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Liquid Biopsy–Based Three-Dimensional Telomere Profiling Distinguishes AL Amyloidosis from Multiple Myeloma at Diagnosis

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INTRODUCTION

Light-chain (AL) amyloidosis and multiple myeloma (MM) are plasma cell dyscrasias characterized by atypical clonal expansion of plasma cells in the bone marrow. AL amyloidosis is defined by tissue deposition of misfolded immunoglobulin light chains, called fibrils, leading to progressive multiorgan dysfunction and poor prognosis. While MM diagnostics increasingly incorporate liquid biopsy approaches, AL diagnosis still relies on detecting a monoclonal immunoglobulin or an abnormal serum free light chain (FLC) ratio, followed by an invasive tissue biopsy to confirm amyloid deposition (**Kukreti V. et al., 2026**). To date, no studies have reported the use of peripheral blood–based liquid biopsy for the diagnosis or risk stratification of AL amyloidosis.

AIM

Spatial three-dimensional (3D) telomere profiling at the single-cell level using TeloView® software has been shown to be a strong prognostic tool across the myeloma disease spectrum, from monoclonal gammopathy of undetermined significance (MGUS) to smoldering MM (SMM) to symptomatic MM. Telomere profiles have been used to identify SMM patients at high risk of progression from precursor states and detect emerging resistance to first-line therapy in newly diagnosed MM (NDMM) (**Kumar S. et al., 2024**). We aim to explore whether single-cell 3D telomere profiling of circulating plasma cells (CTCs) in peripheral blood can differentiate AL amyloidosis from MM.

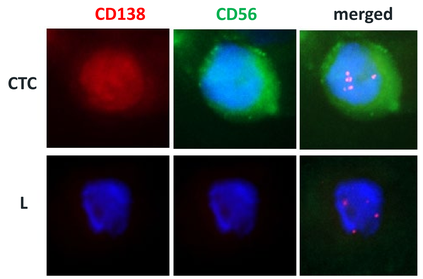
METHOD

- Previously established workflow for isolation, immunophenotyping, and 3D telomere profiling of MM CTCs from peripheral blood (**Shifrin Y. et al., 2026**) was used to isolate CTCs from the peripheral blood samples of a mixed MM/AL cohort of 22 patients (**NCT05530096**), comprised of 5 patients with AL amyloidosis, 2 patient with a strong clinical suspicion for concurrent AL amyloidosis*, and 15 MM cases
- Isolated CTCs were immunophenotyped using CD56/CD138 antibodies.
- Single-cell 3D telomere profiles of the CTCs were evaluated by TeloView®.
- Hierarchical cluster analysis was performed based on spatial telomere architecture parameters.

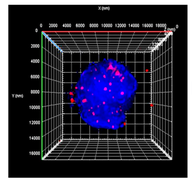
* Patients were too sick to undergo a confirmatory biopsy

RESULTS

Malignant phenotype of isolated CTCs of the mixed AL/MM cohort was verified by immunophenotyping using the **CD56** and **CD138** antibodies



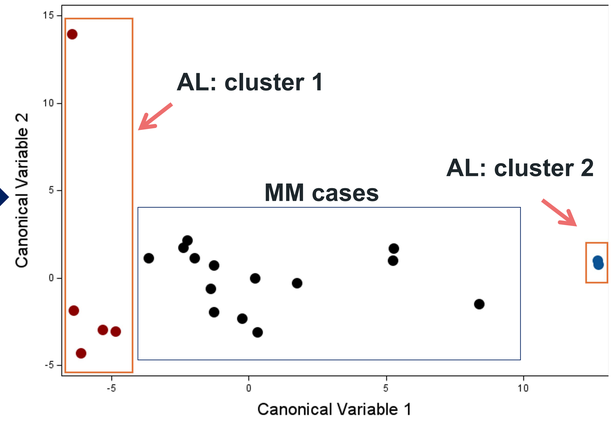
Representative two-dimensional images of CTC and a normal lymphocyte (L) labeled with CD138 and CD56 antibodies; telomeres are labeled with PNA probe; cell nuclei are counterstained with DAPI



Spatial distribution of telomeres (PNA) in the nuclear space (DAPI)

Diagram showing six parameters measured by TeloView

Key parameters of the 3D telomere organization of CTCs were measured by TeloView®. Hierarchical cluster analysis of the 3D telomere architecture stratified patients into distinct clusters, with confirmed/suspected AL amyloidosis cases (n=7) forming two discrete groups clearly separated from MM profiles. The two canonical variables(CAN1 and CAN2) together explained about 95% of the between-cluster variance



Canonical variables	
Can1	**Can2**
Nuclear volume	Overall signal intensity
Distance of signals from the nucleus center	Higher signal count; Number of aggregates

CONCLUSIONS

These findings represent the first indication that liquid biopsy combined with spatial telomere profiling may enable non-invasive identification of AL amyloidosis at diagnosis, potentially reducing reliance on invasive tissue biopsy and opening a new avenue for peripheral blood–based disease classification.

REFERENCES

Kukreti V et al. Guidelines on Diagnosis of Light Chain Amyloidosis. *American Society of Hematology (ASH) 2026 Blood Adv*. 2026 Jan 27:bloodadvances.

Kumar S et al. Three-dimensional telomere profiling predicts risk of progression in smoldering multiple myeloma. *Am J Hematol*. 2024;99(8):1532-1539.

Shifrin Y et al. Isolation and profiling of single circulating tumor cells in myeloma: a new workflow for liquid biopsies. *Biotechniques*. 2026 Jan-Dec;78(1-12):123-136.

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