

DECIPHERING THE LANDSCAPE OF CELL STATES IN GLIOBLASTOMA

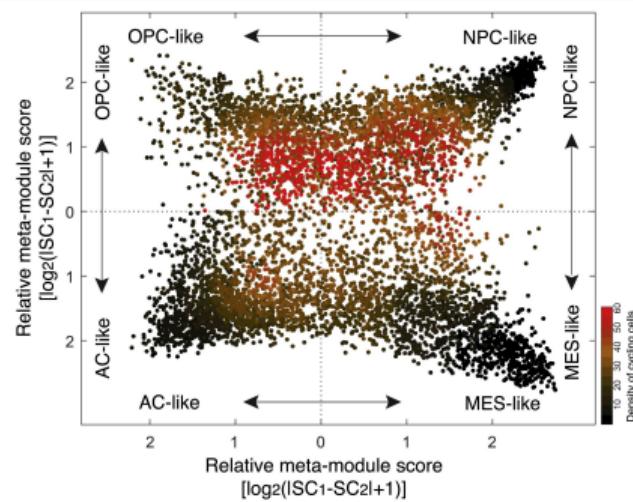
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September 7, 2023

IISc Bangalore

INTRODUCTION

MOLECULAR SUBTYPES OF GBM



(a) Cell states by Neftel et al., 2019

Figure 1: Cellular states defined for Glioblastoma

MOLECULAR SUBTYPES OF GBM

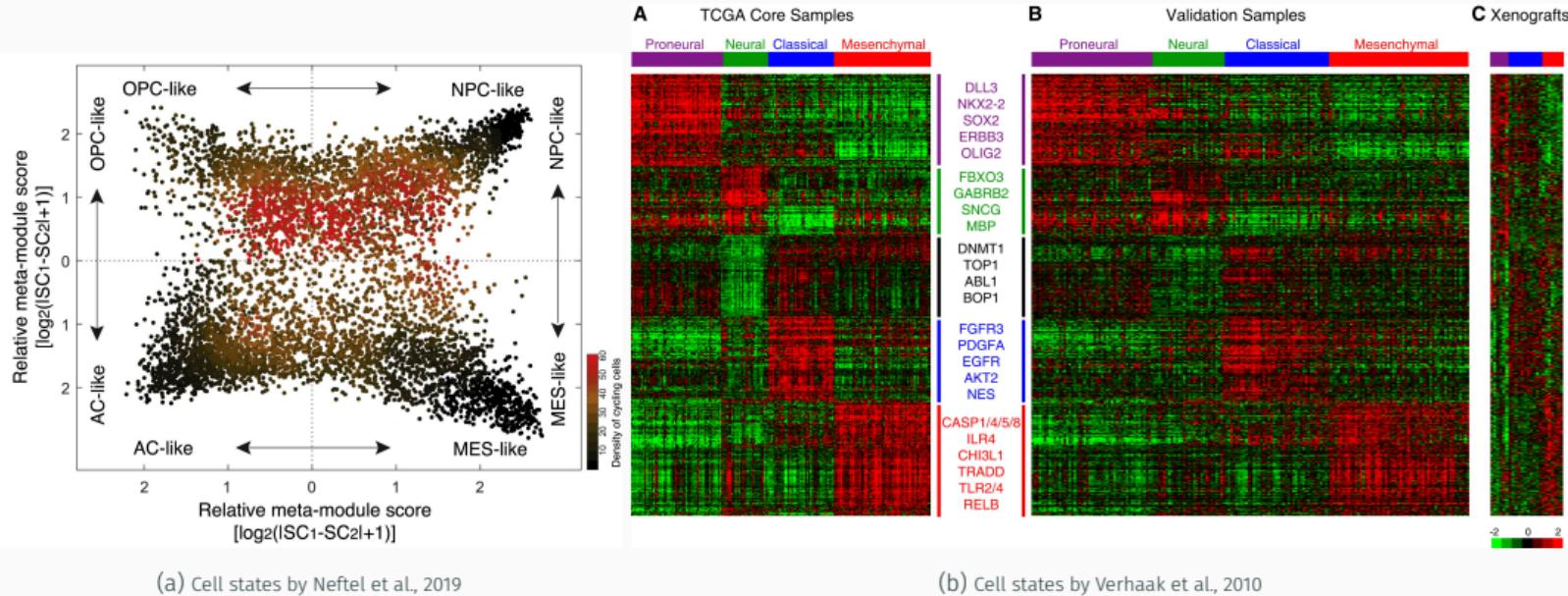


Figure 1: Cellular states defined for Glioblastoma

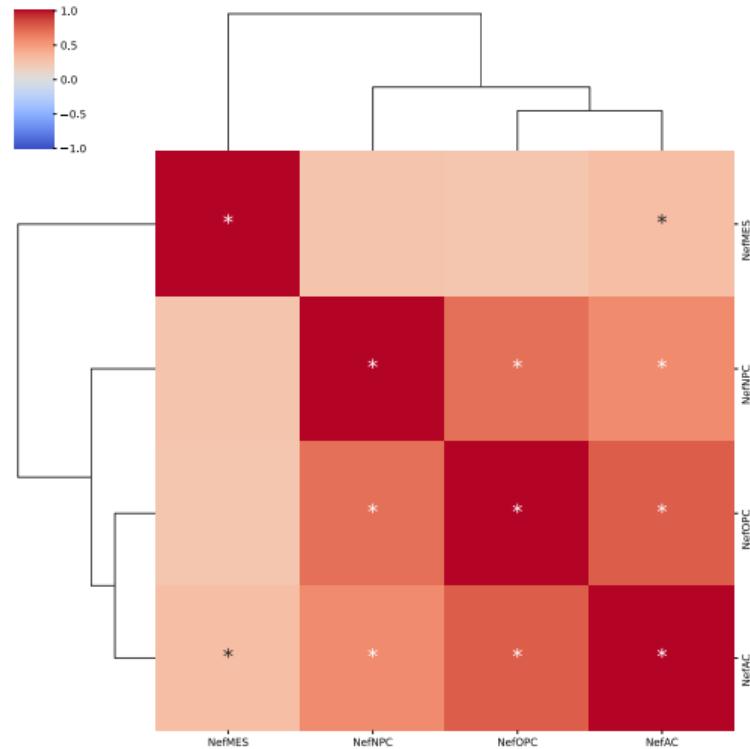
ARE THESE CELL STATES DISTINCT?

DATASETS

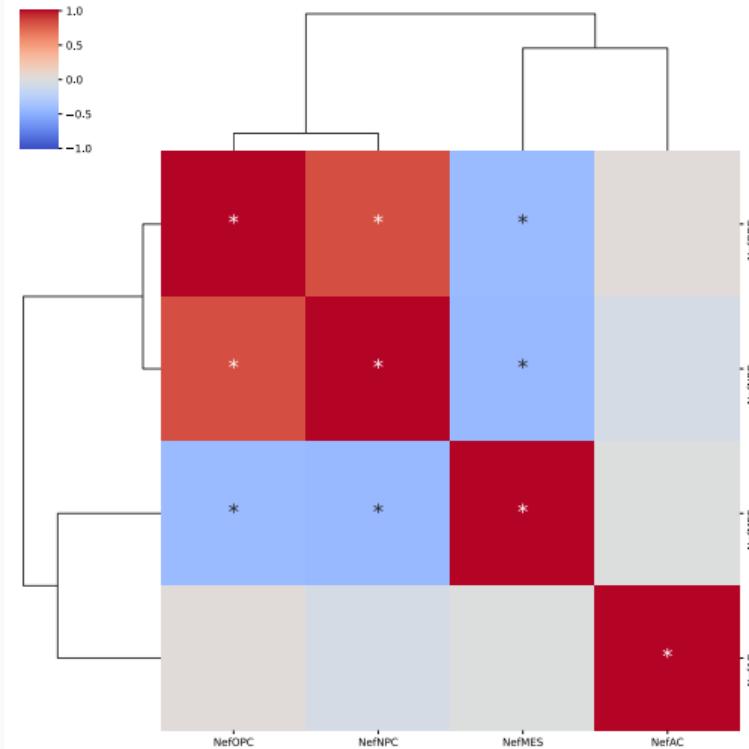
| Dataset | CellLine/Tumour | Bulk/SingleCell | Source |
|-----------|-----------------|-----------------|----------------------|
| CCLE | CellLine | Bulk | Ghandi et al., 2019 |
| TCGA | Tumour | Bulk | Brennan et al., 2013 |
| GSE131928 | Tumour | SingleCell | Neftel et al., 2019 |
| GSE168004 | CellLine | SingleCell | Hara et al., 2021 |

PRELIMINARY RESULTS

GENE-SET ENRICHMENT - NEFTEL ET AL



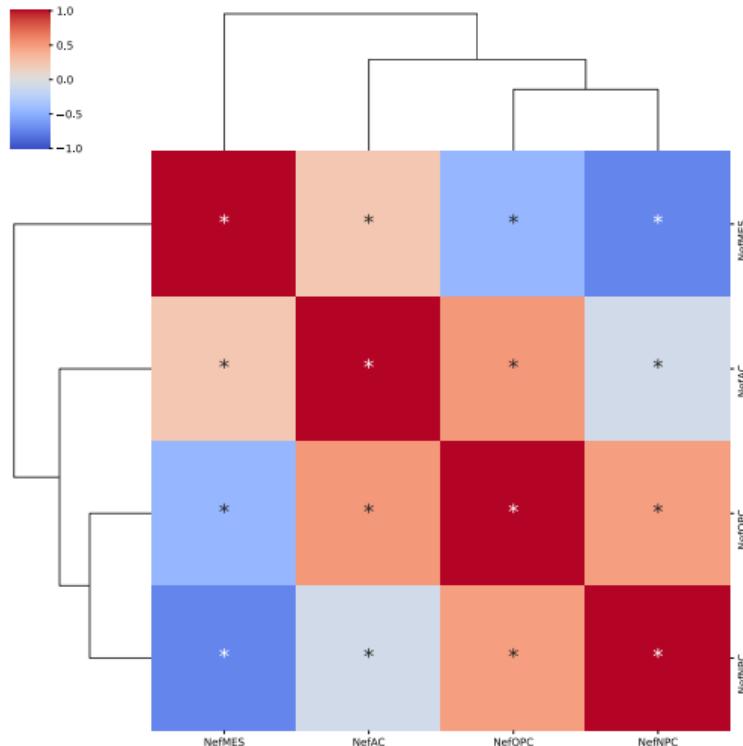
(a) CCLE (Bulk-CellLine)



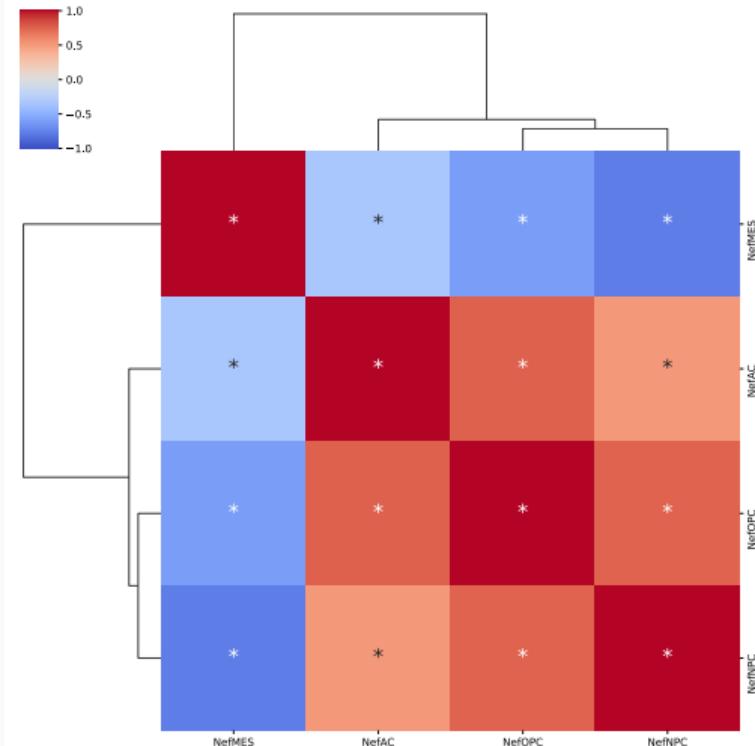
(b) TCGA (Bulk-Tumour)

Figure 2: Correlation of ssGSEA scores - Neftel

GENE-SET ENRICHMENT - NEFTEL ET AL

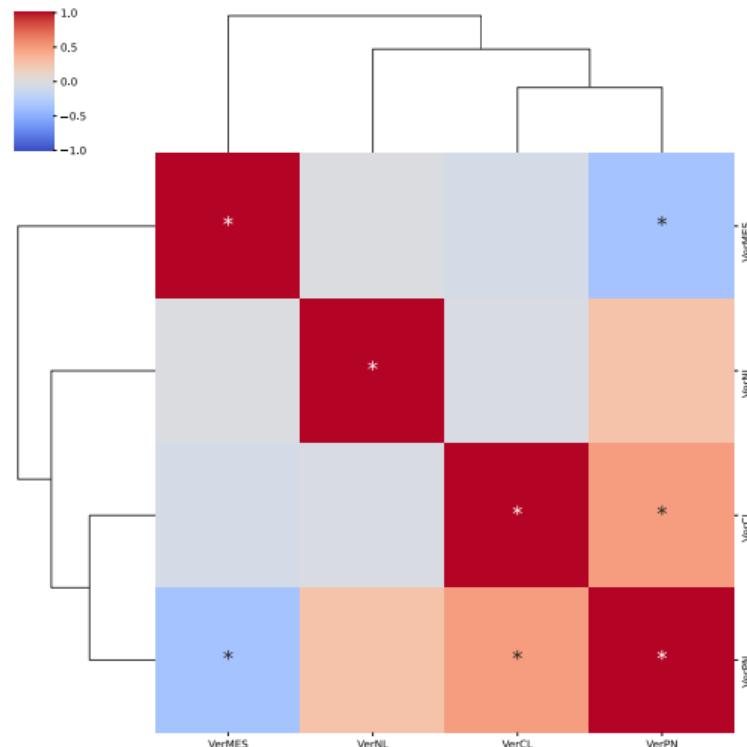


(c) GSE131928 (SingleCell-Tumour)

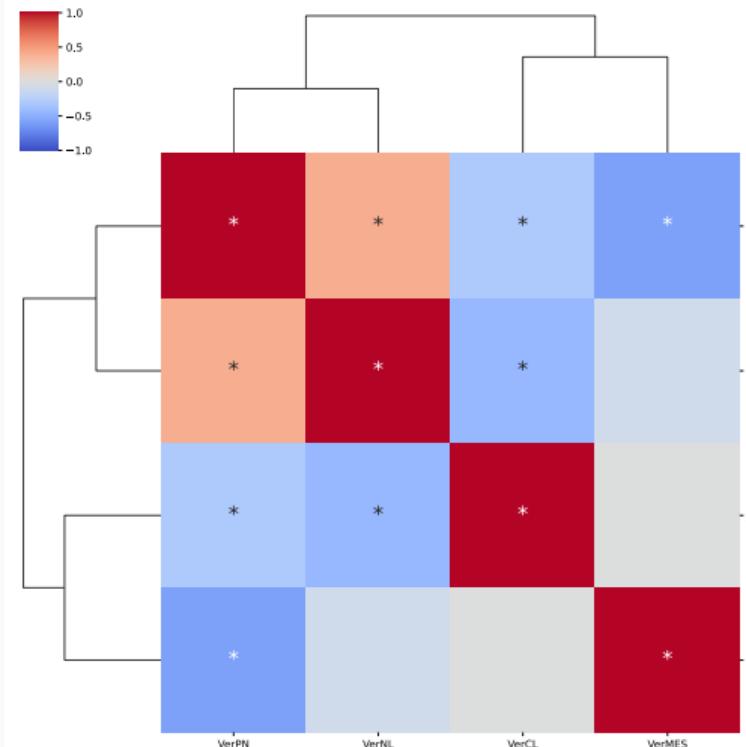


(d) GSE168004 (SingleCell-CellLine)

GENE-SET ENRICHMENT - VERHAAK ET AL



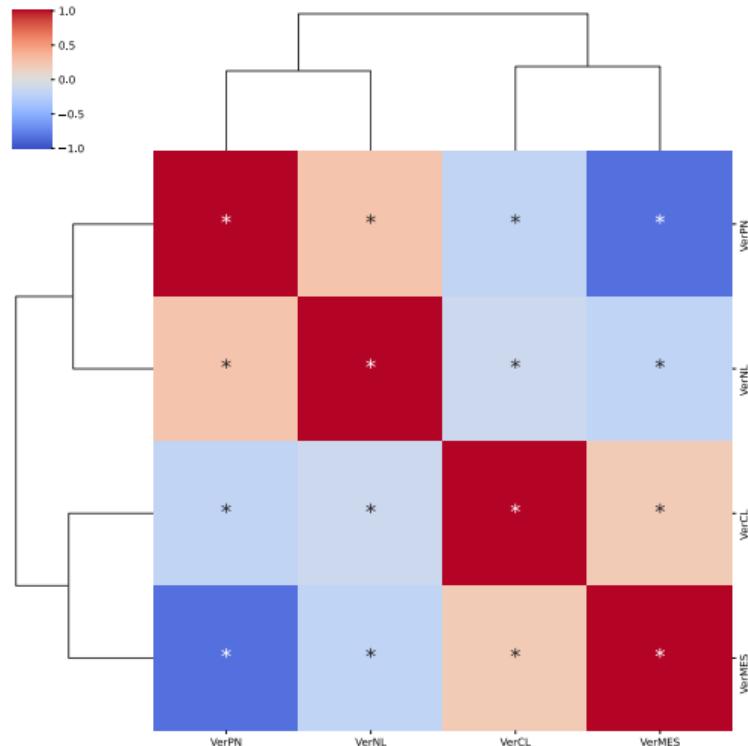
(e) CCLE (Bulk-CellLine)



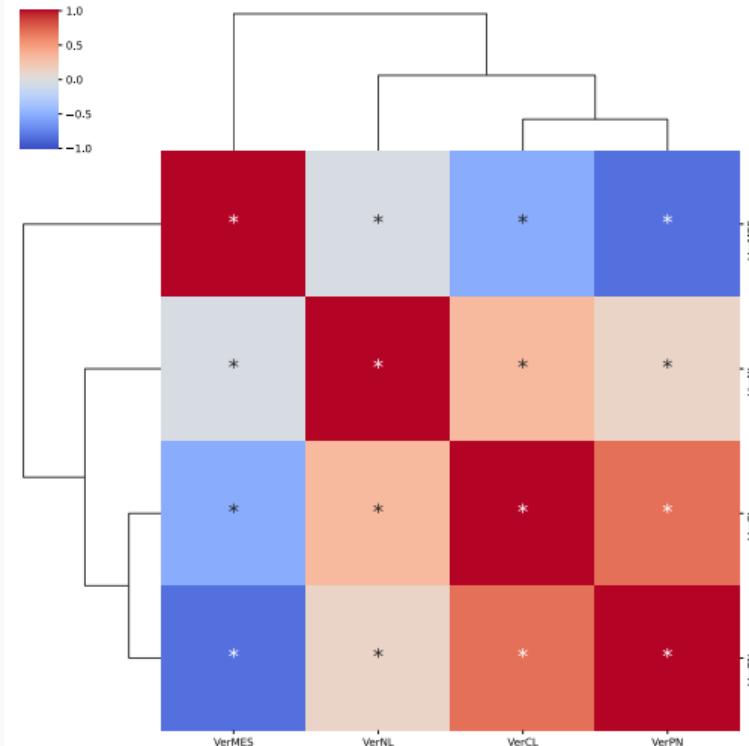
(f) TCGA (Bulk-Tumour)

Figure 2: Correlation of ssGSEA scores - Verhaak

GENE-SET ENRICHMENT - VERHAAK ET AL



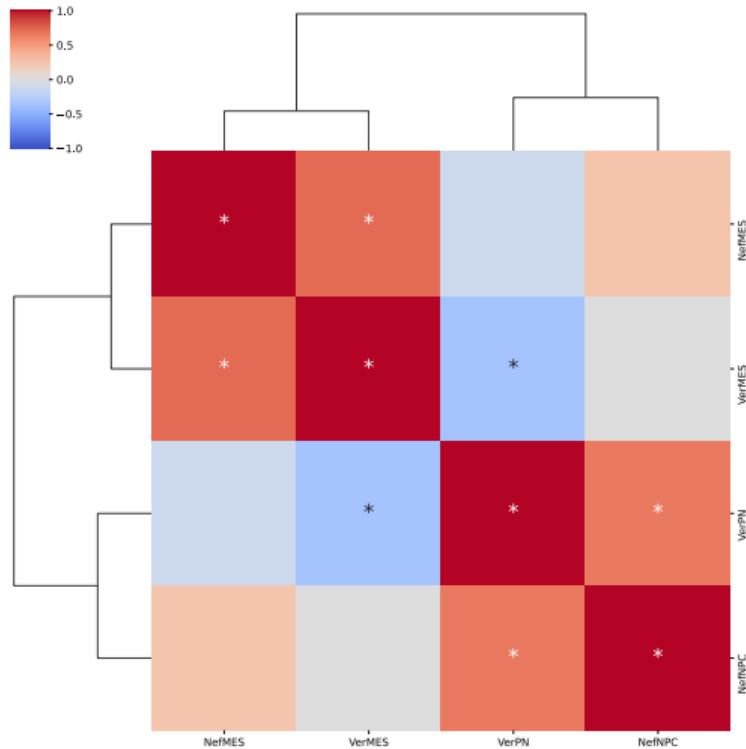
(g) GSE131928 (SingleCell-Tumour)



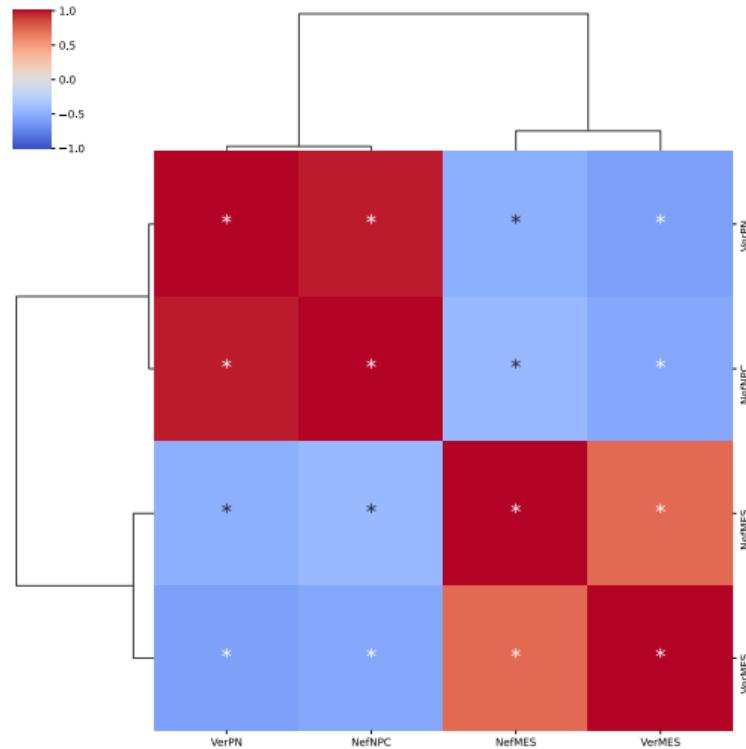
(h) GSE168004 (SingleCell-CellLine)

Figure 2: Correlation of AUCell scores - Verhaak

GENE-SET ENRICHMENT - COMPARISON



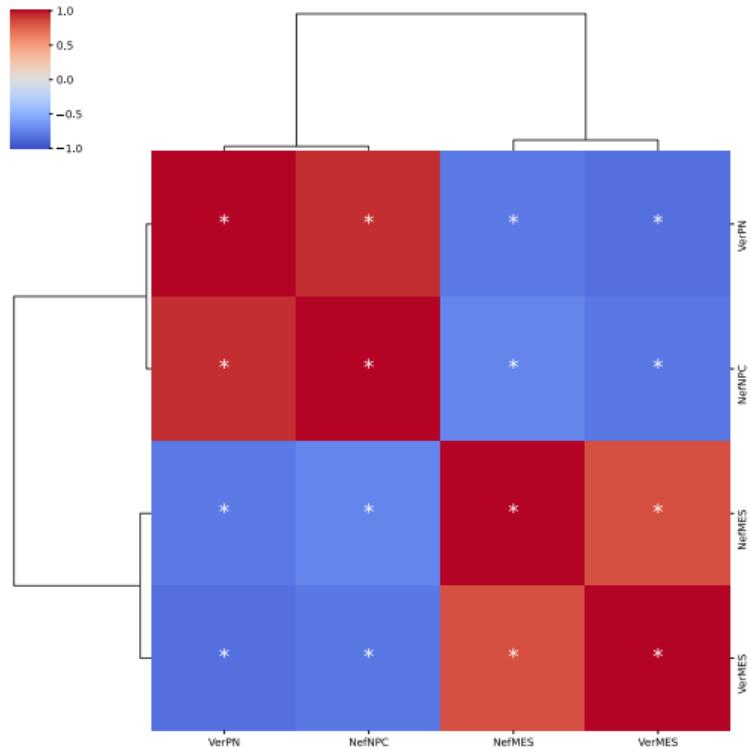
(i) CCLE (Bulk-CellLine)



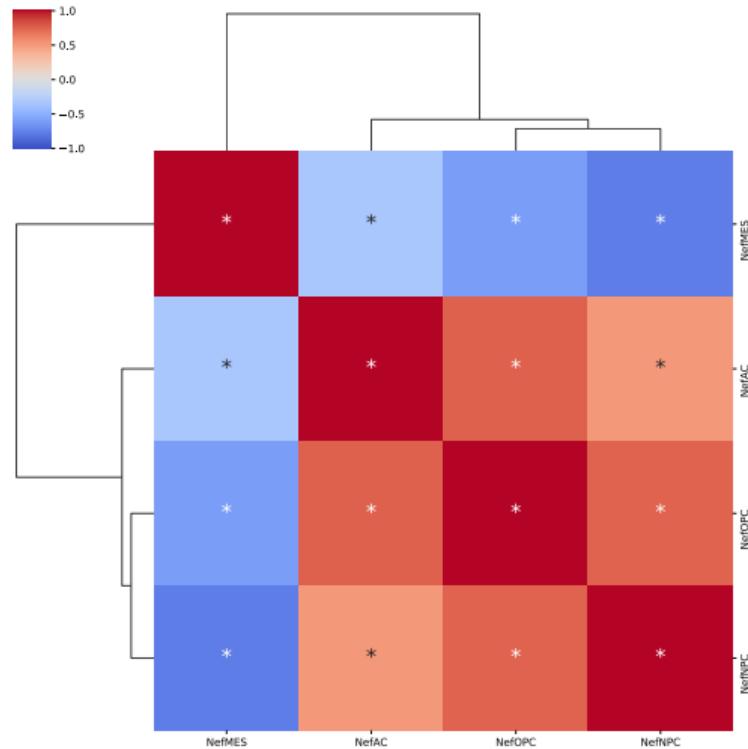
(j) TCGA (Bulk-Tumour)

Figure 2: Correlation of ssGSEA scores - Comparison

GENE-SET ENRICHMENT - COMPARISON



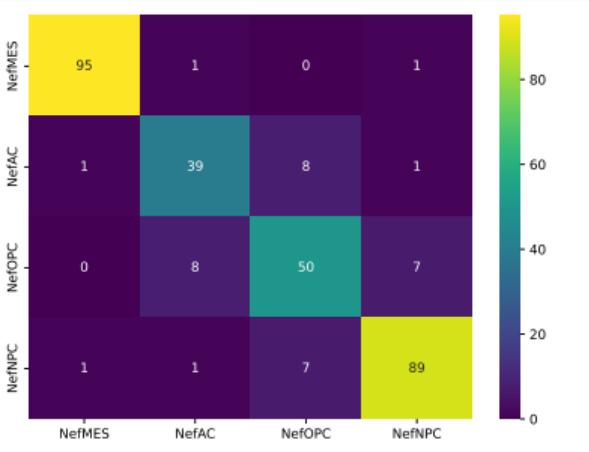
(k) GSE131928 (SingleCell-Tumour)



(l) GSE168004 (SingleCell-CellLine)

Figure 2: Correlation of AUCell scores- Comparison

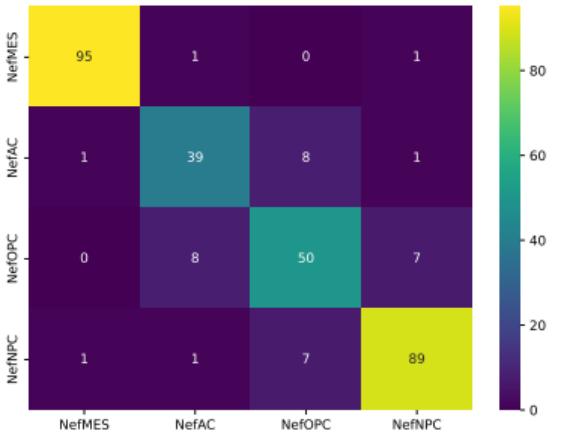
SIGNATURES



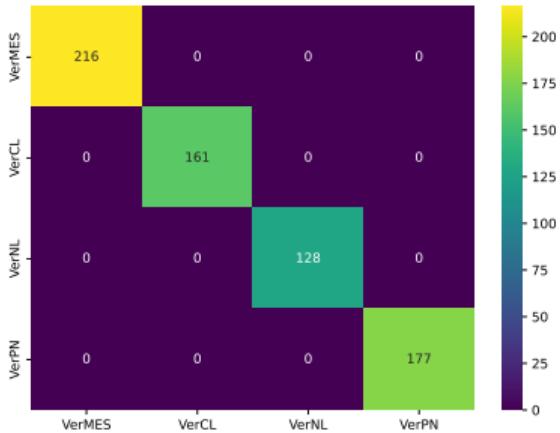
(a) Neftel et al signature

Figure 3: Overlap of genes in the signatures

SIGNATURES



(a) Neftel et al signature



(b) Verhaak et al signature

Figure 3: Overlap of genes in the signatures

SIGNATURES

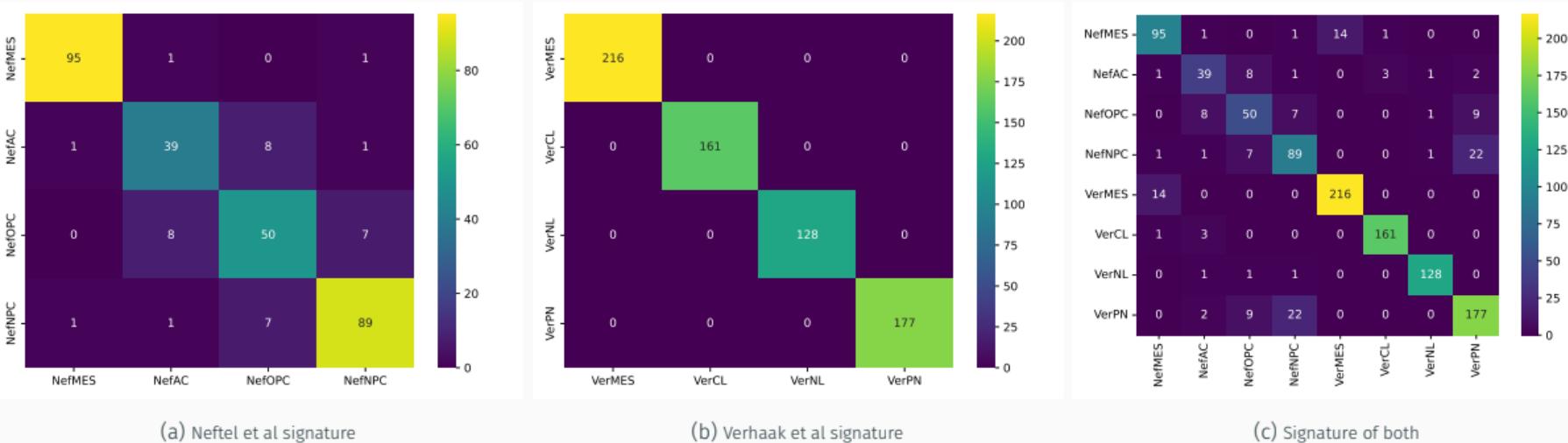
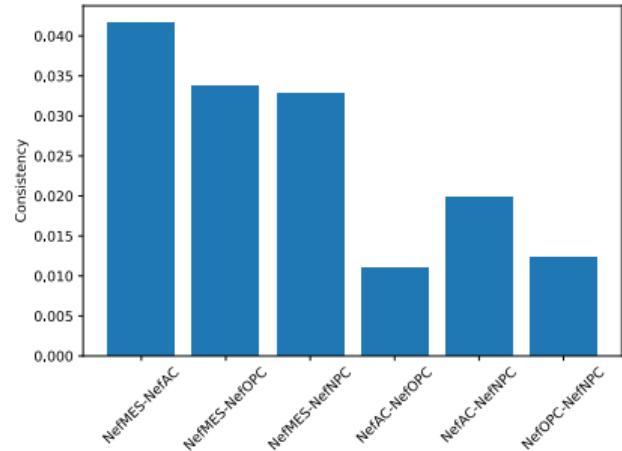
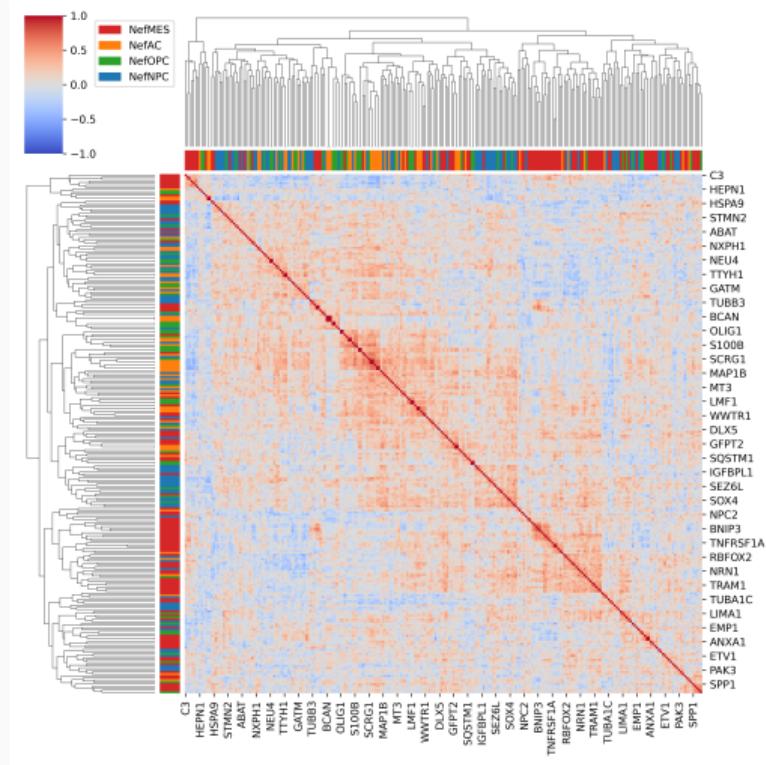


Figure 3: Overlap of genes in the signatures

SIGNATURE EXPRESSION - NEFTEL ET AL



(b) J metric of signature correlation - Neftel

Figure 4: CCLE (Bulk-CellLine)

SIGNATURE EXPRESSION - NEFTEL ET AL

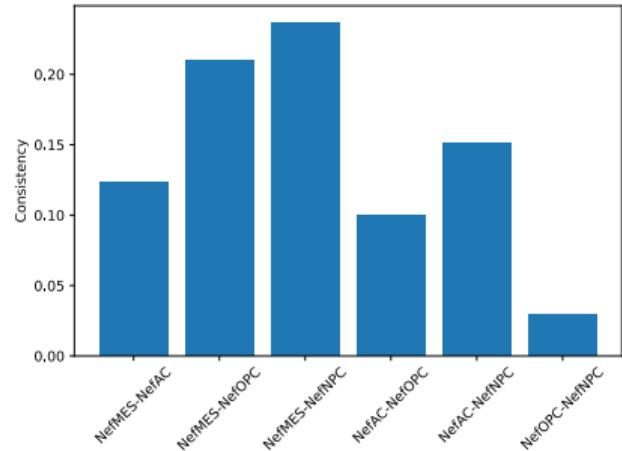
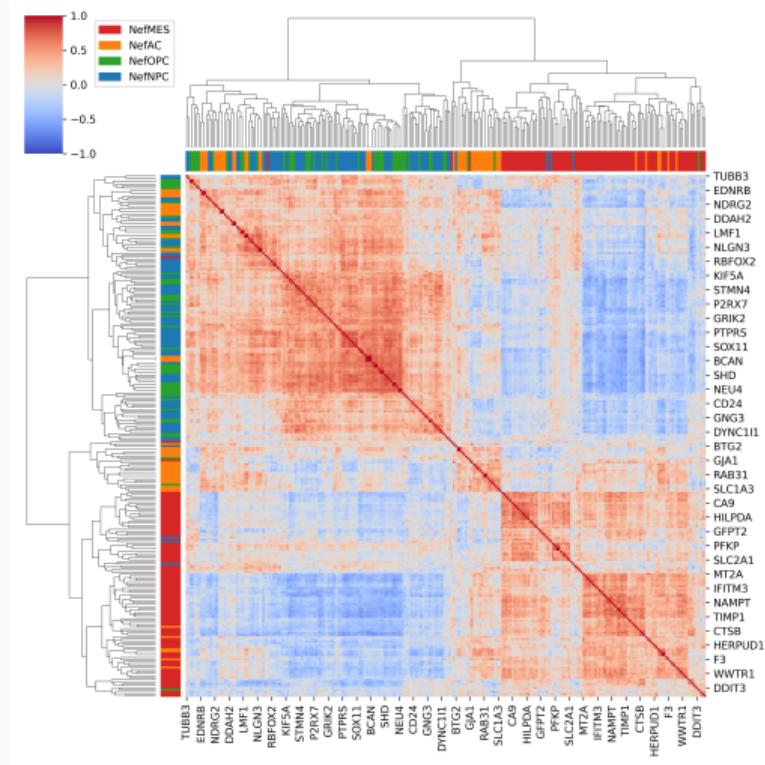
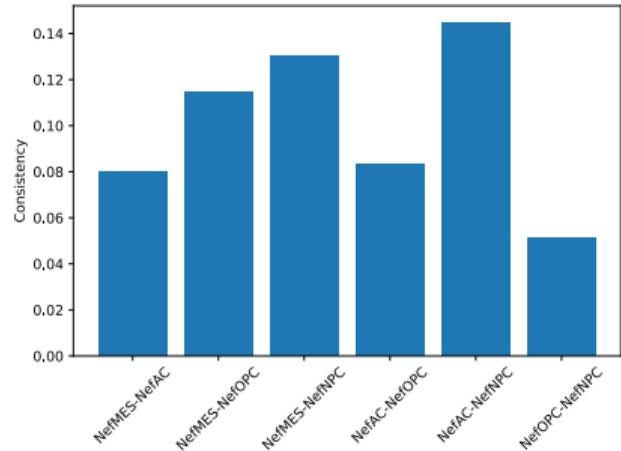
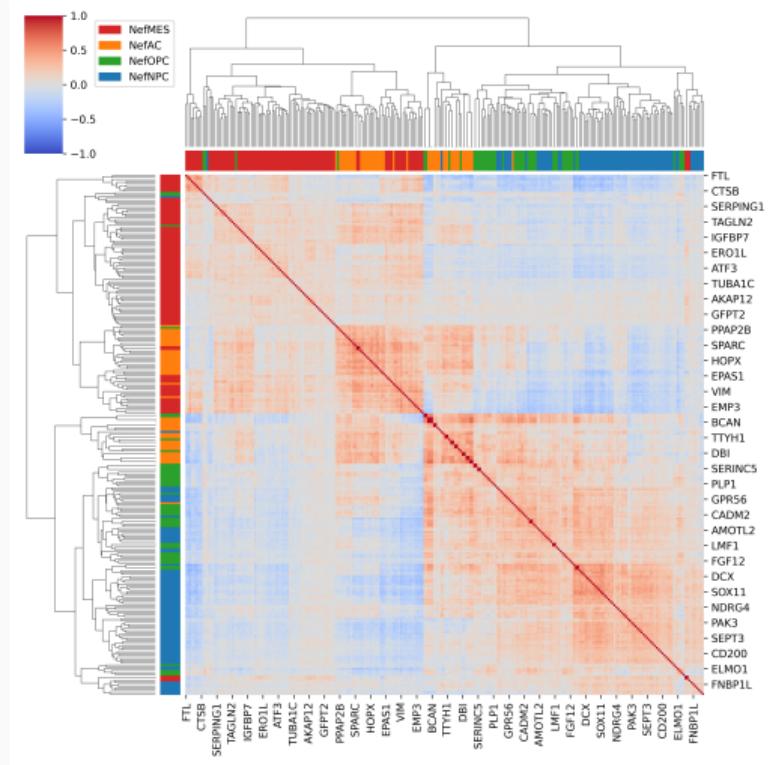


Figure 4: TCGA (Bulk-Tumour)

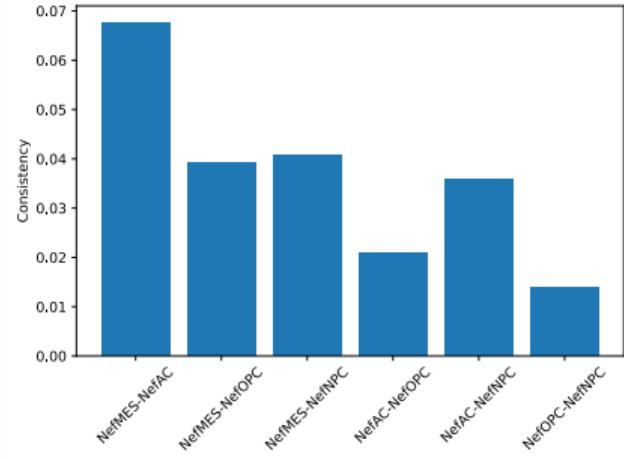
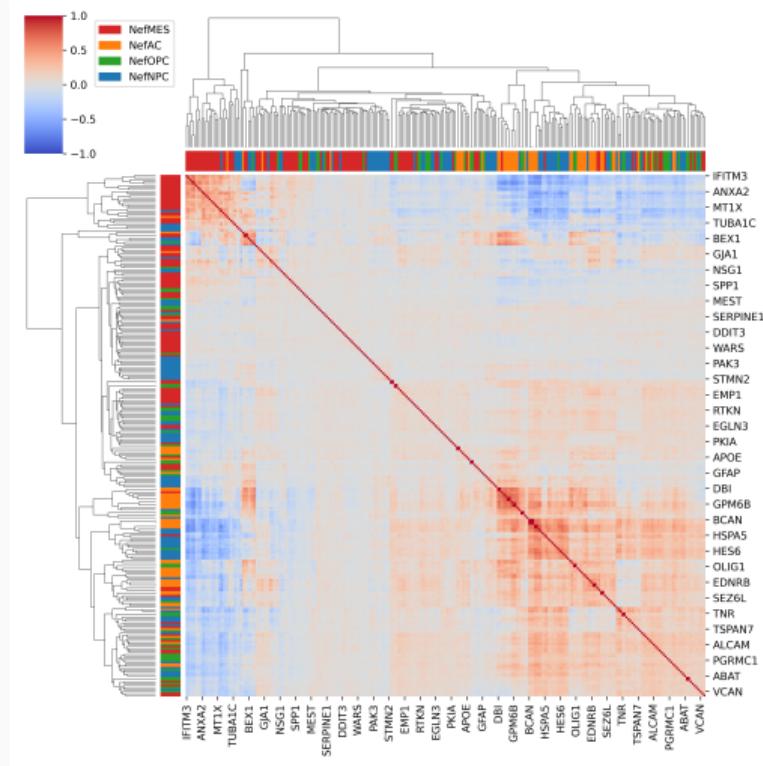
SIGNATURE EXPRESSION - NEFTEL ET AL



(f) J metric of signature correlation - Neftel

Figure 4: GSE131928 (SingleCell-Tumour)

SIGNATURE EXPRESSION - NEFTEL ET AL



(h) J metric of signature correlation - Neftel

Figure 4: GSE168004 (SingleCell-CellLine)

SIGNATURE EXPRESSION - VERHAAK ET AL

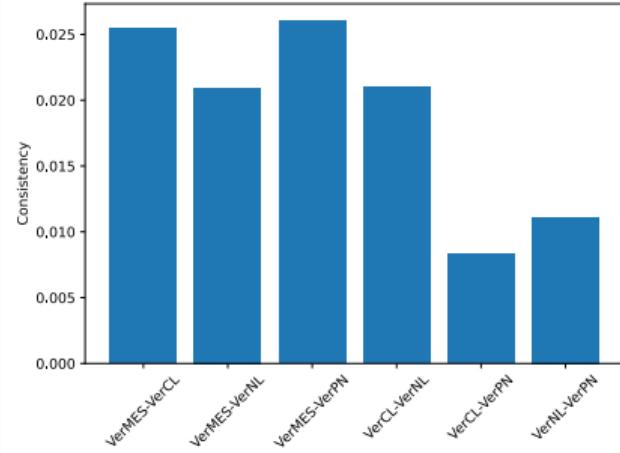
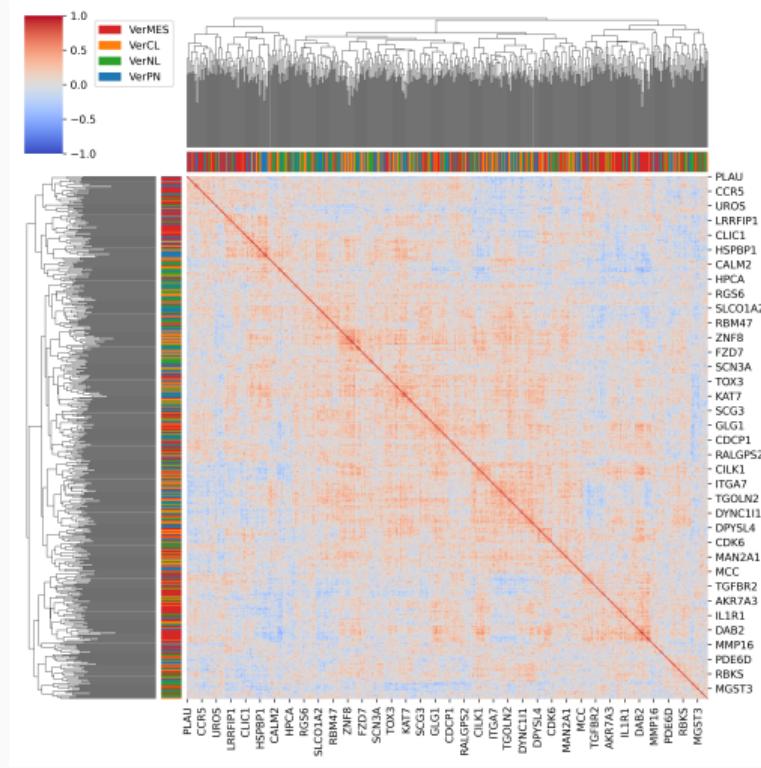
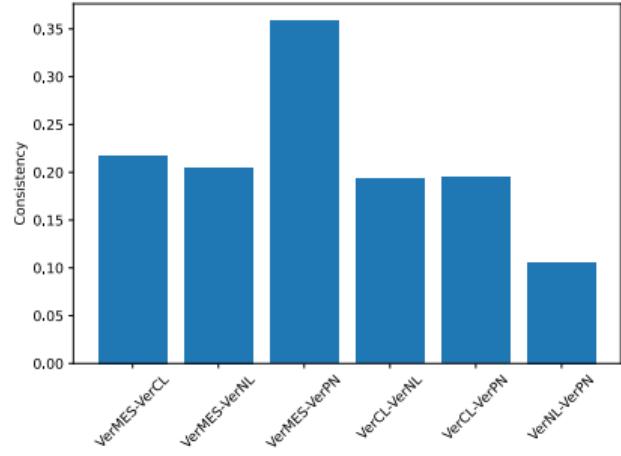
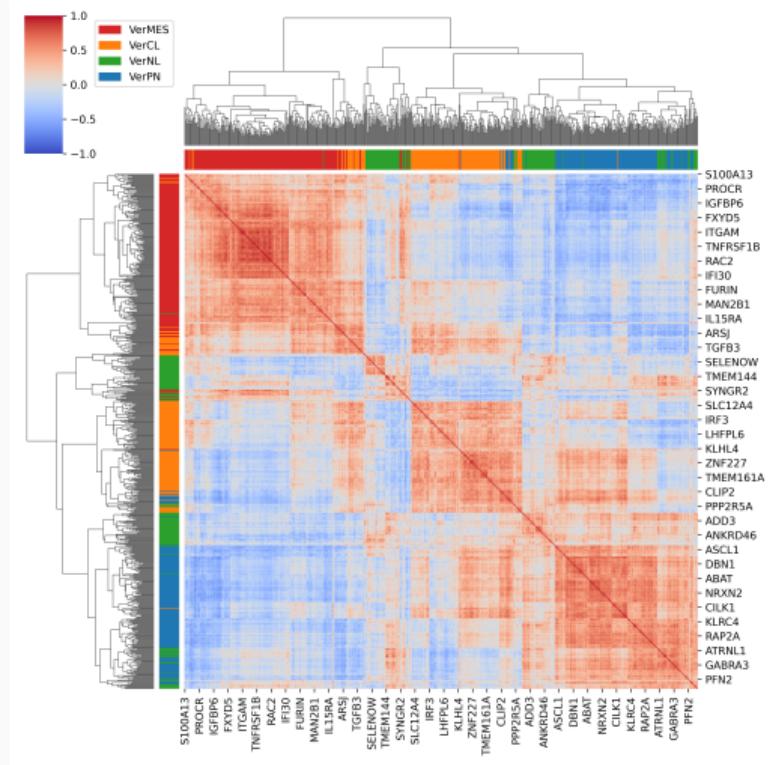


Figure 5: CCLE (Bulk-CellLine)

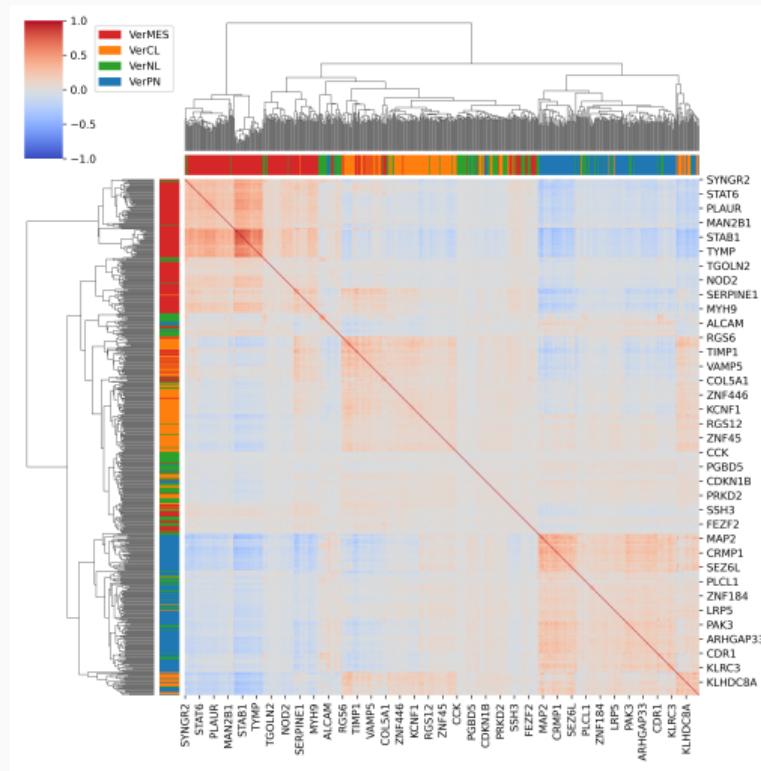
SIGNATURE EXPRESSION - VERHAAK ET AL



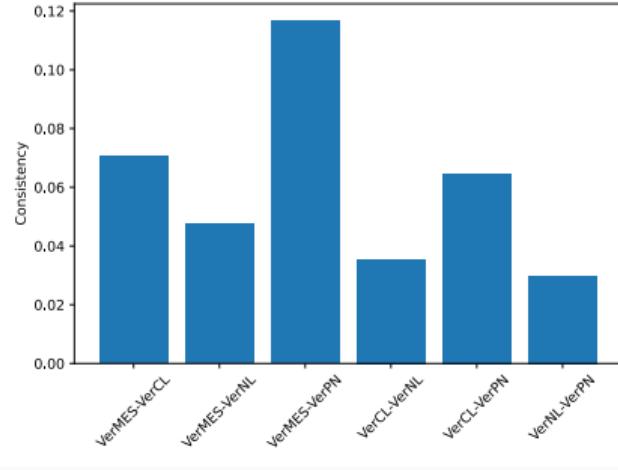
(d) J metric of signature correlation - Verhaak

Figure 5: TCGA (Bulk-Tumour)

SIGNATURE EXPRESSION - VERHAAK ET AL



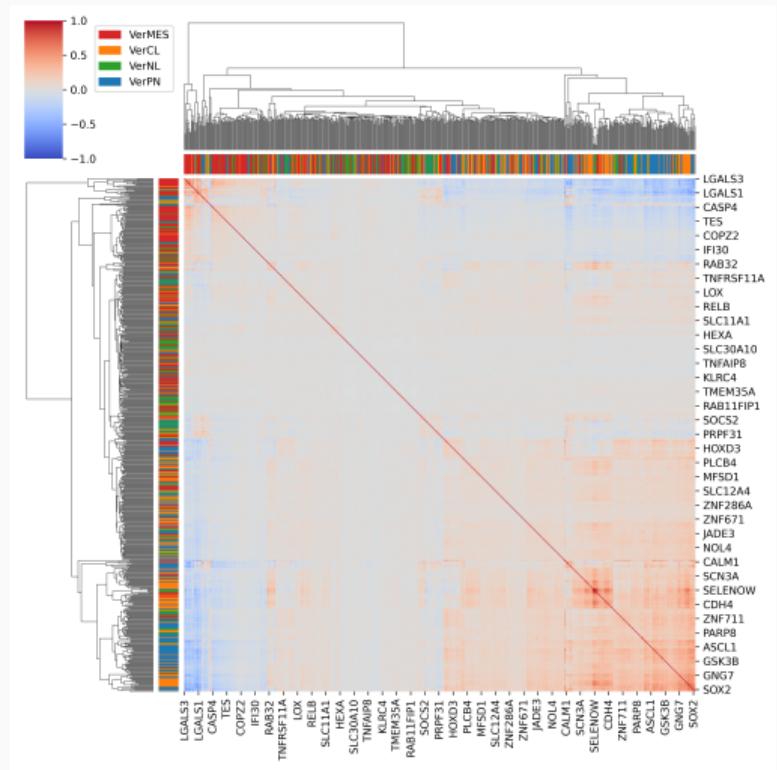
(e) Correlation of signature expression - Verhaak



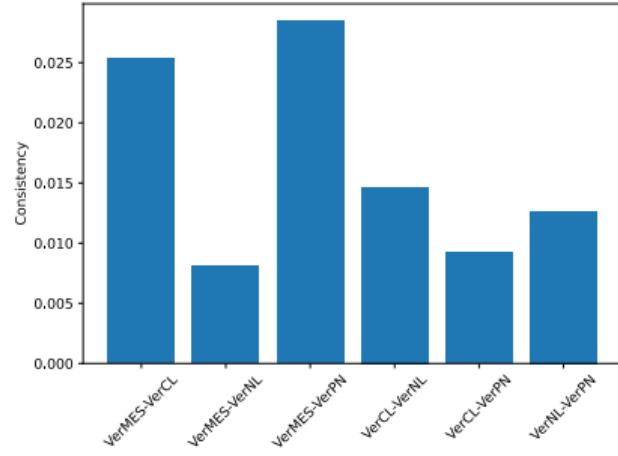
(f) J metric of signature correlation - Verhaak

Figure 5: GSE131928 (SingleCell-Tumour)

SIGNATURE EXPRESSION - VERHAAK ET AL



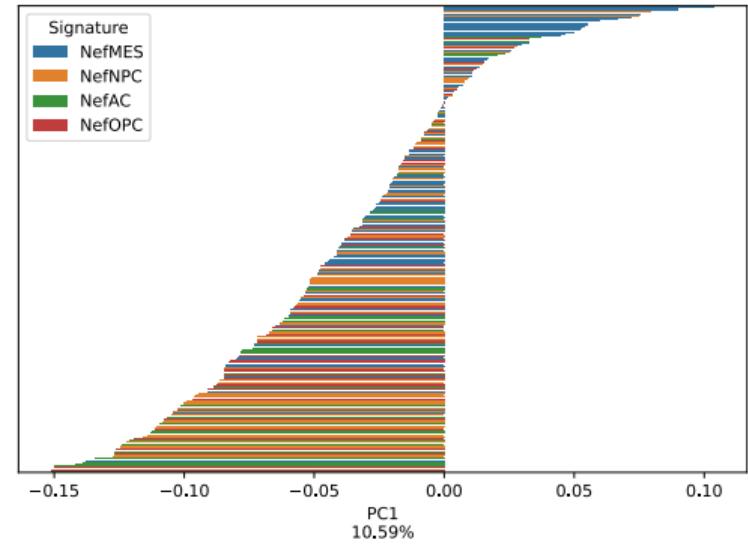
(g) Correlation of signature expression - Verhaak



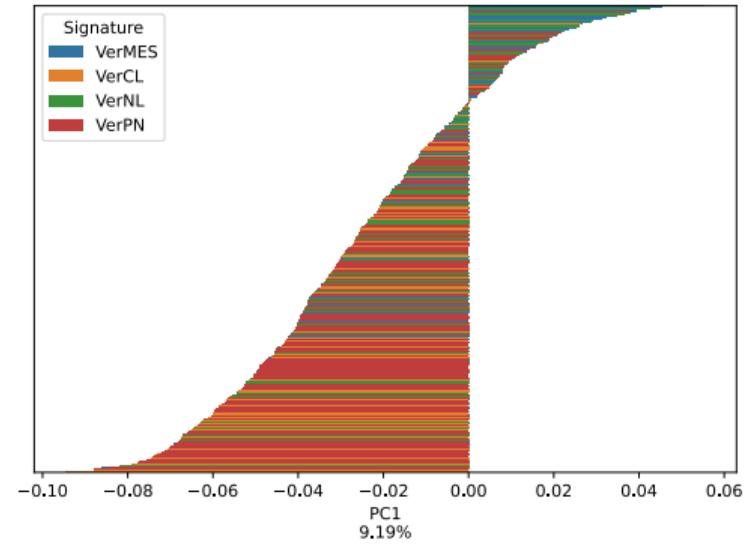
(h) J metric of signature correlation - Verhaak

Figure 5: GSE168004 (SingleCell-CellLine)

PCA OF SIGNATURE



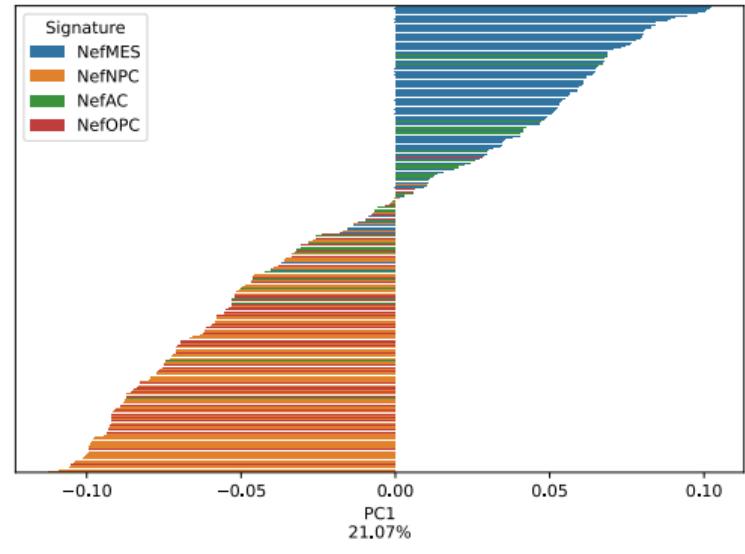
(a) Neftel



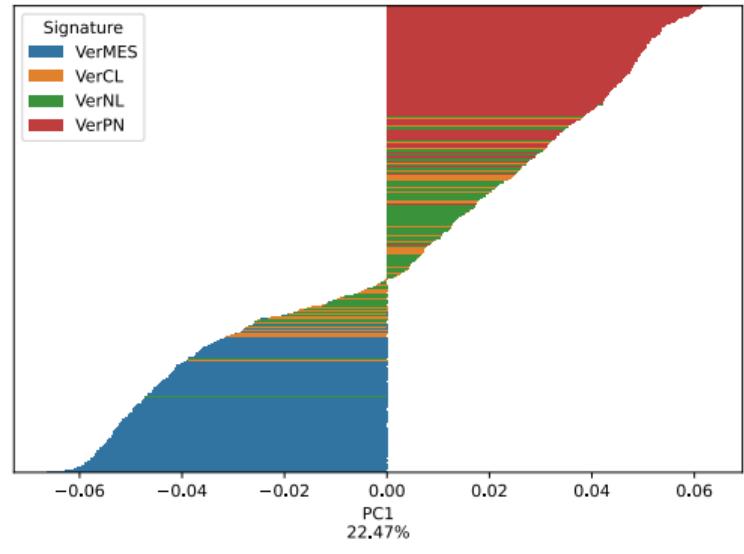
(b) Verhaak

Figure 6: Loadings of PC1 - PCA on signature expression - CCLE (Bulk-CellLine)

PCA OF SIGNATURE



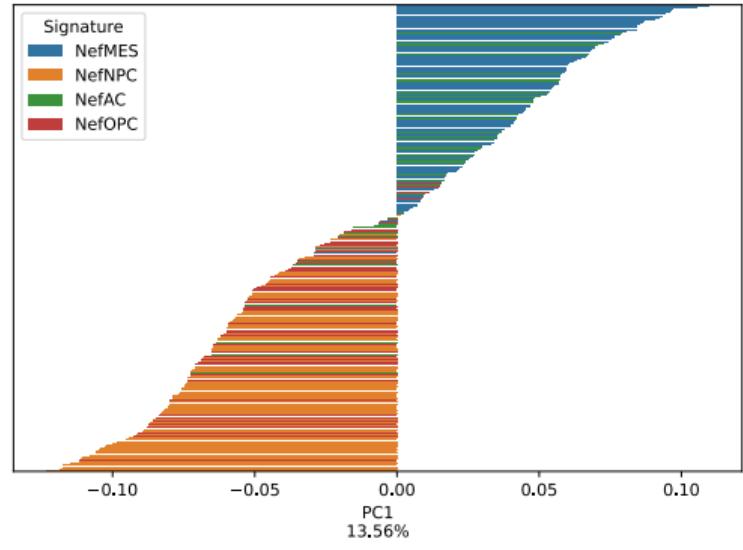
(c) Neftel



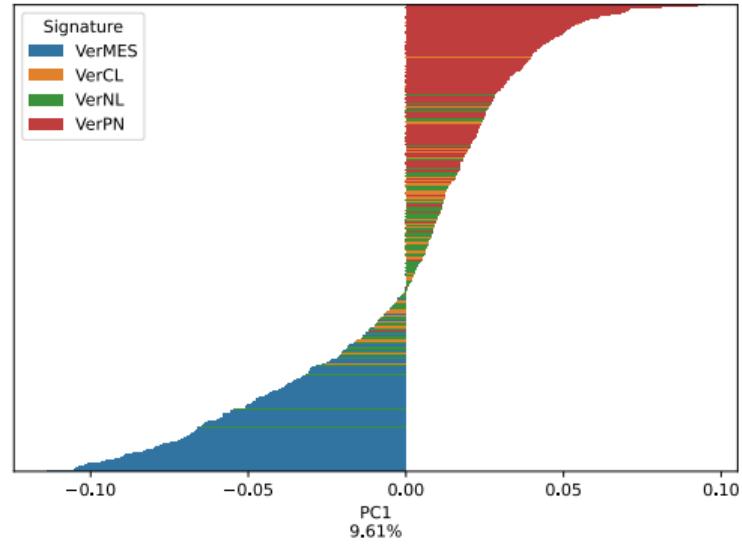
(d) Verhaak

Figure 6: Loadings of PC1 - PCA on signature expression - TCGA (Bulk-Tumour)

PCA OF SIGNATURE



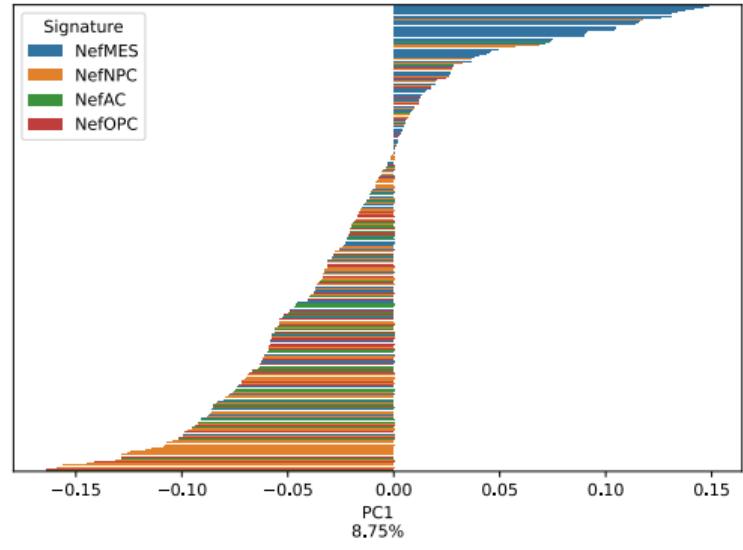
(e) Neftel



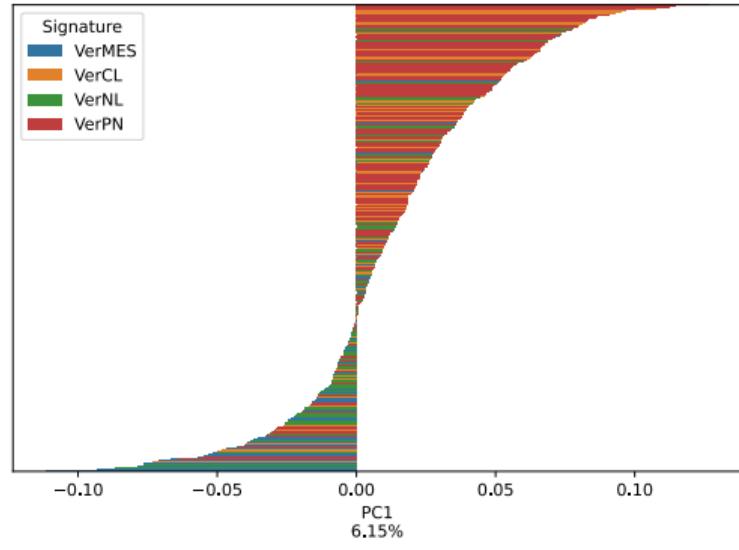
(f) Verhaak

Figure 6: Loadings of PC1 - PCA on signature expression - GSE131928 (SingleCell-Tumour)

PCA OF SIGNATURE



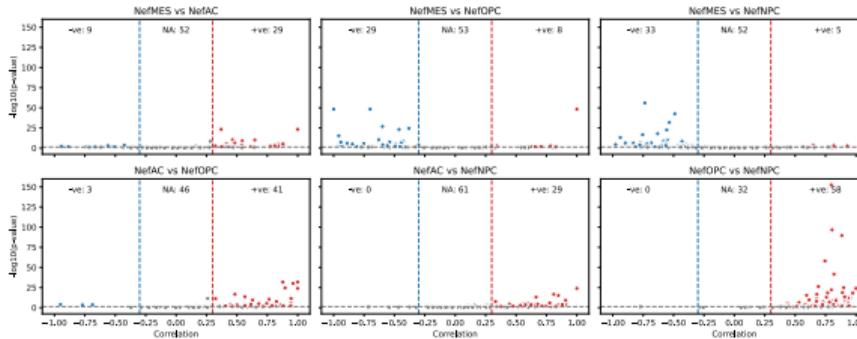
(g) Neftel



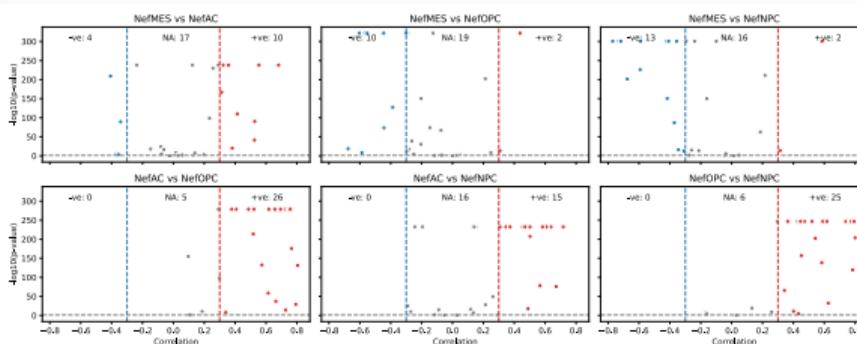
(h) Verhaak

Figure 6: Loadings of PC1 - PCA on signature expression - GSE168004 (SingleCell-CellLine)

META-ANALYSIS - NEFTEL



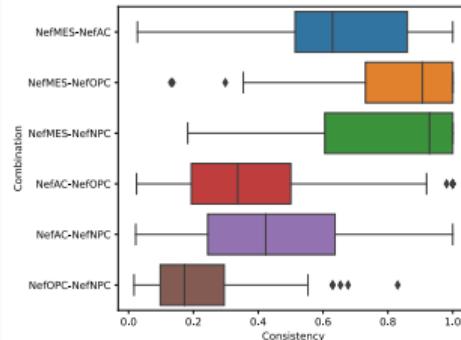
(a) Bulk



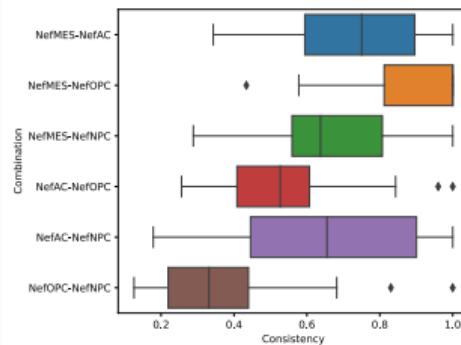
(b) Single-cell

Figure 7: Volcano plots of Neftel et al signature correlation

META-ANALYSIS - NEFTEL

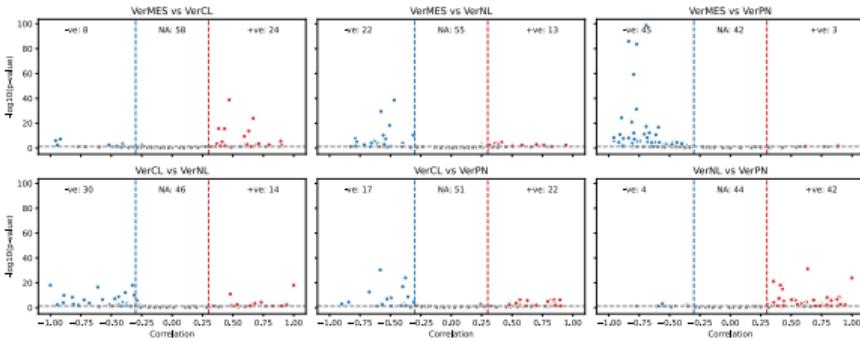


(c) Bulk

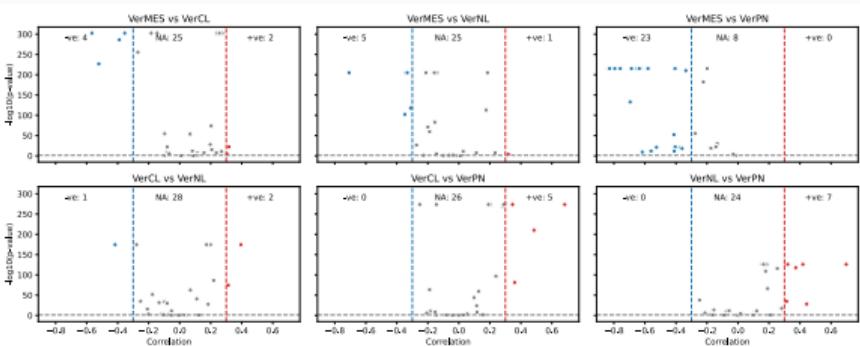


(d) Single-cell

META-ANALYSIS - VERHAAK

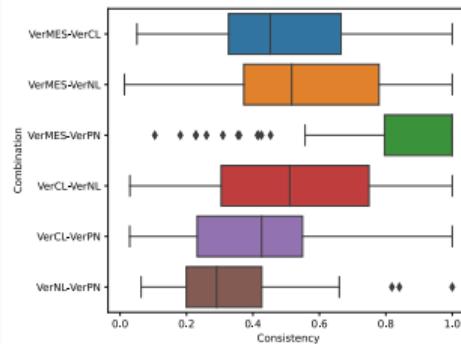


(e) Bulk

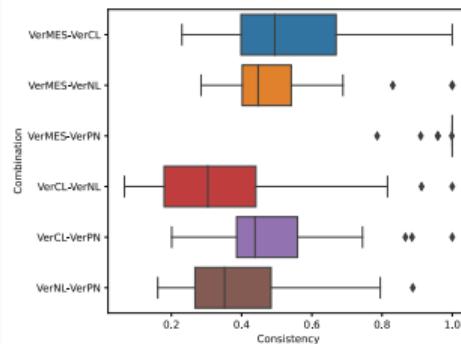


(f) Single-cell

Figure 7: Volcano plots of Verhaak signature correlation

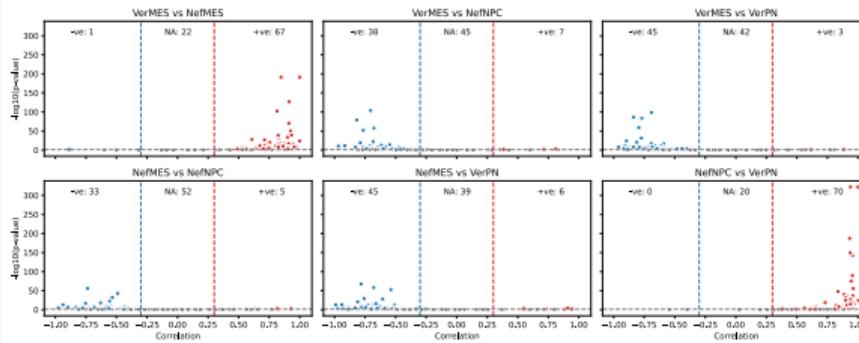


(g) Bulk

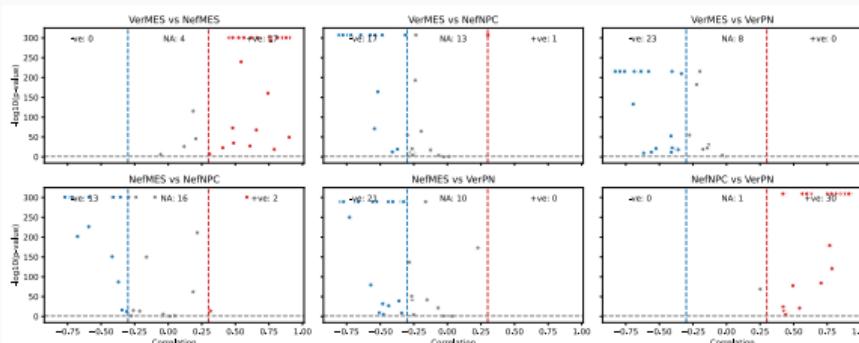


(h) Single-cell

META-ANALYSIS - COMPARISON



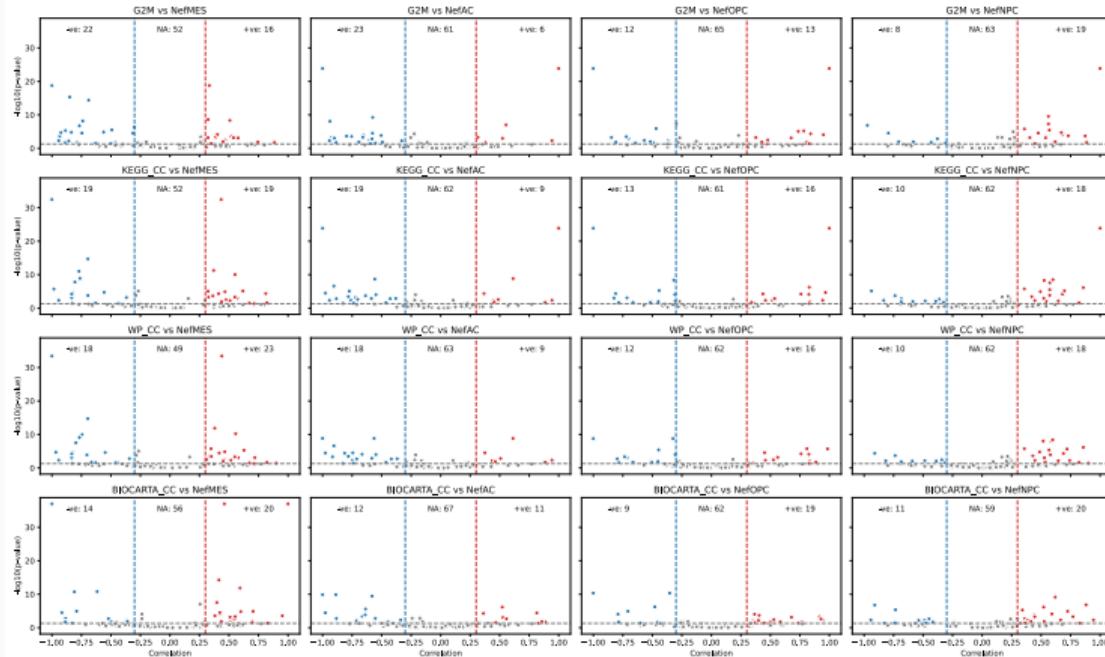
(i) Bulk



(j) Single-cell

Figure 7: Volcano plots of comparison of signature correlation

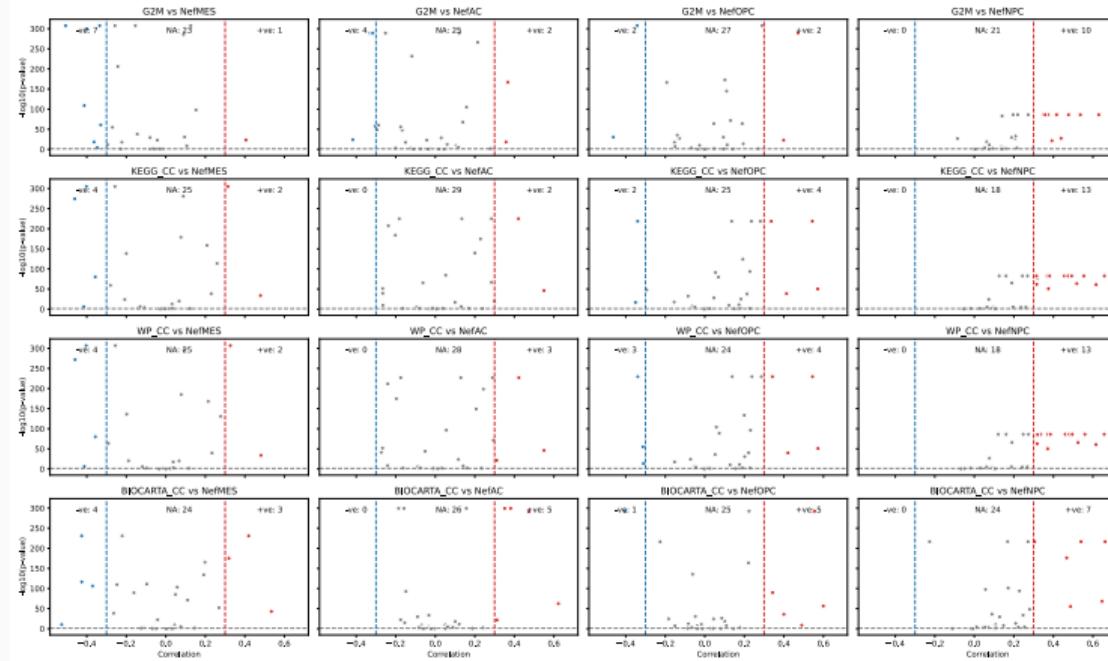
META-ANALYSIS - CELLCYCLE



(a) Bulk

Figure 8: Volcano plots of cell cycle to Neftel signature correlation

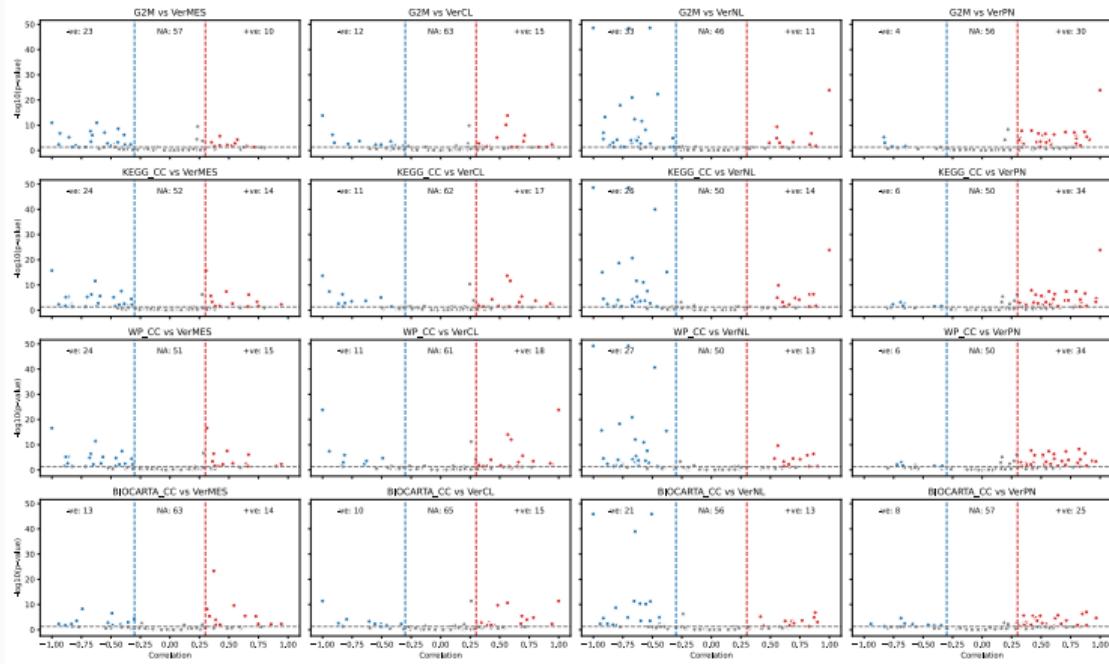
META-ANALYSIS - CELLCYCLE



(b) SingleCell

Figure 8: Volcano plots of cell cycle to Neftel signature correlation

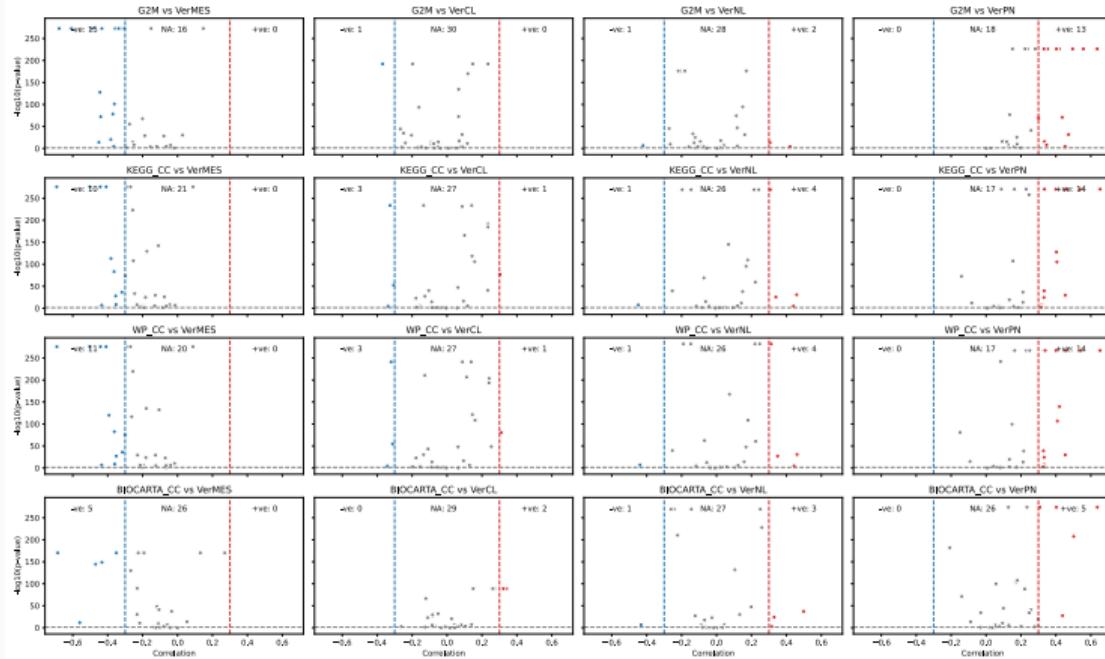
META-ANALYSIS - CELLCYCLE



(c) Bulk

Figure 8: Volcano plots of cell cycle to Verhaak signature correlation

META-ANALYSIS - CELLCYCLE



(d) SingleCell

Figure 8: Volcano plots of cell cycle to Verhaak signature correlation

META-ANALYSIS - METABOLISM

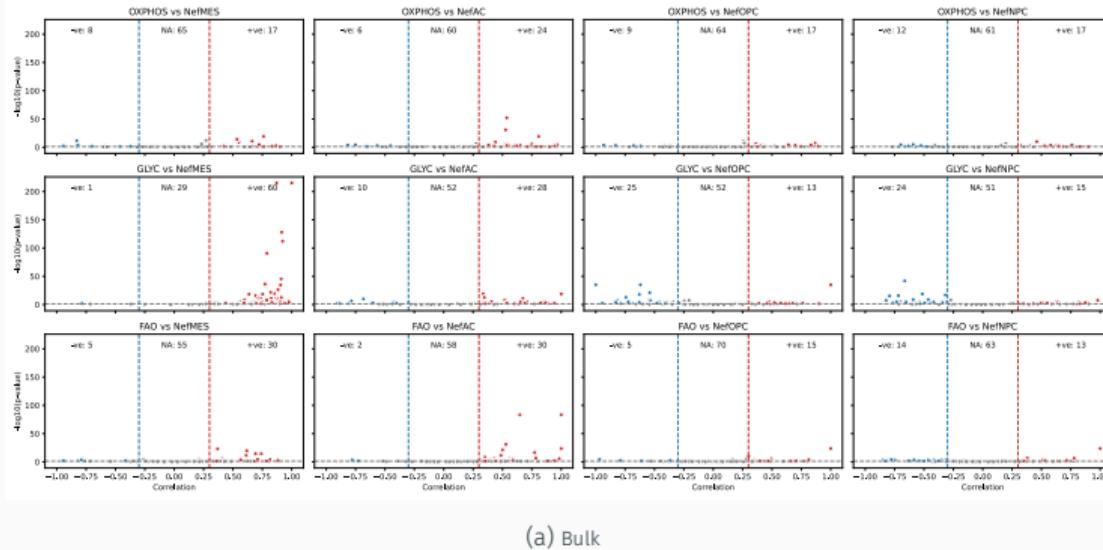
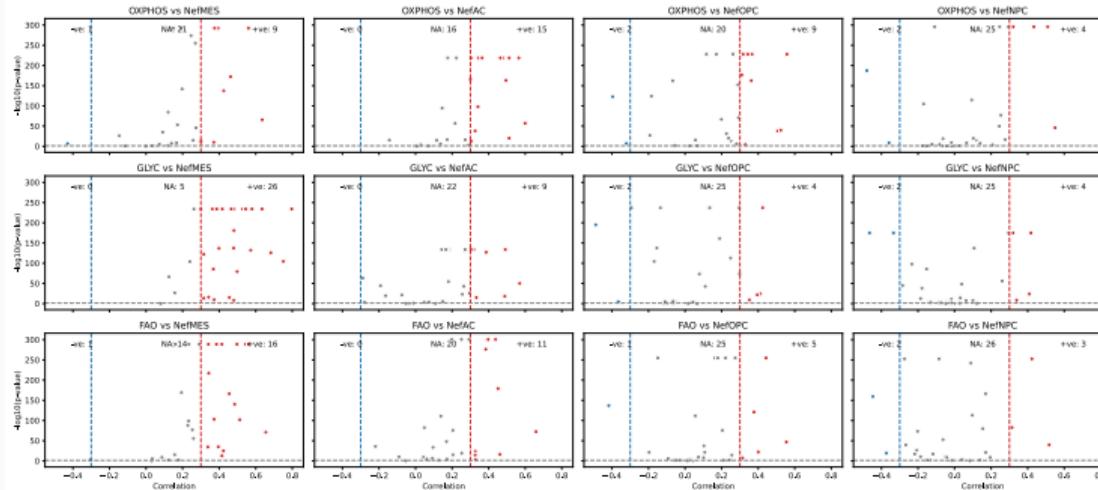


Figure 9: Volcano plots of metabolism to Neftel signature correlation

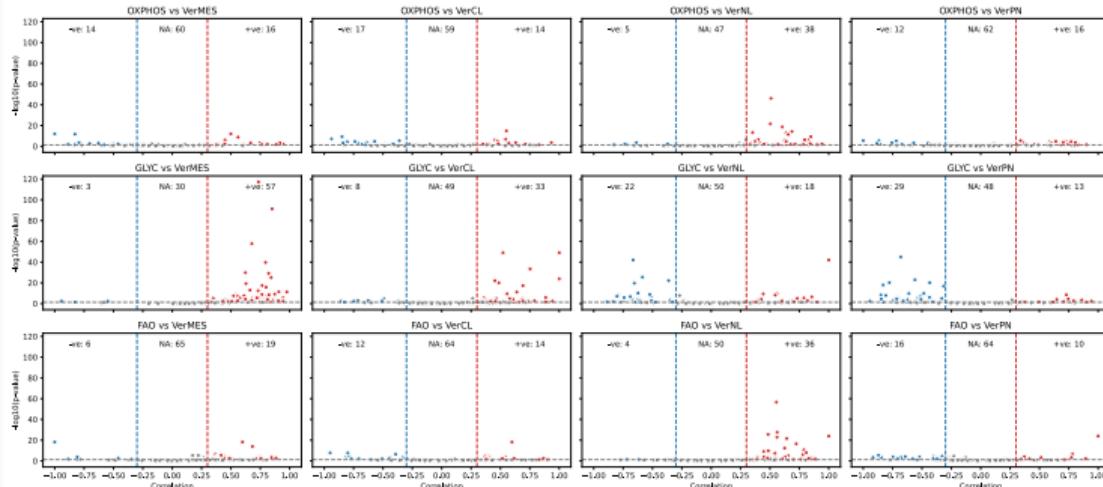
META-ANALYSIS - METABOLISM



(a) SingleCell

Figure 10: Volcano plots of metabolism to Neftel signature correlation

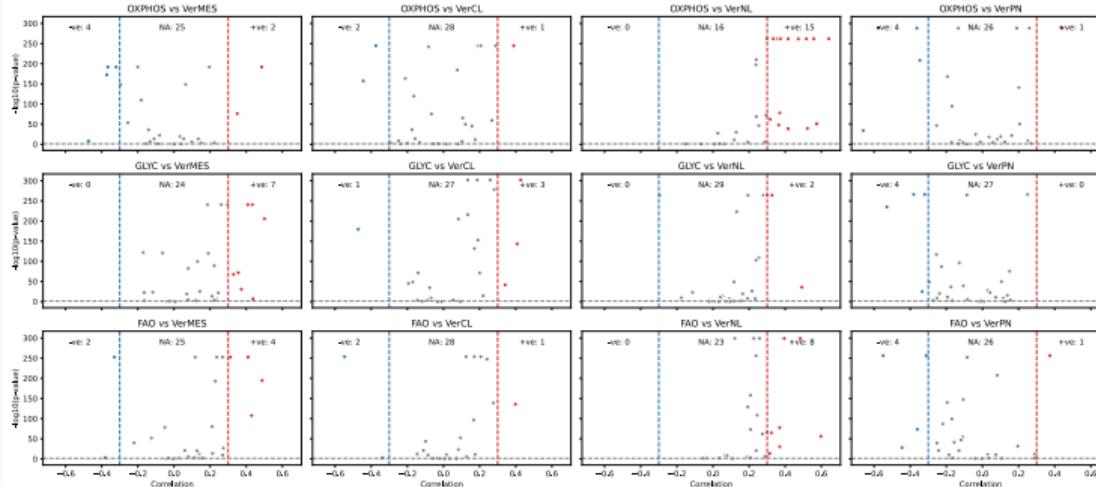
META-ANALYSIS - METABOLISM



(b) Bulk

Figure 10: Volcano plots of metabolism to Verhaak signature correlation

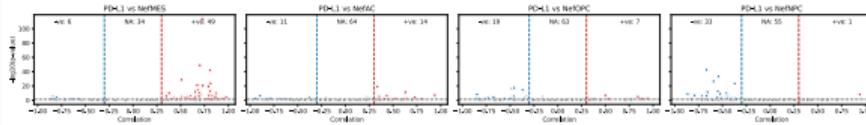
META-ANALYSIS - METABOLISM



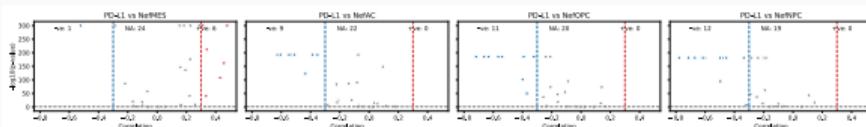
(c) SingleCell

Figure 10: Volcano plots of metabolism to Verhaak signature correlation

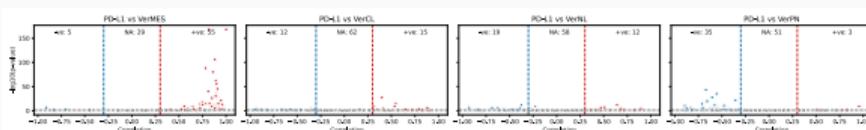
META-ANALYSIS - IMMUNE



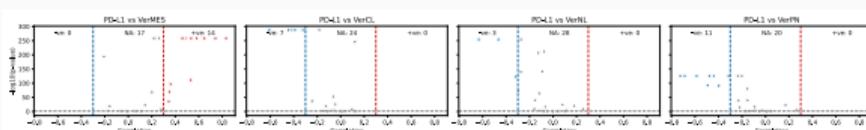
(a) Neftel - Bulk



(b) Neftel - Single-cell



(c) Verhaak - Bulk



(d) Verhaak - Single-cell

Figure 11: Volcano plots of metabolism to signature correlation

CONCLUSION

- We can't find the 4 states mentioned in Neftel or Verhaak to be distinct

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- Most antagonistic pair
 - NPC vs MES - Neftel et al
 - PN vs MES - Verhaak et al

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- Similar states between Neftel vs Verhaak
 - $\text{NPC} \approx \text{PN}$
 - $\text{MES} \approx \text{MES}$

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- Most antagonistic pair
 - NPC vs MES - Neftel et al
 - PN vs MES - Verhaak et al
- Similar states between Neftel vs Verhaak
 - $\text{NPC} \approx \text{PN}$
 - $\text{MES} \approx \text{MES}$
- Holds along other axis
 - metabolism
 - cellcycle
 - immune axis

- Construct a network based on literature which explains the observations

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<https://doi.org/https://doi.org/10.1016/j.cell.2013.09.034>
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-  Hara, T., Chanoch-Myers, R., Mathewson, N. D., Myskiw, C., Atta, L., Bussema, L., Eichhorn, S. W., Greenwald, A. C., Kinker, G. S., Rodman, C., Gonzalez Castro, L. N., Wakimoto, H., Rozenblatt-Rosen, O., Zhuang, X., Fan, J., Hunter, T., Verma, I. M., Wucherpfennig, K. W., Regev, A., ... Tirosh, I. (2021). Interactions between cancer cells and immune cells drive transitions to mesenchymal-like states in glioblastoma. *Cancer Cell*, 39(6), 779–792.e11.
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