Individualized treatment risk stratification using histopathology-based genomics prediction in multiple myeloma: A multicenter study in 1429 participants

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INTRODUCTION

- Multiple myeloma (MM) genomic profiling by NGS/FISH is time-consuming and resource-intensive, limiting universal access to molecular-guided treatment decisions.
- ISS/R-ISS[1,2,3] enables accessible but population-level risk stratification, while individualized models like IRMMa[4] provide superior patient-specific accuracy through comprehensive genomic profiling but remain inaccessible in resource-limited settings.
- Histopathology could democratize precision risk assessment by extracting molecular information from routine H&E bone marrow biopsies.

AIMS

To develop **CORAL-histomorph**, a novel, next-generation machine learning deep whole slide attention-based[5] model that predicts genomic abnormalities directly from routine H&E histopathology bone marrow biopsy images and integrates clinical/treatment data to provide individualized treatment guidance and predict clinical outcomes in MM patients.

METHODS

- **Cohort**: 1,309 MM patients and 120 controls from University of Miami (UM; n=519), HealthTree Foundation (HT; n=805), and Ministry of Health Malaysia (MOHM; n=105).
- **Processing**: H&E bone marrow slides scanned at 40x (Aperio AT2), deep learning trained to predict seven genomic subgroups: t(11;14), t(4;14), 1q gain, del 17p/13q/1p, hyperdiploidy.
- **Validation**: **CORAL-histomorph** trained on UM, validated against FISH (HT, AUC), tested for OS prognostic performance (MOHM cohort, c-index, >3-year follow-up).
- **Analysis**: Unsupervised clustering identified histomolecular and treatment-responsive clusters (TRC) from histopathology features.

RESULTS

Figure 1: **CORAL-histomorph** establishes histopathology-based molecular classification bridging tissue architecture with genomic complexity.

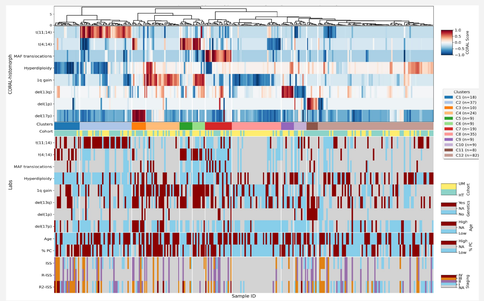


Figure 2: The histopathology image features provide risk stratification with significant p-values based on double hits and IMWG[3] criteria

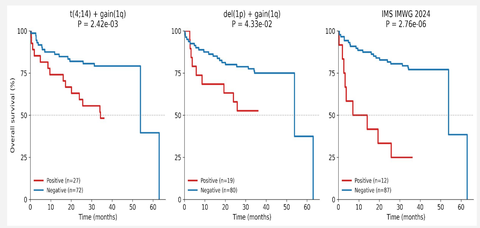


Figure 3: **TRCs showed significant survival differences** (OS p<0.01, PFS p<0.05). Non-ASCT patients (TRC1) demonstrated superior OS benefit (47.5 mo vs 32.2 mo) despite ASCT patients (TRC2) showing better PFS outcomes (28.9 mo vs 26 mo). **High-risk clusters** (TRC4/TRC5) showed poor responses to intensification with rapid progression.

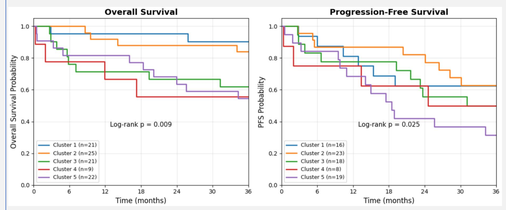


Figure 4: **CORAL-histomorph** deep attention maps of predicted and FISH test as t(11;14) positive.

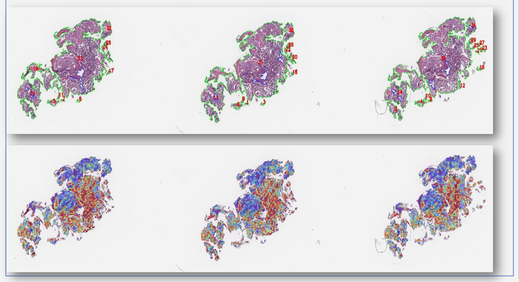
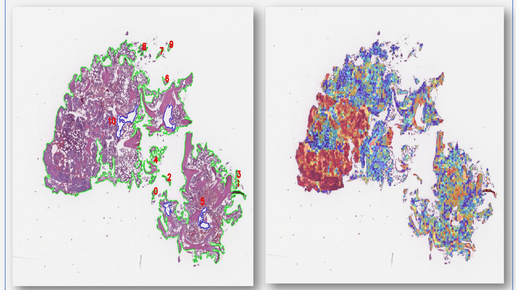
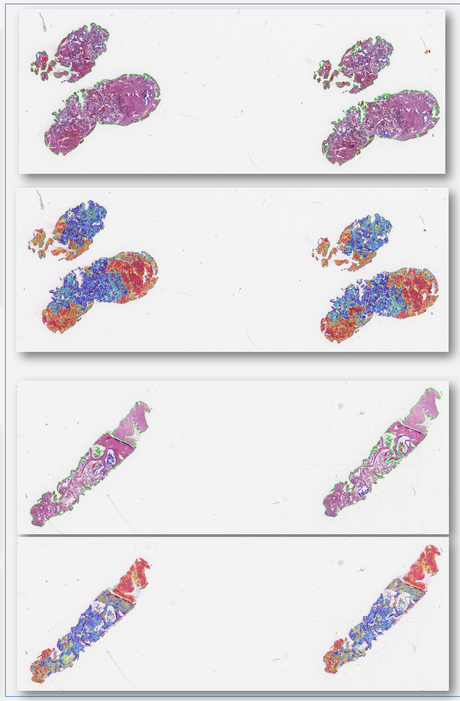


Figure 6: Our model's deep attention maps of predicted and FISH test as t(11;14) negative.





CONCLUSIONS

- **Genomic prediction**: AUCs: amp 1q (0.836), hyperdiploidy (0.800), t(4;14) (0.779), del 13q (0.767), del 17p (0.759), t(11;14) (0.754), 1q gain (0.747), del 1p (0.723); OS c-index (0.7).
- **Novel classification**: 12 histomolecular clusters; 7 genomic subgroups, 3 hyperdiploidy variants, 2 genomically silent.
- **Treatment insights**: 5 TRCs identified; TRC1 superior OS without ASCT (47.5 mo, CR 33.3%); TRC2 better PFS with ASCT (28.9 mo, CR 50%) but shorter OS (32.2 mo) than TRC1; TRC4/5 high-risk with poor responses (CR 14.3%, 25%).
- **Clinical impact**: Accessible genomic classification from routine H&E with scalable multicenter architecture for expansion to other malignancies.

REFERENCES

1. Greipp, P. R., Miguel, J. S., Durie, B. G., Crowley, J. J., Barlogie, B., Bladé, J., ... & Westin, J. (2005). International staging system for multiple myeloma. Journal of clinical oncology, 23(15), 3412-3420.
2. Palumbo, A., Avet-Loiseau, H., Oliva, S., Lokhorst, H. M., Goldschmidt, H., Rosinol, L., ... & Moreau, P. (2015). Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. Journal of clinical oncology, 33(26), 2863-2869.
3. Avet-Loiseau, H., Davies, F. E., Samur, M. K., Corre, J., D'agostino, M., Kaiser, M. F., ... & Munshi, N. C. (2025). International Myeloma Society/International Myeloma Working Group consensus recommendations on the definition of high-risk multiple myeloma. Journal of Clinical Oncology, 43(24), 2739-2751.
4. Maura, F., Rajanna, A. R., Ziccheddu, B., Poos, A. M., Derkach, A., Maclachlan, K., ... & Landgren, O. (2024). Genomic classification and individualized prognosis in multiple myeloma. *Journal of clinical oncology*, *42*(11), 1229-1240.
5. Campanella, G., Hanna, M. G., Geneslaw, L., Miraflor, A., Werneck Krauss Silva, V., Busam, K. J., ... & Fuchs, T. J. (2019). Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nature medicine, 25(8), 1301-1309.

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