's (NHS) Genomic Laboratory Hubs (GLH) have established protocols to extract DNA and RNA from the same sample and deliver highly specialised tumour genetic testing on a daily basis and at high volume, including DNA NGS mutational calling, as well as RNA-based transcriptional, or gene expression profiling (GEP), tests. The latter are reimbursed by the NHS and other public healthcare systems; an example are thousands of breast cancer patients each year receiving GEP testing, as the added prognostic value has been found to be beneficial and cost-effective by the UK National Institute for Health and Care Excellence (NICE) and other healthcare systems [4].

An analysis like that by Chung et al, which evaluates the added prognostic value of DNA mutational signatures, as well as RNA-based GEP signatures in context of the updated IMS-IMWG HR criteria is therefore timely and of potential clinical relevance. The team specifically evaluated the APOBEC mutational signature and chromotripsis, both common in cancer and found in myeloma. Both can be detected by NGS, ideally whole genome sequencing (WGS), which is increasingly available but incurs additional cost. However, analysis pipelines for calling these signatures in line with ISO accredited diagnostics standards are not yet universally established. The RNA GEP signatures evaluated in the article include EMC92, which has been developed as an accredited *in-vitro* diagnostic (IVD) test (MMProfiler/SKY92) [5], as well as the research-only proliferation (PR) signature [6,7].

All tested signatures partially overlapped with IMS-IMWG high-risk markers, but also identified additional patients, which were different between the signatures. However, when de-convoluting overlapping prognostic associations, either through multivariable modelling or by sub-group analysis of patients with the presence of isolated risk markers, the additional prognostic value of GEP exceeded that of the other markers.

Whilst the present study has its limitations, such as the highly heterogeneous treatment patients received in CoMMpass, these findings are in keeping with an increasing number of independent reports confirming the added prognostic value of RNA transcriptional profiling to the 2025 IMS-IMWG risk definition [8-10]. It is also in keeping with the diagnostic and

prognostic value transcriptional profiling has added for other B-cell malignancies, e.g. in B-acute lymphoblastic leukaemia, where integrated diagnostic pathways with DNA and RNA profiling are increasingly used [11].

But as evidence continues to build, how realistically could GEP testing be integrated into routine myeloma diagnostic pathways - provided it took a mere 14 years from publication of the initial myeloma genome to the 2025 IMS-IMWG HR guideline? As described above, diagnostic practice has advanced across oncology, including access to GEP for multiple tumour entities. Of note, health economic evaluation of the MMProfiler/SKY92 assay by UK NICE has recently started [12] and similar evaluations are ongoing elsewhere. If successful, these could provide equitable access to advanced diagnostics for myeloma patients in respective healthcare systems. Importantly, the addition of advanced risk stratification with minimal residual disease tools and others (**Figure 1**) can provide a fully integrated pathway approach to patient care.

Open questions remain regarding how much recalibration of existing risk factors and addition of new factors will be required with novel T-cell engaging (TCE)/redirecting therapies, especially considering bispecific antibodies moving into earlier lines of therapy. For instance, first sub-group analyses of the MajesTEC-3 trial have shown long-lasting remissions in traditional ultra-high-risk subgroups (2+HRCA) that are unprecedented [13]. Nonetheless, this promptly raises new questions such as the optimal duration of TCE therapy, where again an assessment of key prognostic factors is likely to provide valuable information and guidance. The present work adds to a body of evidence suggesting that transcriptional profiling should be considered in clinical routine.

References

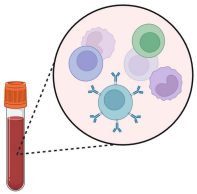
1. Chung TH, Chang JG, Tan TK, Chng WJ. Risk factors and their contributions to prognosis in multiple myeloma. Haematologica. xxx
2. Panopoulou A, Cairns DA, Holroyd A, et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the Myeloma XI trial. Blood. 2023;141(14):1666-1674.
3. Kaiser MF, Sonneveld P, Cairns DA, et al. Co-occurrence of cytogenetic abnormalities and high-risk disease in newly diagnosed and relapsed/refractory multiple myeloma. J Clin Oncol. 2025;43(24):2679-2691.
4. NICE. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. National Institute for Health and Care Excellence. 2024;HTG719.
5. Kuiper R, Broyl A, de Knegt Y, et al. A gene expression signature for high-risk multiple myeloma. Leukemia. 2012;26(11):2406-2413.
6. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. Blood. 2006;108(6):2020-2028.
7. Skerget S, Penaherrera D, Chari A, et al. Comprehensive molecular profiling of multiple myeloma identifies refined copy number and expression subtypes. Nat Genet. 2024;56(9):1878-1889.
8. Beer SA, Cairns DA, Pawlyn C, et al. Challenging the concept of functional high-risk myeloma through transcriptional and genetic profiling. Blood. 2025;146(22):2670-2680.
9. Biran N, Dhakal B, Niesvizky R, et al. Enhancing risk stratification and treatment decision in multiple myeloma with SKY92 gene expression profiling in real-world data. Br J Haematol. 2025;206(6):1642-1653.
10. McAvera RM, Cymer I, Quinn J, et al. SKY92 identifies high-risk newly diagnosed multiple myeloma with inferior progression-free survival and implicates NUF2 as a candidate driver. Eur J Haematol. 2026 Aug 7. doi: 10.1111/ejh.70282. [Epub ahead of print]
11. Wolgast N, Beder T, Mondal M, et al. IntegrateALL: An end-to-end RNA-seq analysis pipeline for multilevel data extraction and interpretable subtype classification in B-precursor ALL. Hemasphere. 2026;10(4):e70366.
12. NICE: MMprofiler for estimating risk in newly diagnosed multiple myeloma. National Institute for Health and Care Excellence. 2026;GID-HTG10153.
13. Plenary Abstracts Session & Oral Presentations. Hemasphere. 2026;10:e70419.

Figure Legend 1: Outline of an integrated diagnostic workflow in multiple myeloma. Combining DNA genomics and RNA transcriptomics for currently accredited diagnostics and potential future diagnostic applications. MRD, minimal residual disease; CTPC, circulating tumour plasma cells. *Requires definition of diagnostically accredited calling criteria.

Currently accredited diagnostics

Future potential diagnostic capacity*

Single bone marrow sample

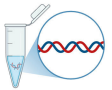


CD138 purification

Parallel DNA and RNA extraction from the same diagnostic sample possible

no splitting of rare material required

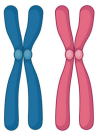
DNA GENOMICS



1

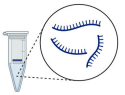
Updated IMS/IMWG-HR consensus incl.

- t(4; 14), t(14;16), t(14; 20)
- Del(1p32)
- Del(17p)/ *TP53*mut
- Gain(1q21)



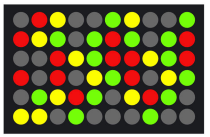
- APOBEC mutational signature
- Chromothripsis
- Monitoring of therapeutic targets (e.g., BCMA, GPRC5D)
- Other future applications

RNA TRANSCRIPTOMICS



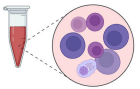
2

Gene expression risk signatures (e.g., EMC92/SKY92)



- Proliferation index (PR)
- Molecular classification and dependencies (e.g., IGH translocation calling, BCL2 expression)
- Expression of therapeutic targets (e.g., BCMA, GPRCD5)

MRD DIAGNOSTICS



+

- Flow/NGS bone marrow
- Mass spectrometry peripheral blood

- Circulating tumour plasma cells (CTPCs)
- Immune cell profiling

→ Individualized patient pathway stratification