NDMM patients with high levels of circulating tumor cells are distinguished by increased bone marrow plasma cell proliferation

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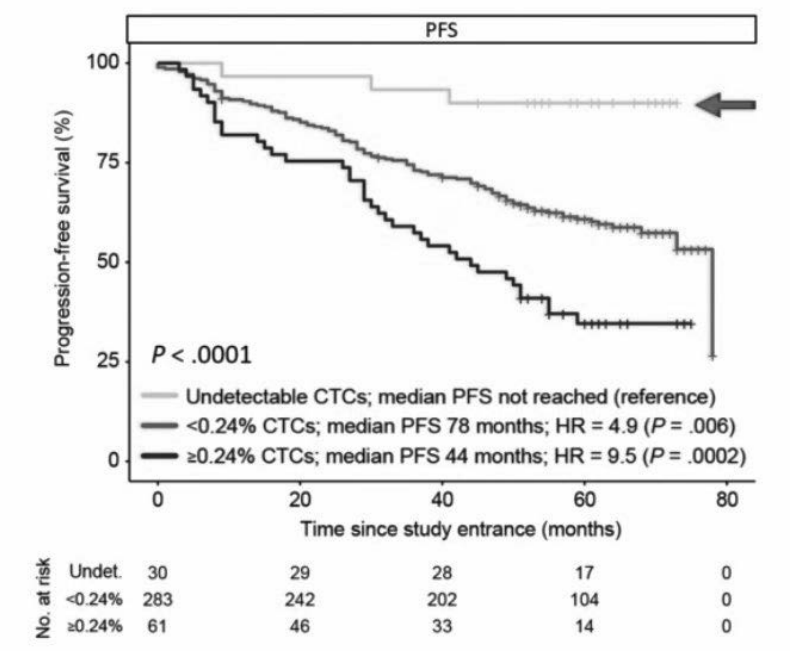
Disclosures

A.C. Fokkema has no relationships to disclose

High levels of circulating tumor cells are associated with unfavourable disease outcome



J.J. Garcés et al. ***EHA*** *(2021)*

W.I. Gonsalves et al. ***Leukemia*** *(2014)*

M. Granell et al. ***Haematologica*** *(2017)*

R. Chakraborty et al. ***Haematologica*** *(2017)*

S. Huhn et al. ***Bone Marrow Transplant.*** *(2017)*

L. Sanoja-Flores et al. ***Blood Cancer J.*** *(2018)*

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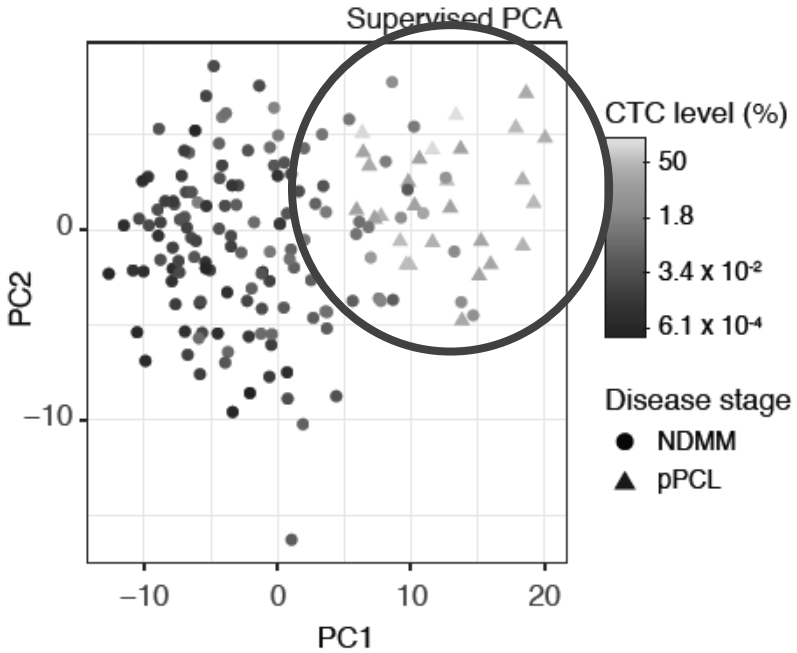
MM patients with high levels of CTCs have a gene signature comparable to PCL patients

BM samples of primary PCL and a subset of NDMM patients cluster based on their **transcriptomic profiles.**

→ These patients have relatively **high levels of circulating tumor cells (CTCs)**

→ PCL-like Myeloma



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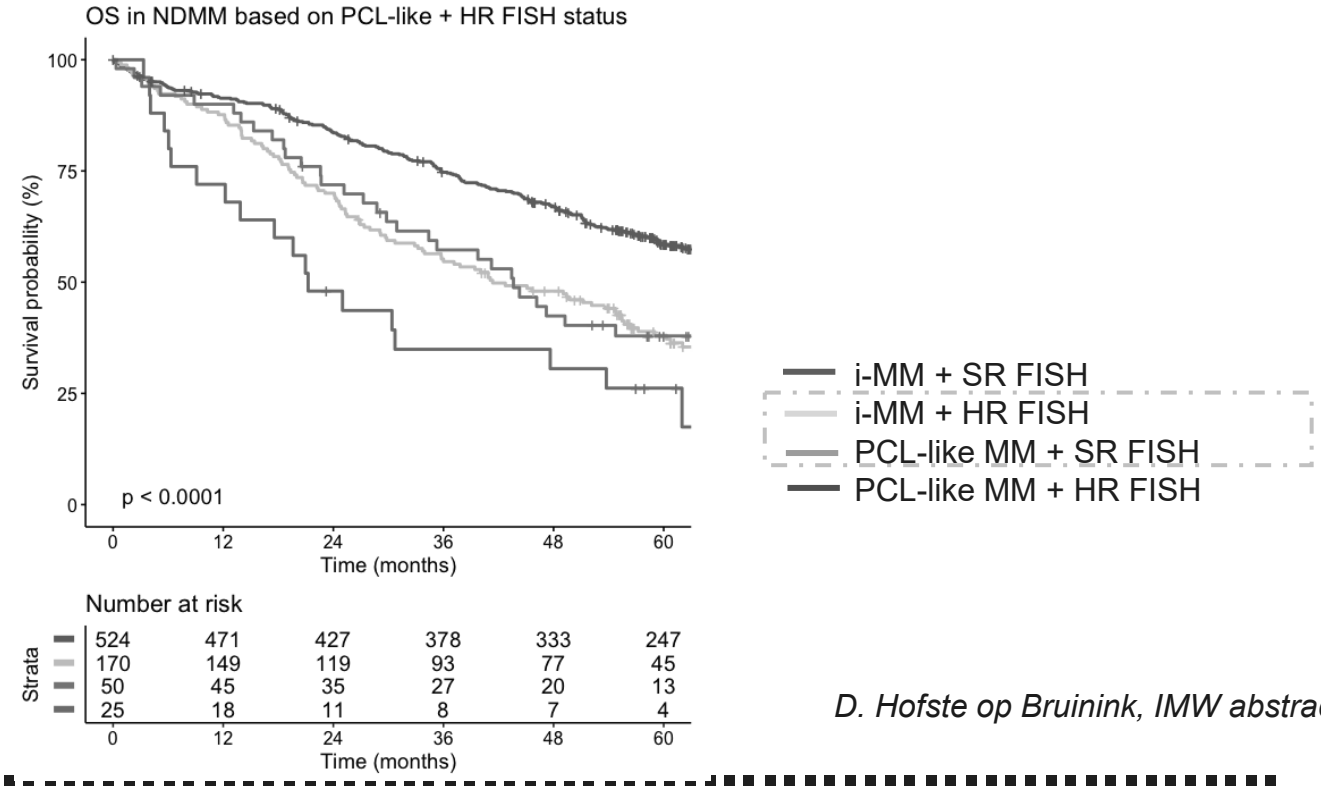
NDMM patients with a PCL-like gene signature have a worse OS



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Hypothesis

High levels of circulating tumor cells in MM patients are a reflection of agressive disease biology.

Unfavourable disease course: due to a unique **circulating clone** or due to **altered bone marrow** environment?

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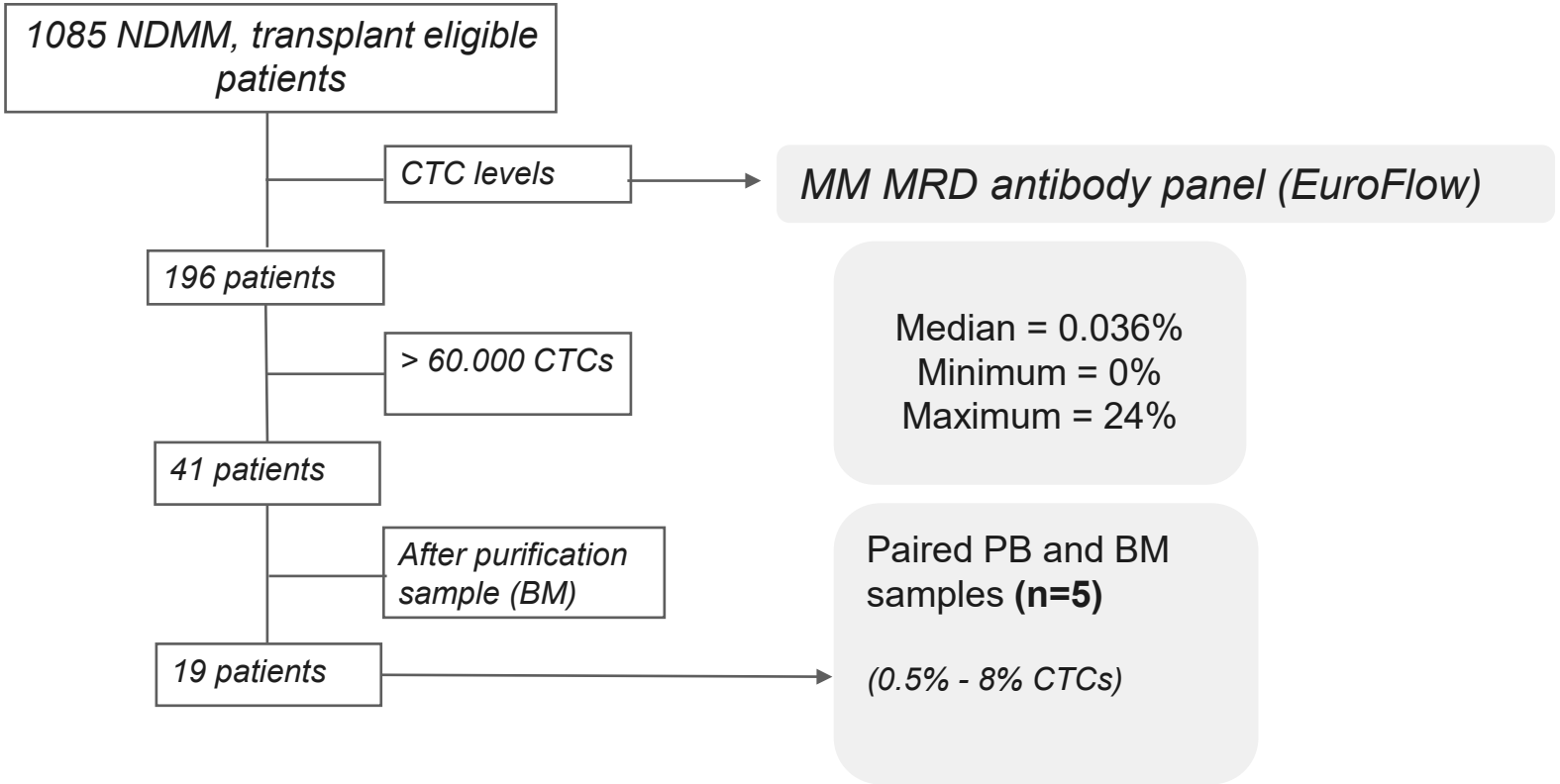
1. Can we identify a unique circulating clone in PB of patients with high levels of CTCs?

Study design: paired samples from BM and PB



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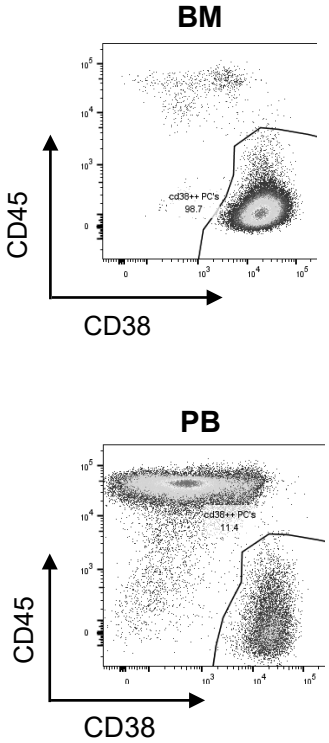
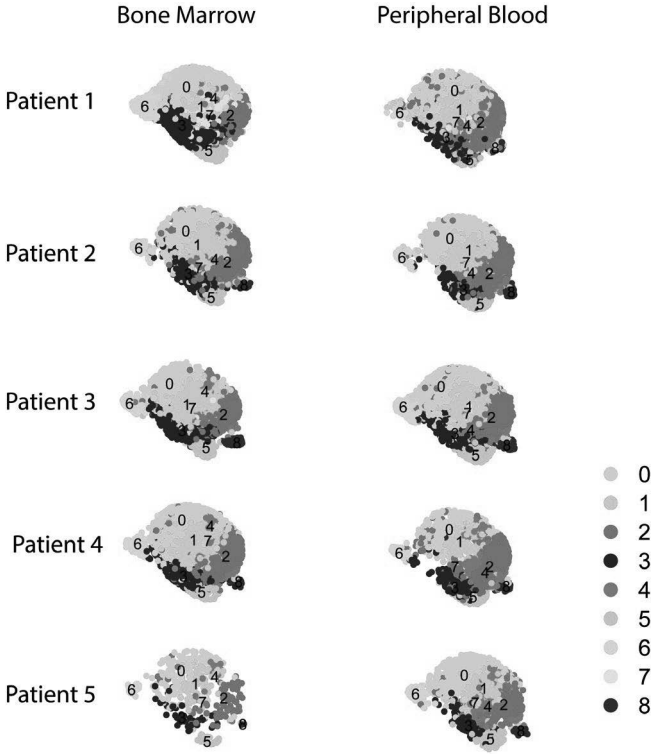
Defining MM cell clusters by single cell sequencing

Cryopreserved matched BM and PB samples (n=5)

Sort plasma cells



Compare BM and PB by scRNA-seq



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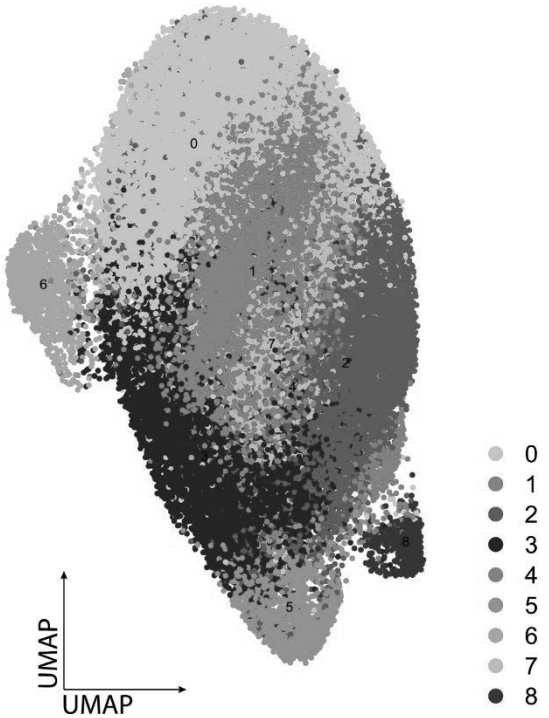
scRNAseq reveals distinct subpopulations



45,953 plasma cells from 5 patients
paired BM and PB samples.

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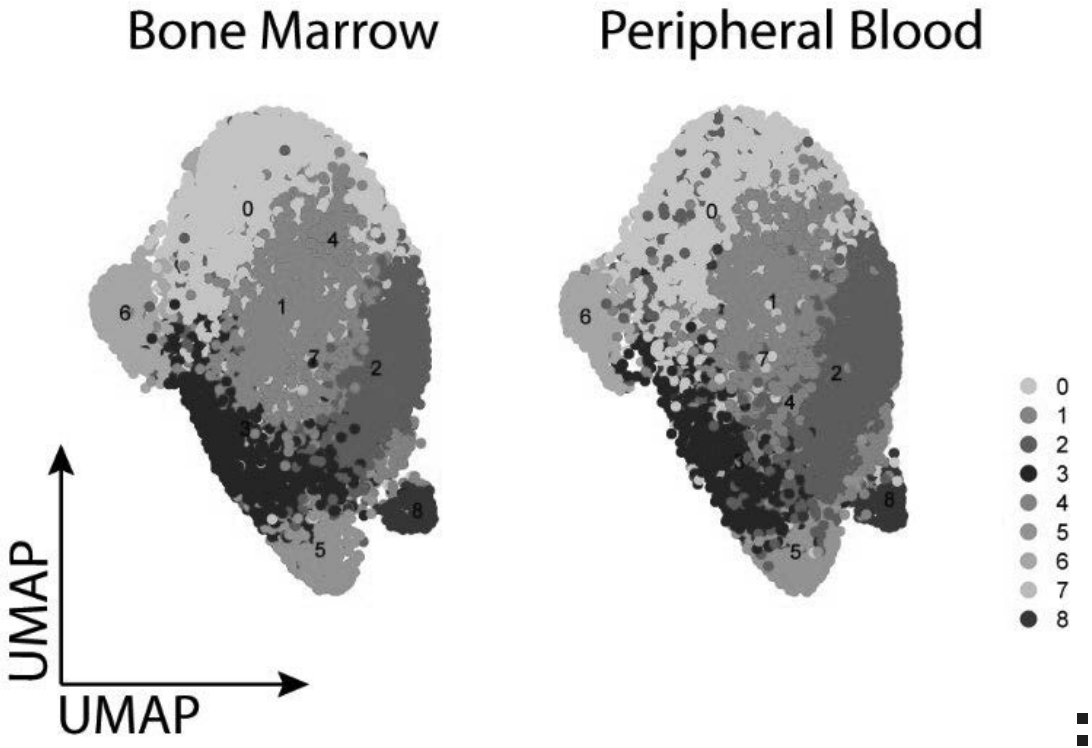
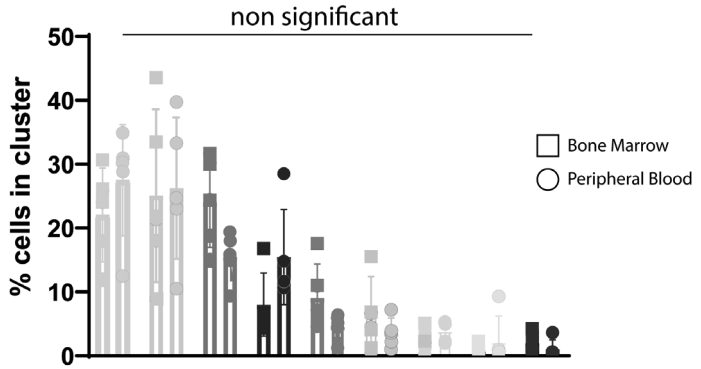
Plasma cells from BM and PB contain similar clusters and gene expression





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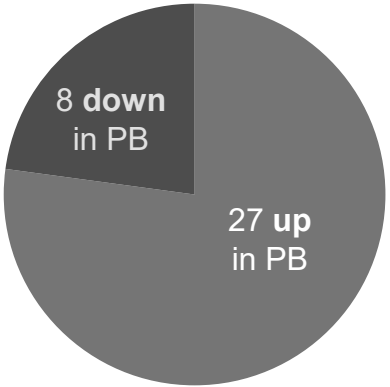
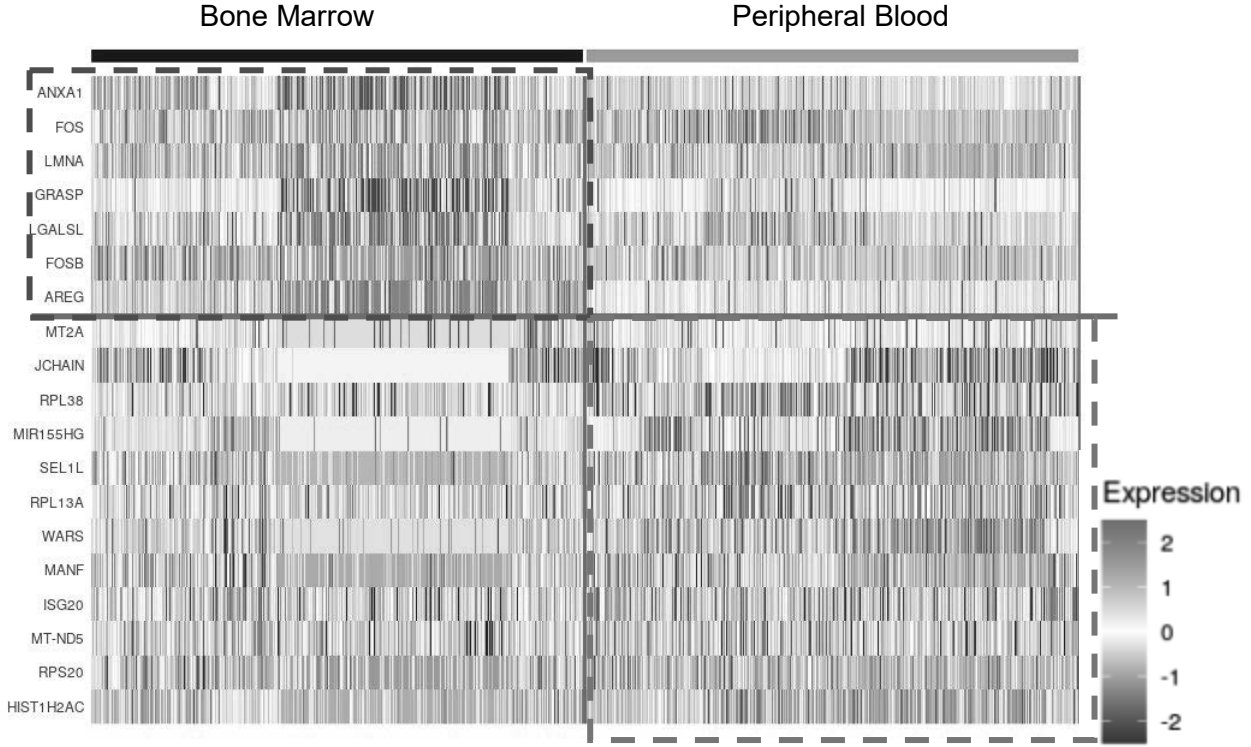
Plasma cells from BM and PB display similar gene expression



***35** differential genes*



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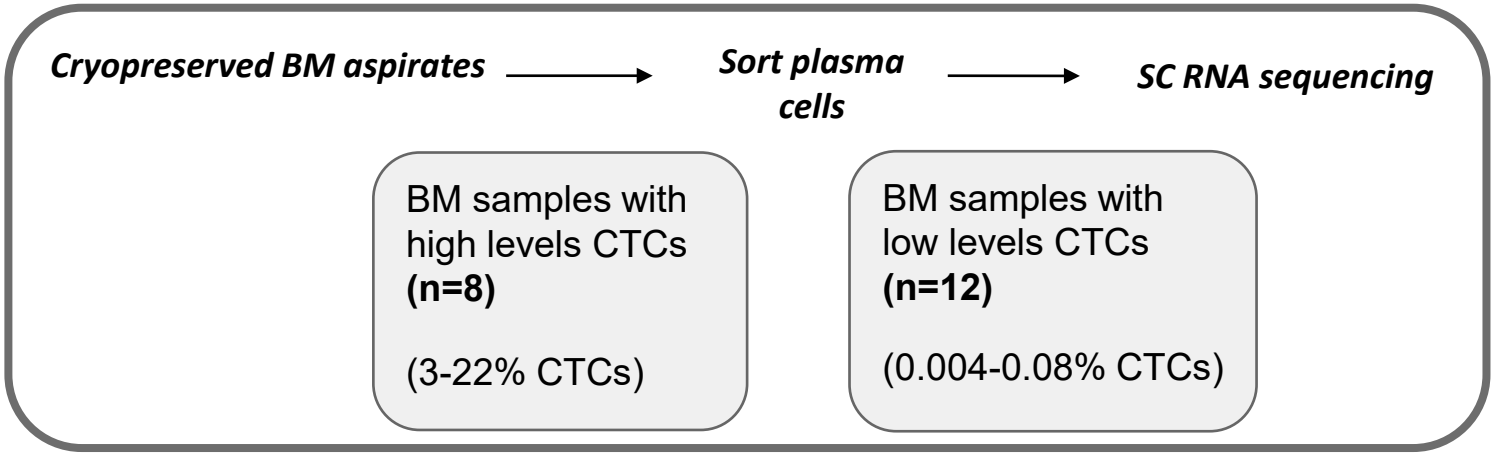
Conclusion

Circulating tumor cells and bone marrow plasma cells display similar transcriptional states.

No evidence for a unique **circulating clone** in more aggresive disease.

2. Can we identify unique characteristics of BM plasma cells in patients with high versus low levels of CTCs?



~ Common Myeloma mutations are evenly divided ~

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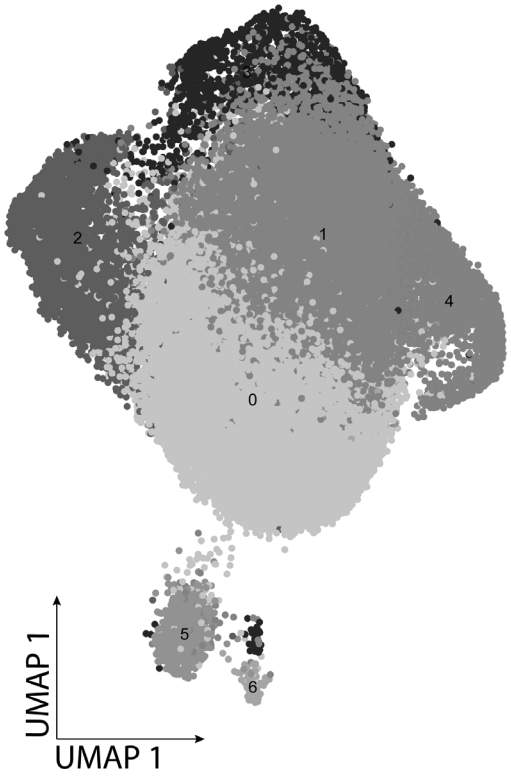
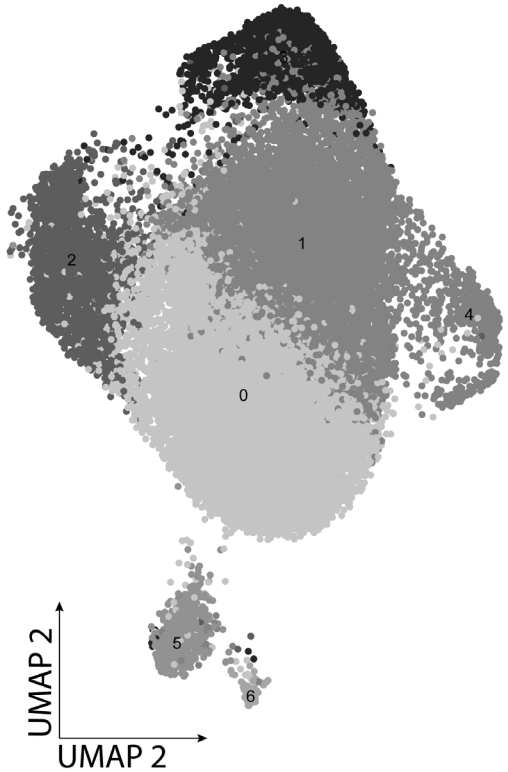
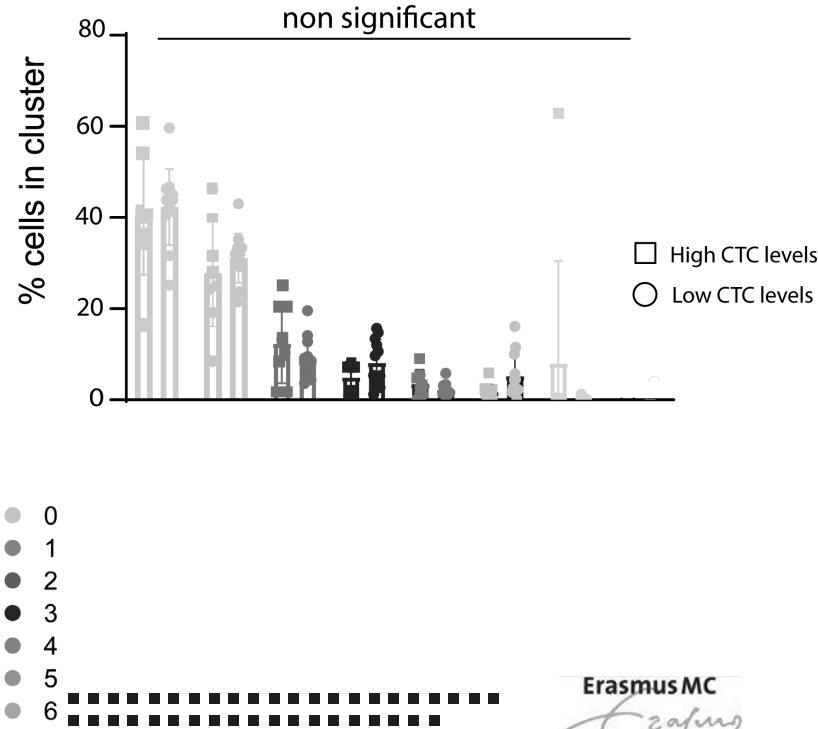
Patients with different levels of CTCs have similar clusters

High levels of CTCs



Low levels of CTCs





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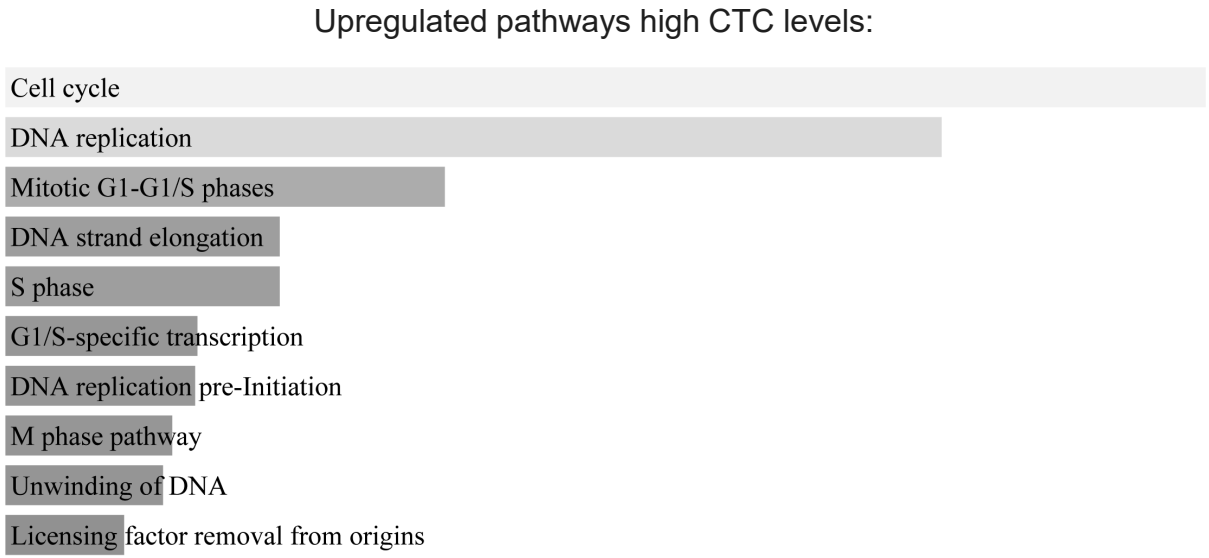
Patients with high levels of CTCs upregulate genes related to cell cycle and proliferation



Chen EY et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics. 2013

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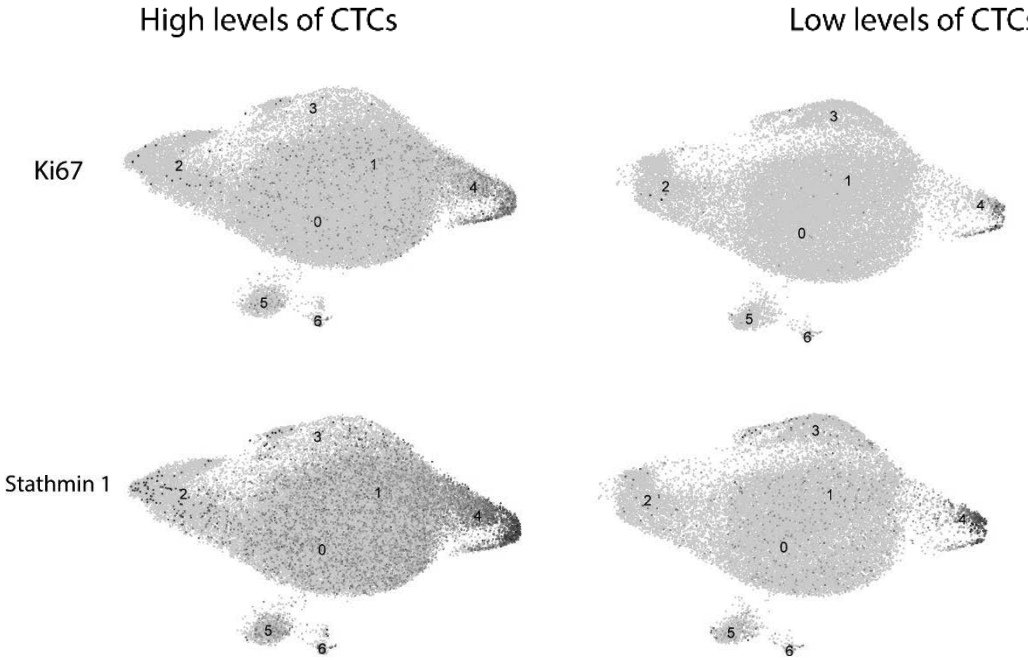
Ki67 and Stathmin 1 are present in all clusters of patients with high CTC levels



Ki-67 is a nuclear protein associated with cell proliferation

Stathmin 1 plays an important role in cell progression, clonogenicity, differentiation and survival.

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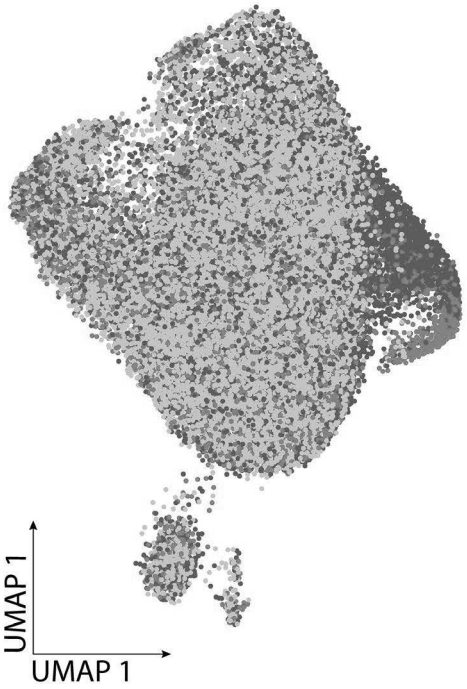
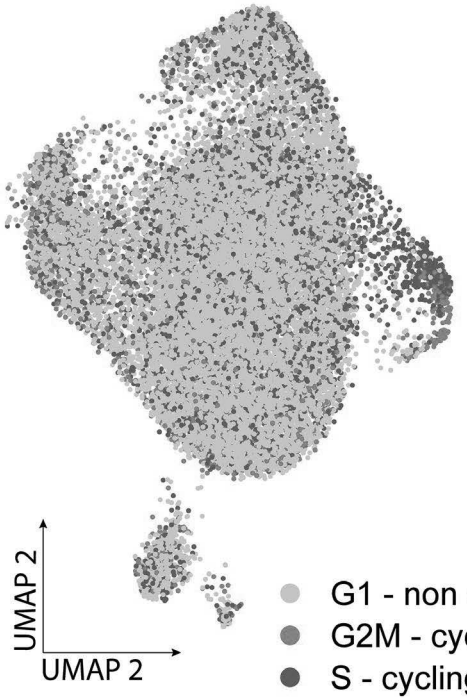
The number of cycling cells is significantly increased in patients with a high levels of CTCs

High levels of CTCs

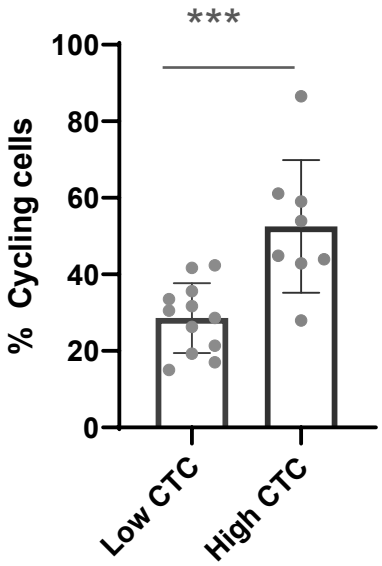


Low levels of CTCs



G1 - non cycling
G2M - cycling
S - cycling

M and S phase markers. Cells



Cell-Cycle Scoring and Regression, R package: Seurat

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Conclusions

- No transcriptionally unique circulating clone in patients with high CTC levels.
- Proliferation of BM PCs is increased in patients with high levels of CTCs.

Increased bone marrow **plasma cell proliferation** may be one of the mechanisms driving CTC levels and disease course

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Paola Pisterzi

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More single cell data from the Cupedo group?

www.bmbrowser.org

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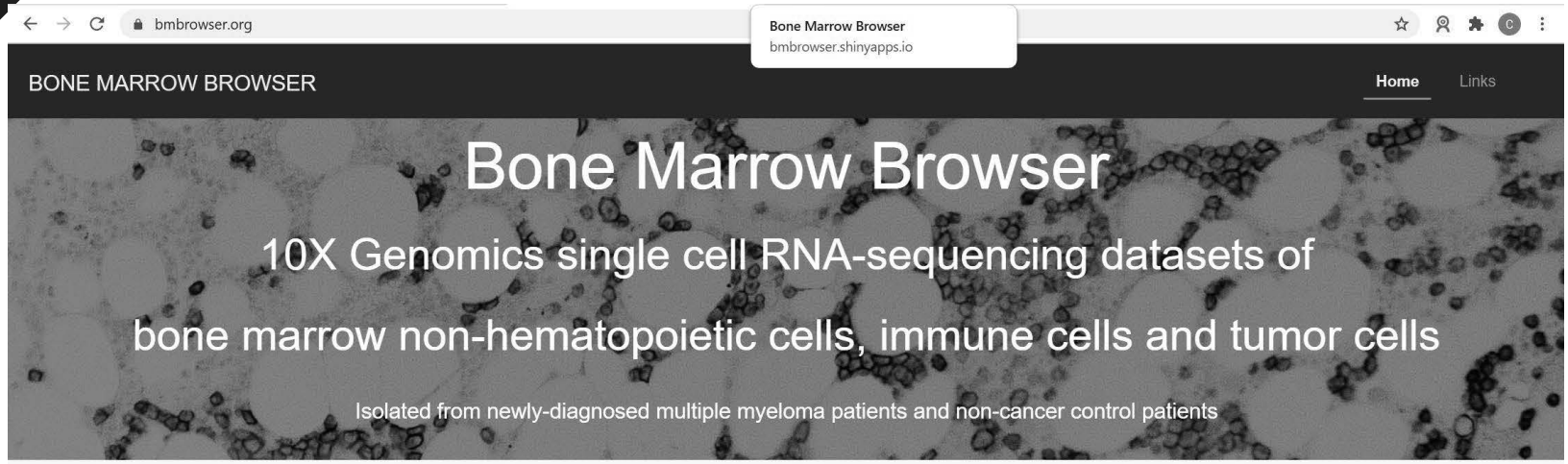
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Links
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10X Genomics single cell RNA-sequencing datasets of
bone marrow non-hematopoietic cells, immune cells and tumor cells
Isolated from newly-diagnosed multiple myeloma patients and non-cancer control patients
For full description of datasets and methods please see Links page and: De Jong et al., Nat Immunol. 2021 Jun;22(6):769-780
Datasets generated by Myeloma Research Rotterdam, part of the ErasmusMC Cancer Institute
Click on a subset below to analyze gene expression (opens in a new tab)
Non-hematopoietic cells
CD38-positive immune cells
CD38-negative immune cells
Multiple Myeloma cells
Comments and feedback are appreciated: bmbrowser@erasmusmc.nl
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bmbrowser.shinyapps.io/Myeloma/

Bone Marrow Browser | EXPLORER | HELP

DATA VISUALIZATION | EXPRESSION BY GROUP

Choose Sample:

Myeloma Cells

Choose Projection:

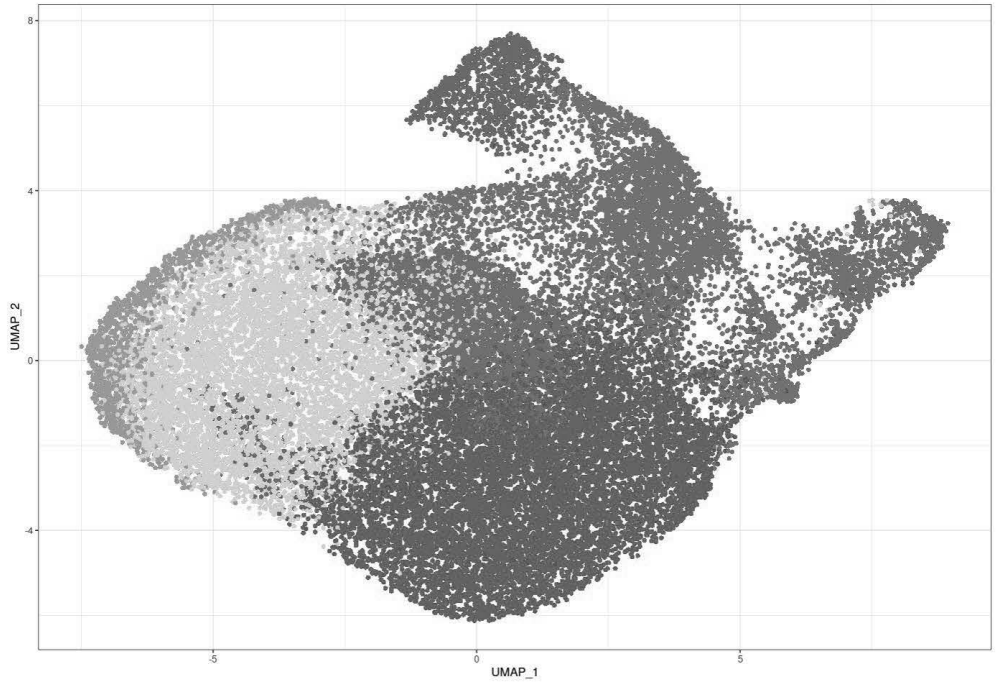
UMAP [2D]

Color By:

clusternames

Search Gene:

Choose Cells:



Hint: Mouse over points to see the detailed annotation. Drag on plots to select cells. Set plot aesthetics (legend etc.) using cog button on topright.

de Jong et al. The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape.
Nat Immunol. 2021 Jun;22(6):769-780. doi: 10.1038/s41590-021-00931-3. Epub 2021 May 20. PMID: 34017122.