EDITORIAL

Relapse as a return, not a reinvention — genomic stability and pre-existing resistance in mantle cell lymphoma

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Received: February 12, 2026.
Accepted: March 30, 2026.
Early view: April 9, 2026.

https://doi.org/10.3324/haematol.2025.289129

Mantle cell lymphoma (MCL) remains a paradigmatic example of a B-cell malignancy that responds well to initial therapy yet ultimately relapses in nearly all patients. Despite deep, minimal residual disease-negative remissions following frontline chemoimmunotherapy, relapse is nearly inevitable, with progressively shorter subsequent responses. A long-standing question has been whether relapse arises through the *acquisition* of new genomic events under therapeutic pressure or through the *re-emergence* of pre-existing resistant clones present at diagnosis.

In this issue of *Haematologica*, Joffe *et al*. provide important further data towards answering that question.[1] Their comprehensive genomic profiling of 214 MCL specimens, including 25 paired diagnostic and relapse samples, revealed striking genomic stability across disease progression. The findings in this study suggest that relapse is not driven by *de novo* mutational evolution but instead reflects the persistence and later expansion of resistant subclones that survive frontline therapy.

A stable genome through remission and relapse

Using high-depth targeted sequencing, the investigators compared treatment-naïve and post-treatment samples separated by remission periods exceeding 3 years. The mutational and copy number landscapes were remarkably conserved between diagnosis and relapse. While occasional copy number alterations such as deletions of *ATM*, *TP53*, or *CDKN2A* and amplifications of *CARD11* were observed, these were sporadic and lacked recurrent patterns, arguing against an ongoing genomic evolutionary process.

These observations closely mirror the longitudinal analysis by Karalova *et al*.,[2] who performed whole-exome sequencing in 25 paired MCL cases and similarly reported highly stable mutational profiles. Only isolated copy number alterations appeared at relapse, and no shared evolutionary trajectories were identified. Taken together, both studies strongly support a model in which relapse reflects selection of pre-existing resistant clones rather than evolution of new ones.

TP53: an early and defining determinant of poor prognosis

Among all genomic alterations, *TP53* disruption stands out as the dominant predictor of adverse outcome. In the paper by Joffe *et al*., *TP53* mutations, more than deletions alone, were associated with markedly inferior progression-free survival, even in patients achieving complete remissions or undergoing autologous stem-cell transplantation.[1] These results are consistent with the transcriptomic and genomic clustering reported by Yi *et al*.,[3] who identified a "*TP53*-deregulated" subgroup of MCL characterized by blastoid morphology, genomic instability, and dismal prognosis.

Notably, *TP53* mutations were detectable at diagnosis and remained stable at relapse, confirming that this alteration is an early and durable event rather than an acquired mechanism of resistance. The high response rates but short durability observed among *TP53*-mutant cases underscore the need for non-chemotherapeutic or cellular strategies in this molecular subset.

Integration with established genomic frameworks

The hierarchical clustering performed by Joffe *et al*. revealed three principal MCL genomic subgroups:[1] (i) double-hit *ATM* alterations (mutation + deletion); (ii) double-hit *TP53* alterations; and (iii) *ATM*-mutant, *TP53*-wild-type tumors. These align closely with the molecular architecture described by Yi *et al*.,[3] reaffirming the biological significance of these categories.

Earlier, Nadeu *et al*. delineated MCL into distinct epigenomic and genetic lineages, classical/"conventional" SOX11^{+} and indolent leukemic SOX11^{-} forms arising from different cells of origin and exhibiting variable chromosomal instability.[4] The present findings extend this framework by demonstrating that, despite the baseline heterogeneity, the fun-

damental genomic configuration of each subtype remains largely static through relapse. The heterogeneity defining MCL therefore seems to originate early and not through progressive genomic divergence during therapy.

Chromosomal instability: subtle but relevant

Although major mutational shifts were uncommon, relapsed samples displayed a modest enrichment for deletions in *CDKN2A* and *ATM*. Similar patterns were reported by both Karalova *et al.*[2] and Nadeu *et al.*,[4] suggesting that chromosomal instability may facilitate disease persistence or relapse. Whether these copy number alterations represent stochastic events, therapy-induced stress, or secondary drivers of clonal survival remains uncertain. High-resolution single-cell and spatial genomic studies will be essential to clarify whether such instability fosters microclonal selection or merely reflects the genomic fragility inherent to MCL.

Clinical and biological implications

If the genomic blueprint of relapse already exists at diagnosis, this should influence the focus of clinical management in MCL. Clinical trials should include: (i) early risk stratification, because comprehensive genomic assessment at baseline (particularly for *TP53* and *CDKN2A* lesions) should guide treatment intensity and consideration of novel or cellular therapies in first line; (ii) minimal residual disease monitoring although, given the paucity of new driver mutations, sequencing at relapse offers limited new information. Instead, ultra-sensitive minimal residual disease and circulating tumor DNA assays may more effectively track persistence of resistant subclones; and (iii) targeting functional evolution, given that, as Nadeu *et al.*[4] and Yi *et al.*[3] emphasized, transcriptional and epigenetic plasticity likely underlies adaptive resistance in the absence of genetic change. Integrative multi-omic approaches including methylation, chromatin, and single-cell RNA profiling will be key to uncovering these non-genetic survival mechanisms.

Conclusions

The work by Joffe *et al.* consolidates a model of MCL biology demonstrating that this lymphoma is genetically heterogeneous yet largely stable over time, and its clinical trajectory is determined at presentation by the genomic features of the dominant clone. Relapse potentially represents not the emergence of a novel genome, but the resurgence of a pre-existing one. In later relapses, a different scenario, including a divergent evolution, could occur, in which a new clone might drive progression.

For clinicians, this means that the battle against relapse must be waged at diagnosis by identifying and eradicating resistant subclones before they reappear. For researchers, it highlights the need to explore the epigenetic and microenvironmental landscapes that permit these clones to endure. Understanding and overcoming MCL relapse will define the next era of precision therapy for this disease.

Disclosures

No conflicts of interest to disclose.

References

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