

# Genomic Subtypes of Smoldering Multiple Myeloma Are Associated with Distinct Pathogenic Phenotypes & Clinical Outcomes

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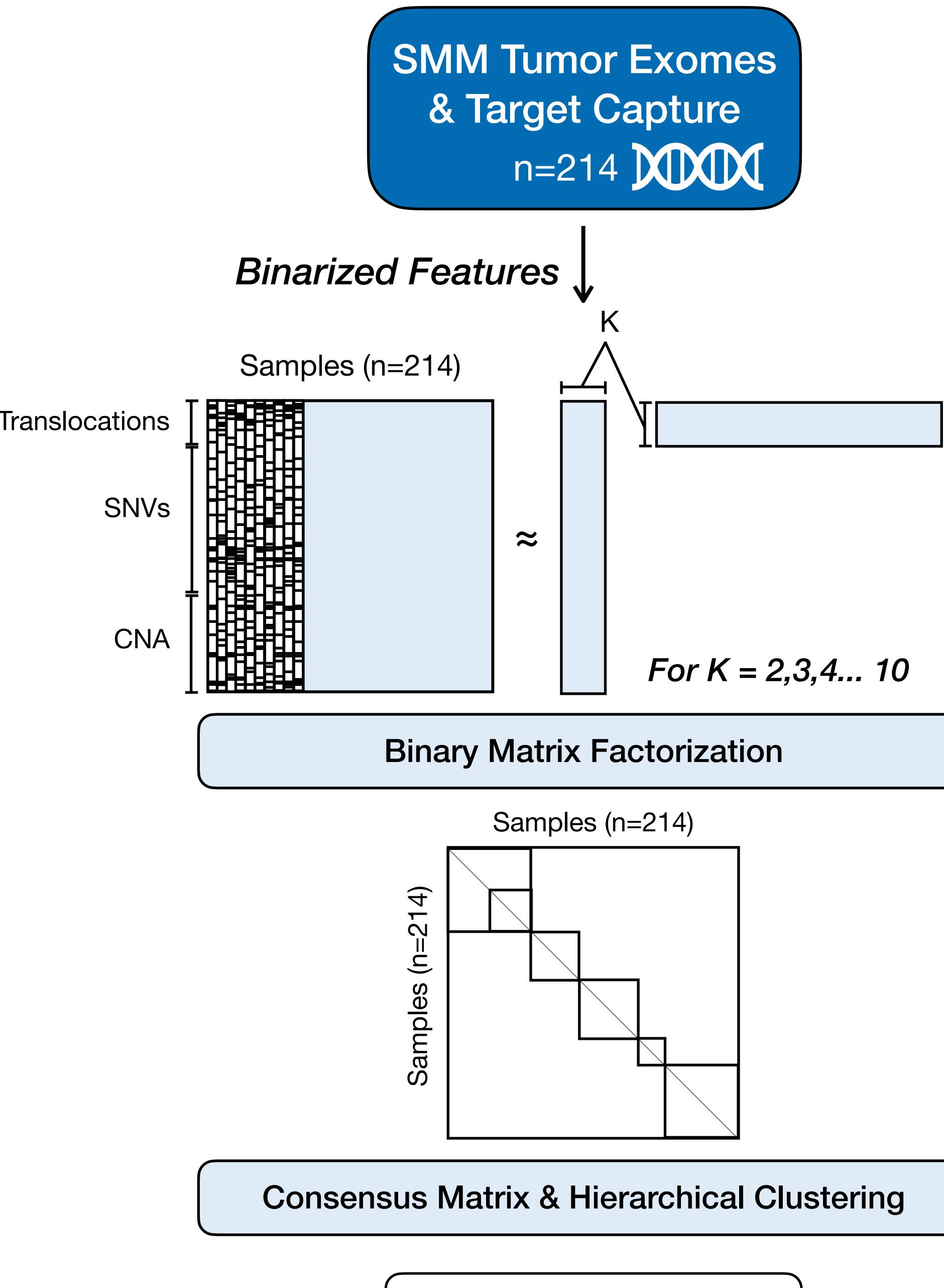
## Abstract | Genomic Subtypes of SMM

Smoldering multiple myeloma (SMM) is a precursor condition of multiple myeloma (MM) with significant heterogeneity in disease progression. Existing clinical models of progression risk do not fully capture this heterogeneity. Here we integrated 42 genetic drivers of 214 SMM patients using unsupervised binary matrix factorization (BMF) clustering and identified six distinct genetic subtypes. These subtypes were differentially associated with established MM-related RNA signatures, oncogenic and immune transcriptional profiles, and evolving clinical biomarkers. Three subtypes were associated with increased risk of progression to active MM and can be used to subdivide the high- and intermediate-risk groups within the IMWG 20-2-20 model.

## Background | Risk Modeling for SMM

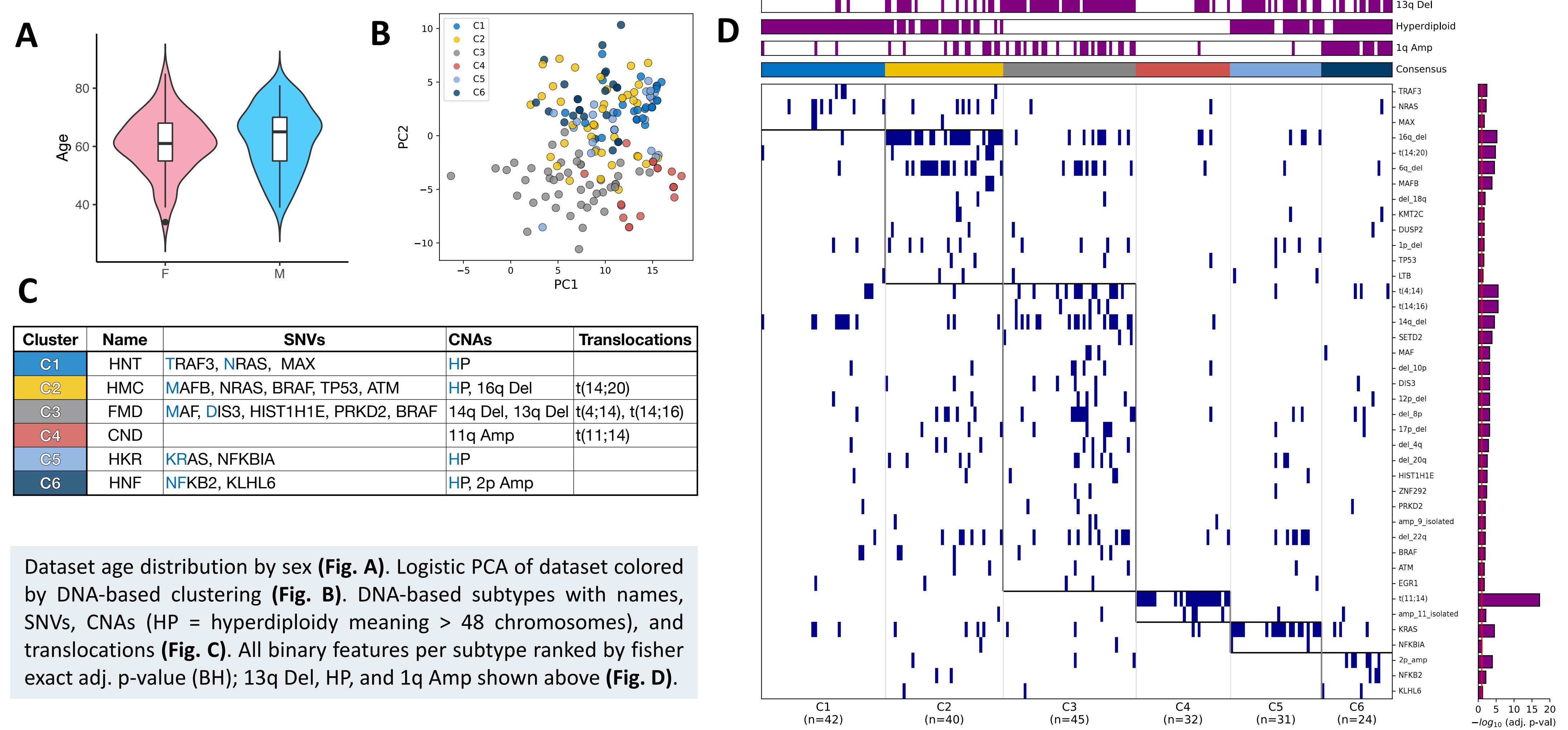
- SMM is highly heterogeneous regarding which patients will progress to active MM - SMM patients have a 10% risk of progression.
- Risk models rely solely on clinical markers and fail to fully capture risk
  - patients classified as low/intermediate risk may still progress.
- The genomic makeup of MM tumor clones has been shown to be acquired at time of SMM diagnosis.

### CAN WE DEVELOP A MORE SUITABLE RISK MODEL USING GENETIC ALTERATIONS?

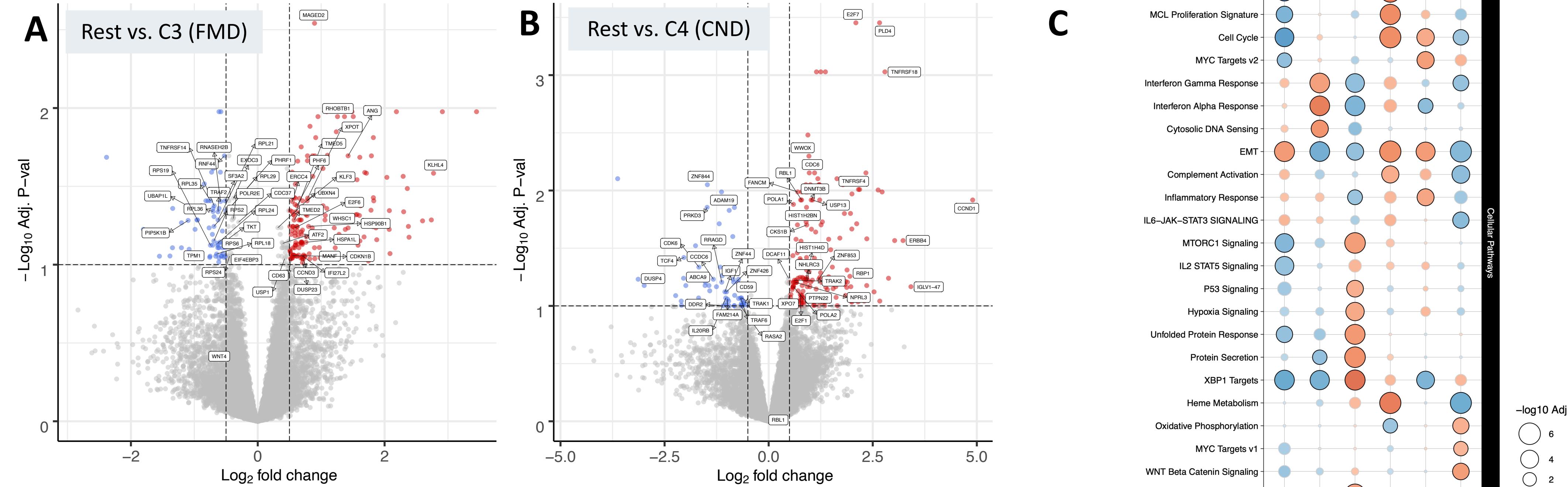


(Above) Analysis overview of 214 SMM patients.

## Clustering 214 DNA Samples | Binary Matrix Factorization

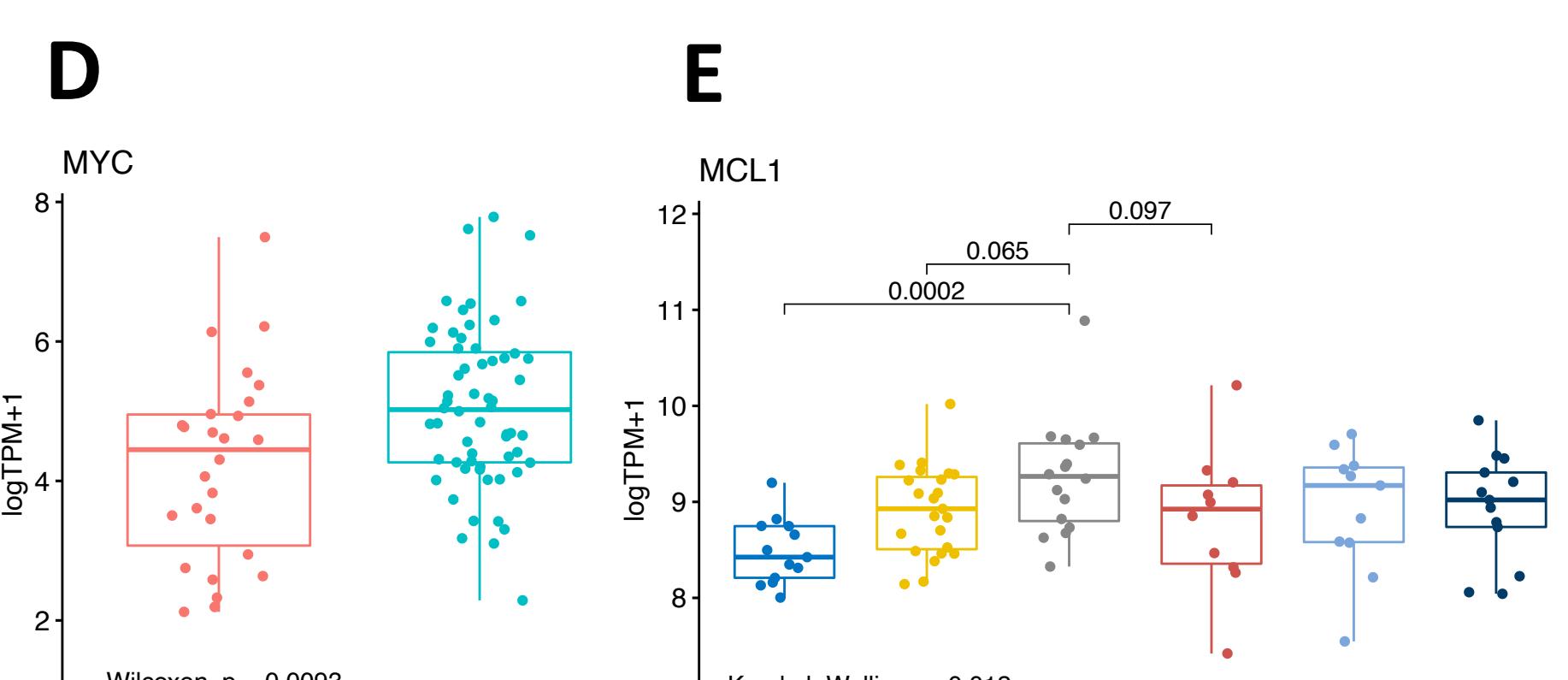


## Transcriptomes | Upregulated Genes / Pathways



Differentially expressed (limma-voom) genes in subtypes C3 (FMD) (Fig. A) and C4 (CND) (Fig. B) vs. rest. RNA-based pathways further describe subtypes. (Fig. C) C2 (HMC): NFkB, cytosolic DNA sensing, JAK-STAT, high Treg & NK-cell. C3 (FMD): protein secretion, unfolded protein response, glycolysis, hypoxia, mTOR signaling, high plasmacytoid dendritic. IFN $\alpha$  & IFN $\gamma$  were high in C2 but low in C3. C4 (CND): E2F targets, cell-cycle, heme metabolism, complement, proliferation. C5 (HKR): TNFa inflammatory response, high T-reg & NK-cell. C6 (HNF): oxidative phosphorylation, WNT-beta-catenin, TGF-beta signaling.

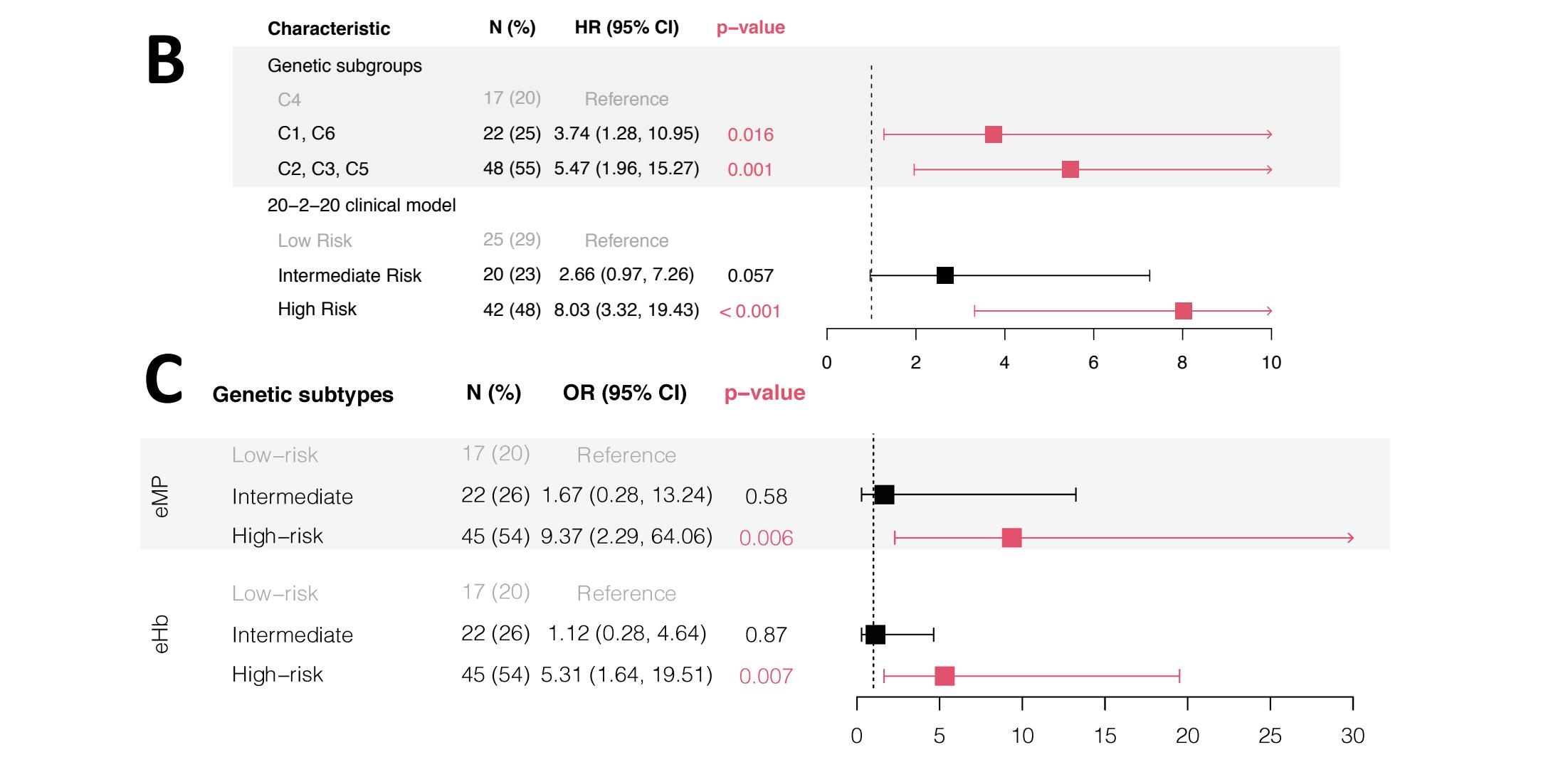
MYC is upregulated in HP subtypes (C1, C2, C5, C6) (Fig. D). MCL1 expression varies by subtype & is upregulated in C3 (FMD) (Fig. E).



The high risk RNA MMSET (MS) signature and MAF & MAFB genes are upregulated in C3 (FMD). Cyclin D (CD) signature and B-cell markers CD20 & CD79A are upregulated in C4 (CND). The low bone (LB) disease signature was upregulated in C2, C3 and C6 (previously unmapped) to specific MM alterations. Notably, these subtypes have 1q Amp (Fig. C).

## Clinical Course | Hazard Analysis & Serial Samples

57 of 87 patients (66%) progressed while 30 (34%) remained asymptomatic. Median follow-up was ~7 years. Kaplan Meier curves and Cox proportions hazards of progression based on subtype denotes high (C2, C3, C5), intermediate (C1,C6) and low (C4) risk subtypes. (Fig. A, B)



Clinical biomarkers (M-protein, hemoglobin and free light chain ratio) were taken at serial time points (6, 12, 18, 24 months & 2,4,5 years). The odds of having evolving M protein (eMP) and evolving hemoglobin (eHB) were 9.4 and 5.3 times higher in high risk subtypes at 1 year (Fig. C). High risk subtypes had significant M protein increase and hemoglobin decrease over further follow-up (Fig. D).

## Discussion | Genomic Subtypes of SMM

- Consensus binary matrix factorization identifies 6 genetic subtypes with distinct driver events and phenotypic profiles
- Based on risk of progression to active MM, we identified 3 high-risk (C2, C3, C5) that are independent predictors of progression
- C3 (FMD) tumors showed enrichment for transcriptome pathways unfolded protein response (UPR), ER stress, upregulated glycolysis, and mTOR signaling and, clinically, highest increase in M-protein at 6 & 12 months – these patients may benefit from drugs inducing cellular stress
- C4 (CND) tumors are enriched in B-cell signaling genes and had clinically lowest M protein levels and no increase in serial timepoints

This clustering approach followed by matched RNA & clinical analyses provides a framework to identify SMM patients truly at a high risk of disease progression and guide precision medicine efforts to match therapies with optimal patient groups.

## Acknowledgements

Funding: NIH (R01 CA205954), Multiple Myeloma Research Foundation (MMRF) Perleman Prevention Program Grant, Leukemia and Lymphoma Society (LLS) SCOR grant, Stand Up to Cancer (SU2C) Dream Team grant, Adelson Medical Research Foundation (AMRF), Cancer Research UK (CRUK) Early Detection Program grant. Thank you to the patients & their families for their contributions to this study.