Discovering Structural Variant Signatures in Cancer

Greg Raskind

1 Background and Motivation

DDR Pathways are Critical For Maintaining Genomic Integrity

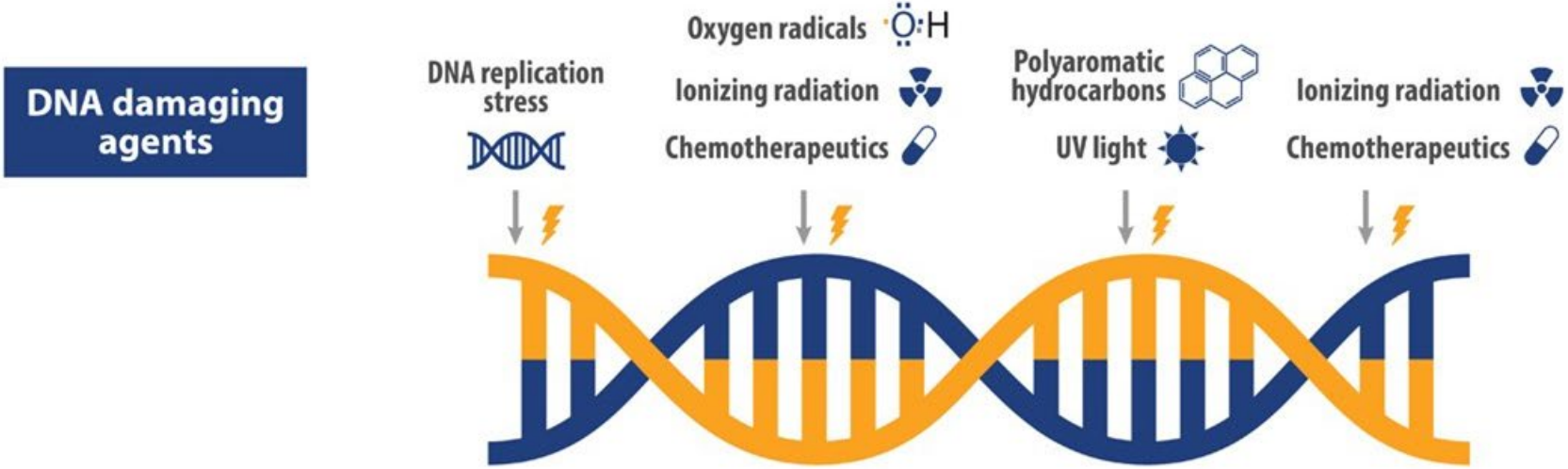


Image Credit: https://blog.crownbio.com/dna-damage-response

DDR Pathways are Critical For Maintaining Genomic Integrity

DNA damage types

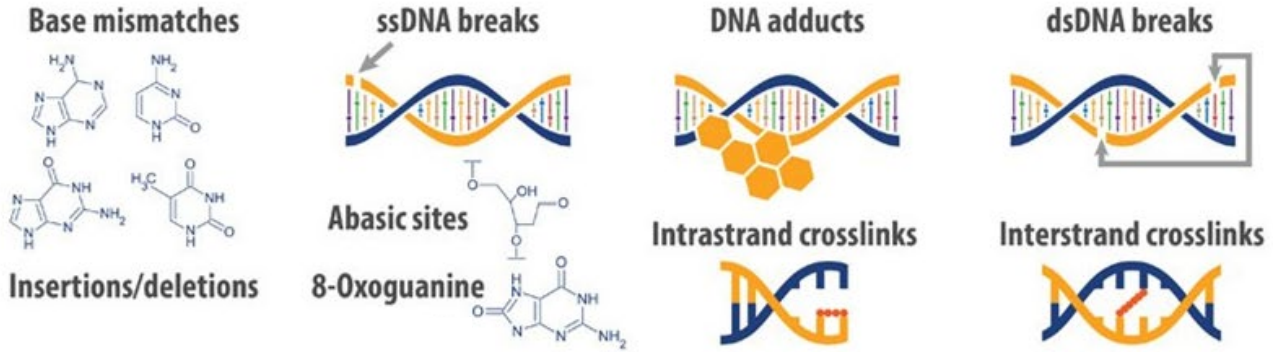


Image Credit: https://blog.crownbio.com/dna-damage-response

DDR Pathways are Critical For Maintaining Genomic Integrity

Image Credit: https://blog.crownbio.com/dna-damage-response

HR deficiency is a biomarker for PARP inhibitor sensitivity

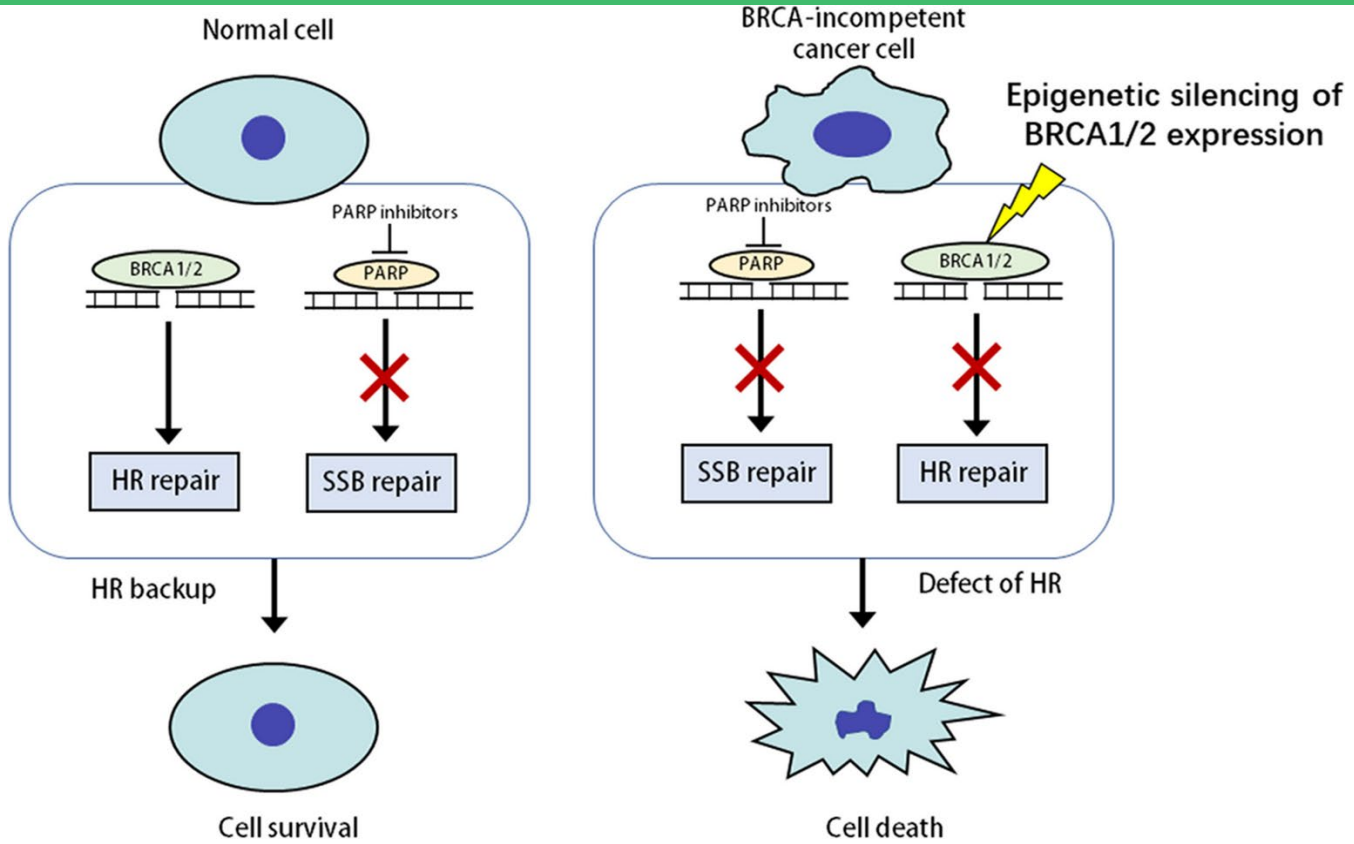


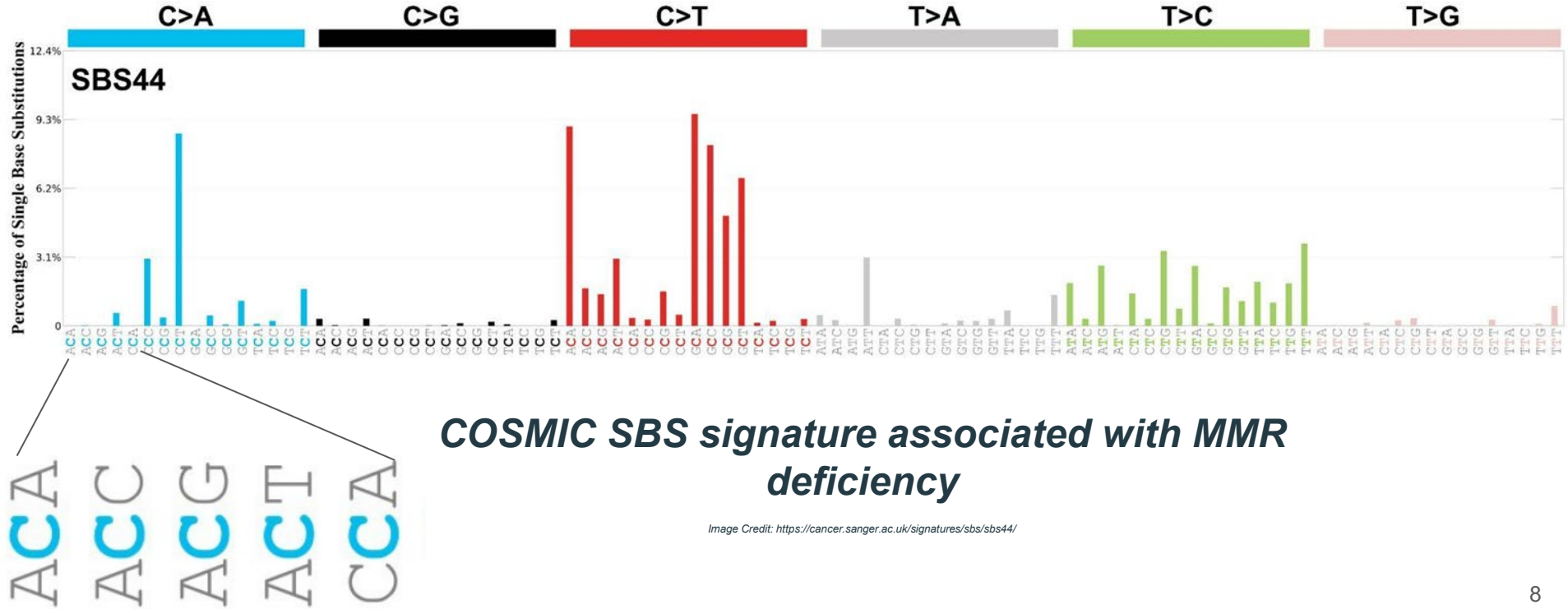
Image credit: Hu, Y. & Guo, M. *Cancer Sci.* (2020)

DDR defects in cancer can be exploited therapeutically

- MGMT methylation predicts improved response to radiation/chemotherapy in glioblastoma patients
- MMR deficiency is predictive of immunotherapy response in some cancers (e.g. colorectal)

Mutational signatures can serve as biomarkers of DDR state

Mutational signatures are patterns of mutations left behind by DNA damage/repair processes



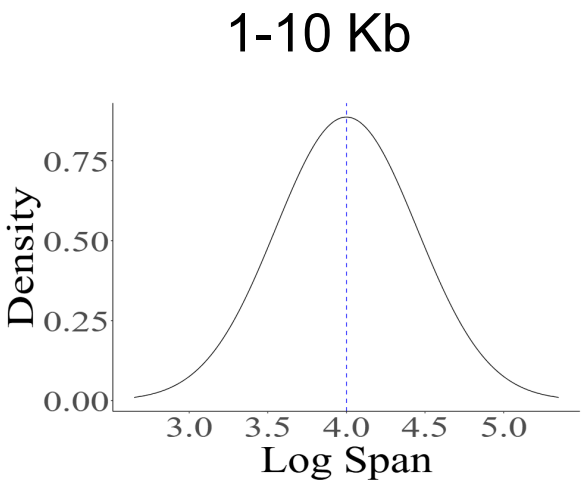
COSMIC SBS signature associated with MMR deficiency

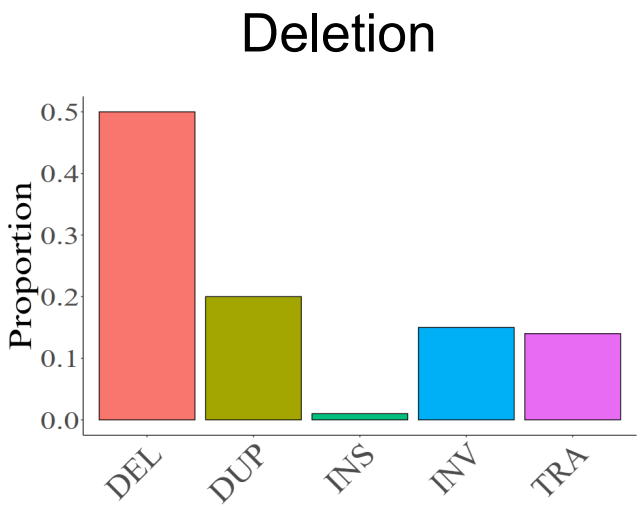
Image Credit: https://cancer.sanger.ac.uk/signatures/sbs/sbs44/

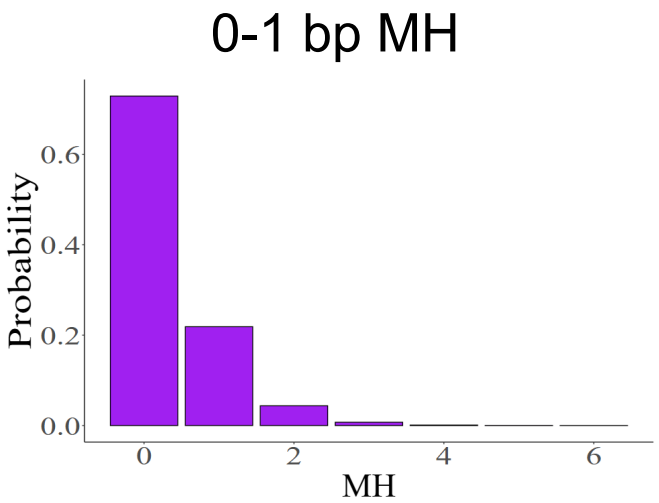
Structural variant signatures are understudied

- Current signature detection approaches largely focus on point mutations
- However, many DDR alterations are more likely to be reflected in structural variant (SV) signatures
  - Particularly those involved in double strand break repair

Our Approach: Represent features in a way that reflects underlying mechar



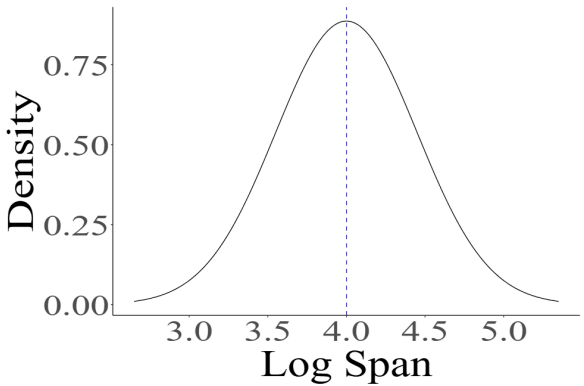




- Chosen distributions reflect our knowledge of the underlying biology
- Natural representation of quantitative/continuous variables
  - E.g. 1 Kb deletion is more similar to 10 Kb deletion than 10 Mb deletion

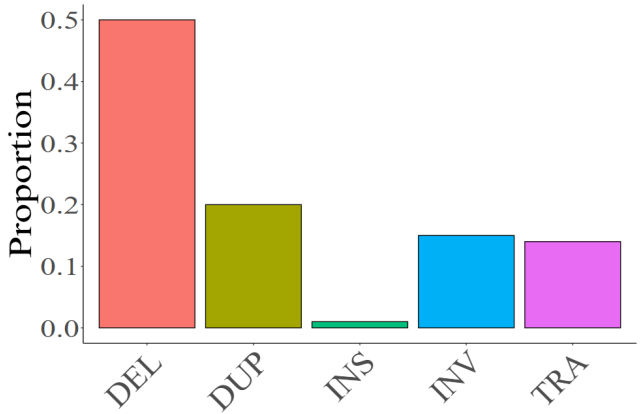
Our Approach: Fit model parameters that best explain observed data

1-10 Kb



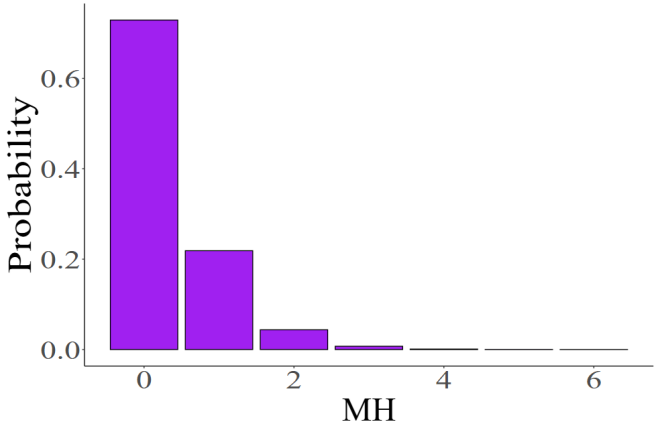
μ, σ

Deletion



c1, c2, c3, c4, c5

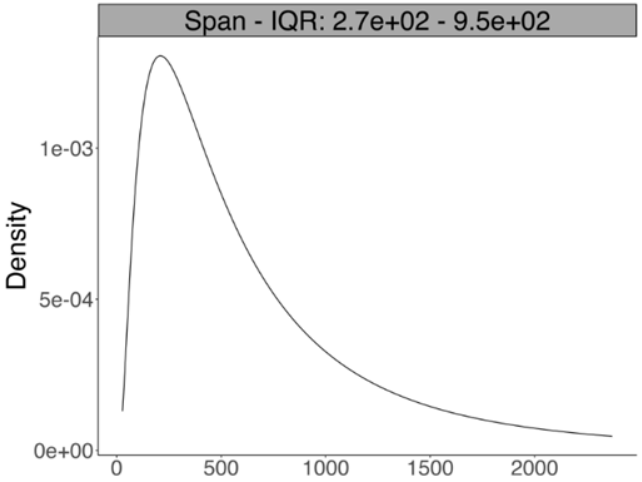
0-1 bp MH

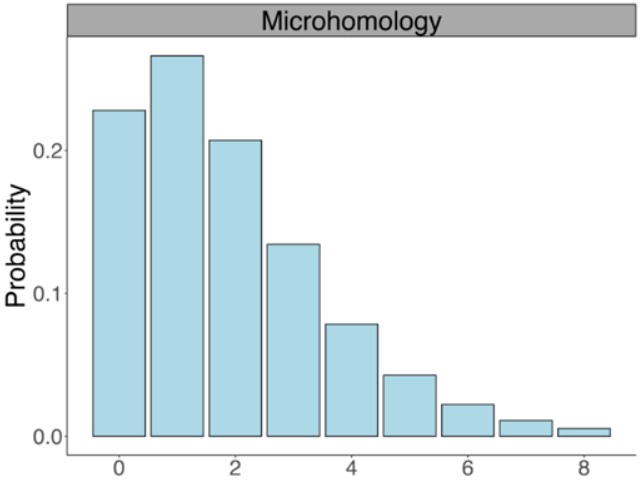


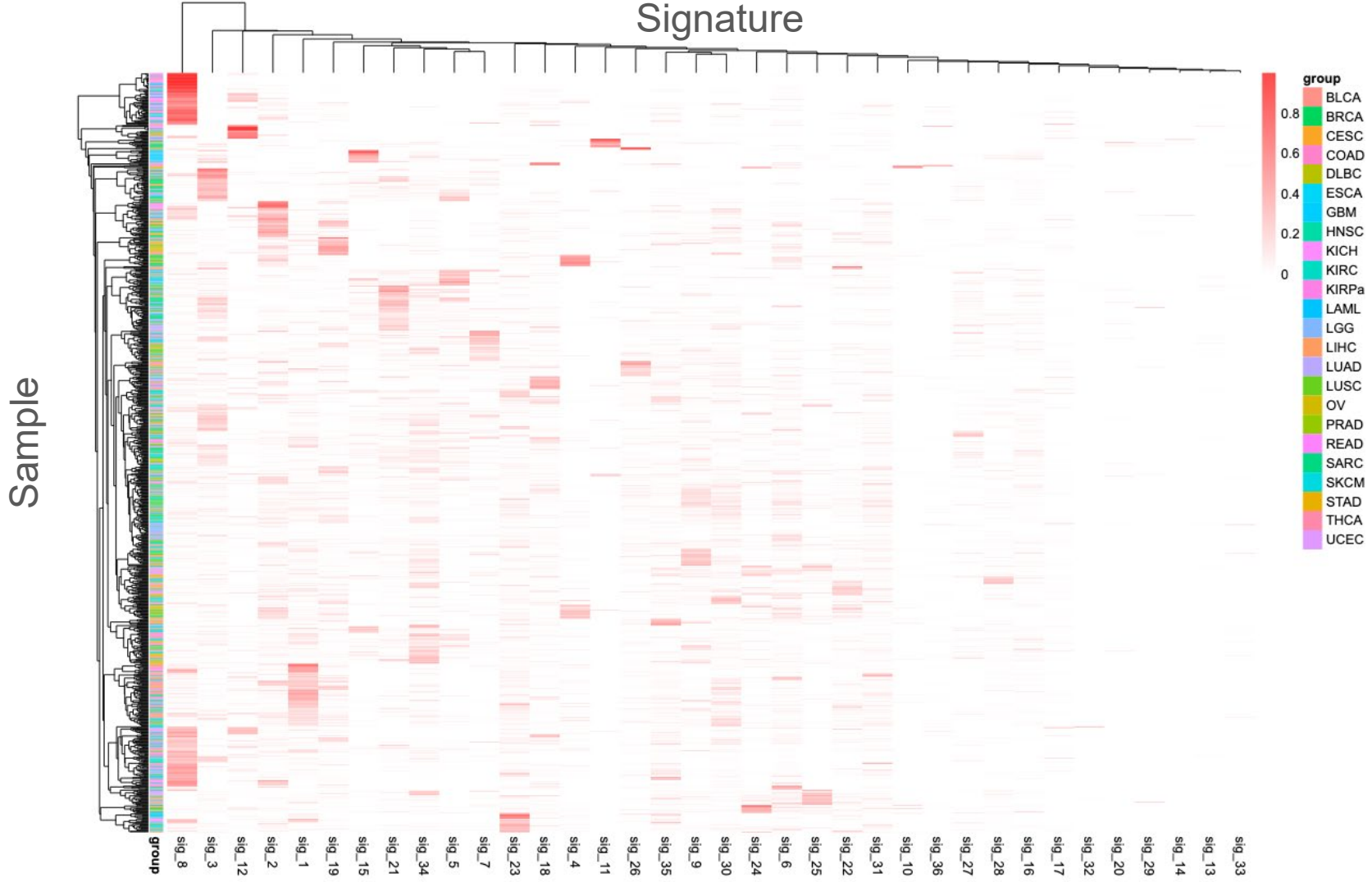
r, p

- Each feature only requires learning a few more parameters
- New features can be added without requiring a large increase in sample size to learn signatures

Analyzed 115,161 SV calls from 946 samples spanning 24 cancer types



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BRCA
CESC
COAD
DLBC
ESCA
GBM
HNSC
KICH
KIRC
KIRPa
LAML
LGG
LIHC
LUAD
LUSC
OV
PRAD
READ
SARC
SKCM
STAD
THCA
UCEC
0.8
0.6
0.4
0.2
0
group
sig_8
sig_3
sig_12
sig_2
sig_1
sig_19
sig_15
sig_21
sig_34
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sig_7
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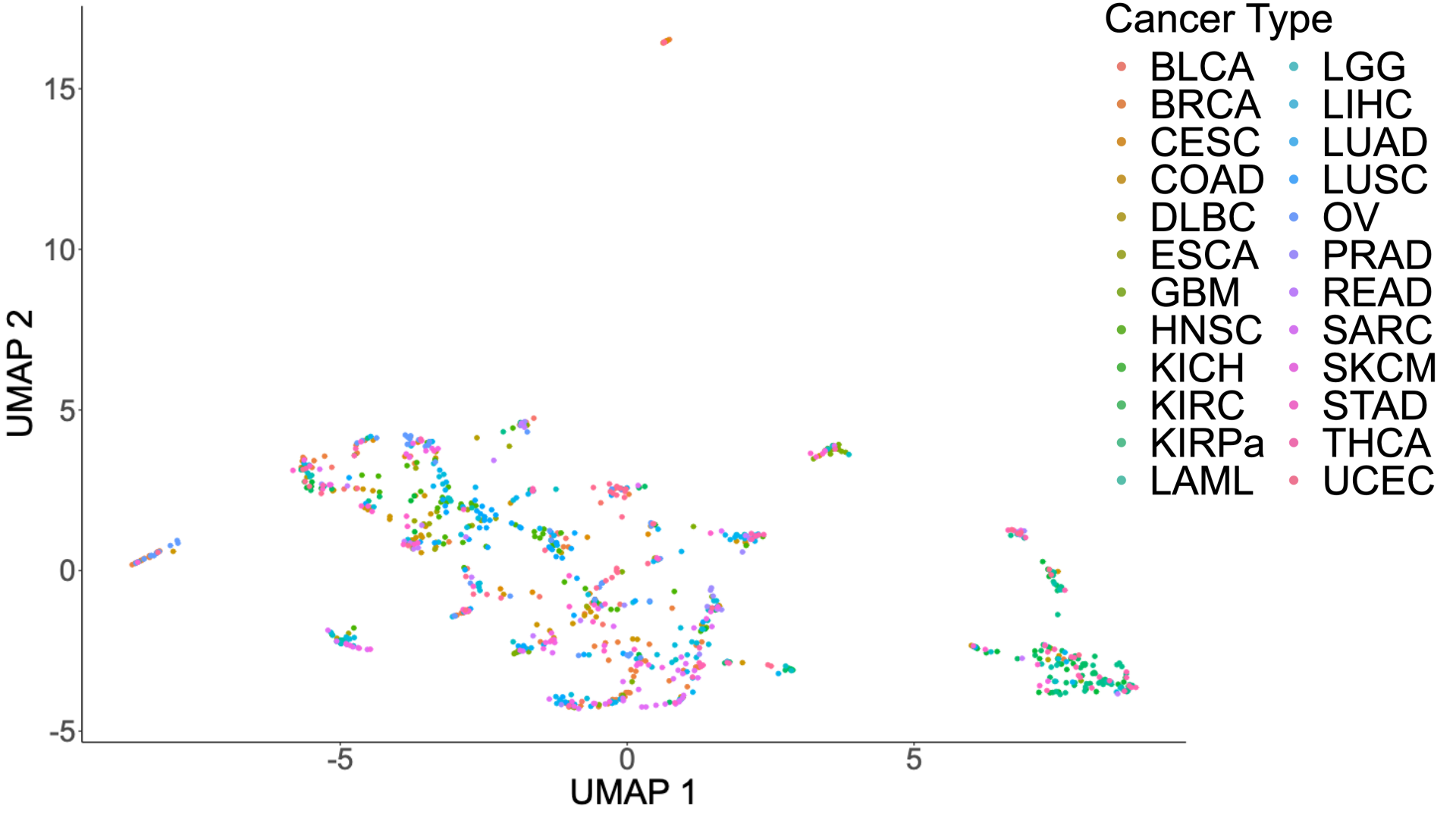
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LUAD
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READ
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15
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5
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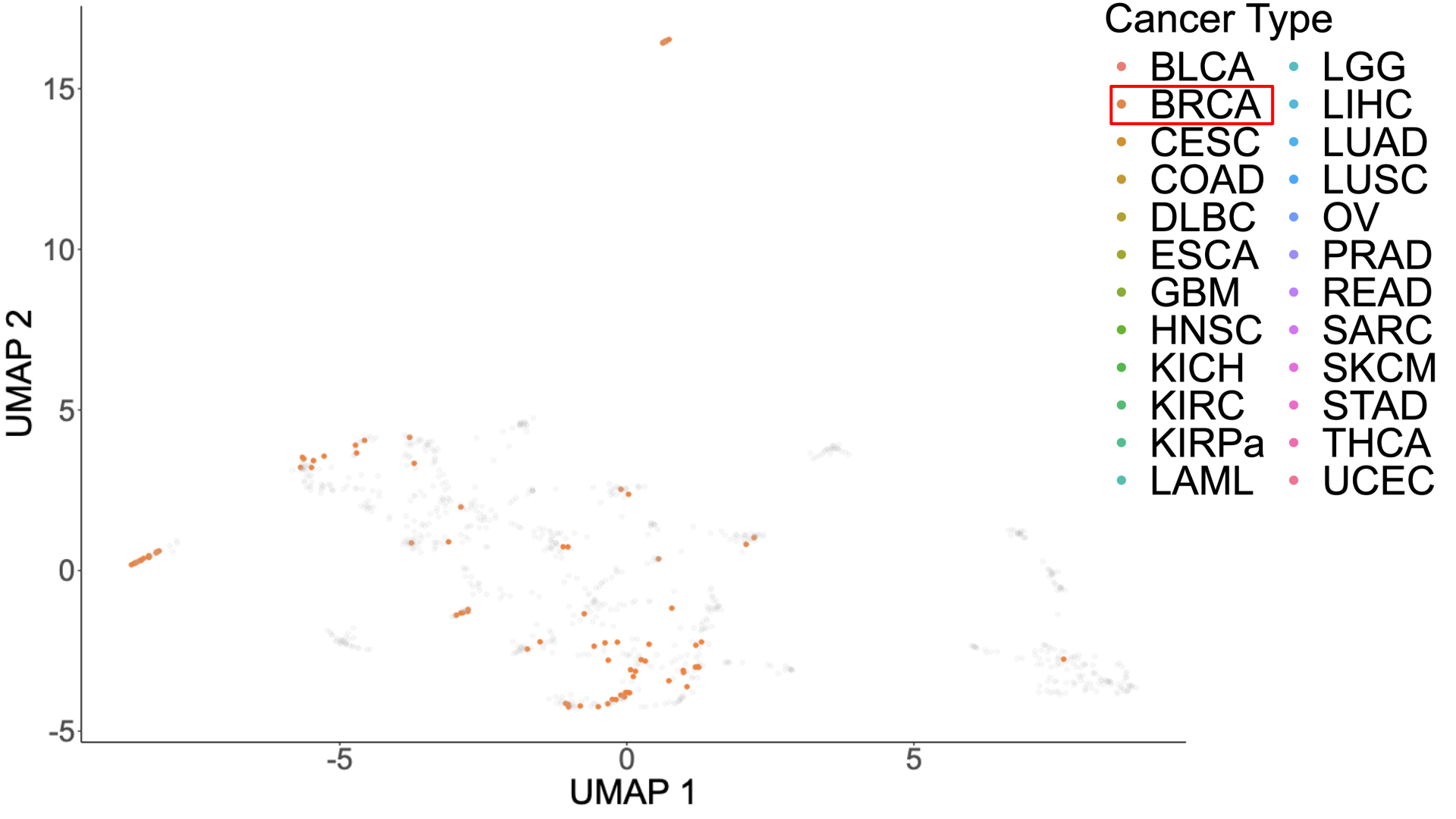
0
5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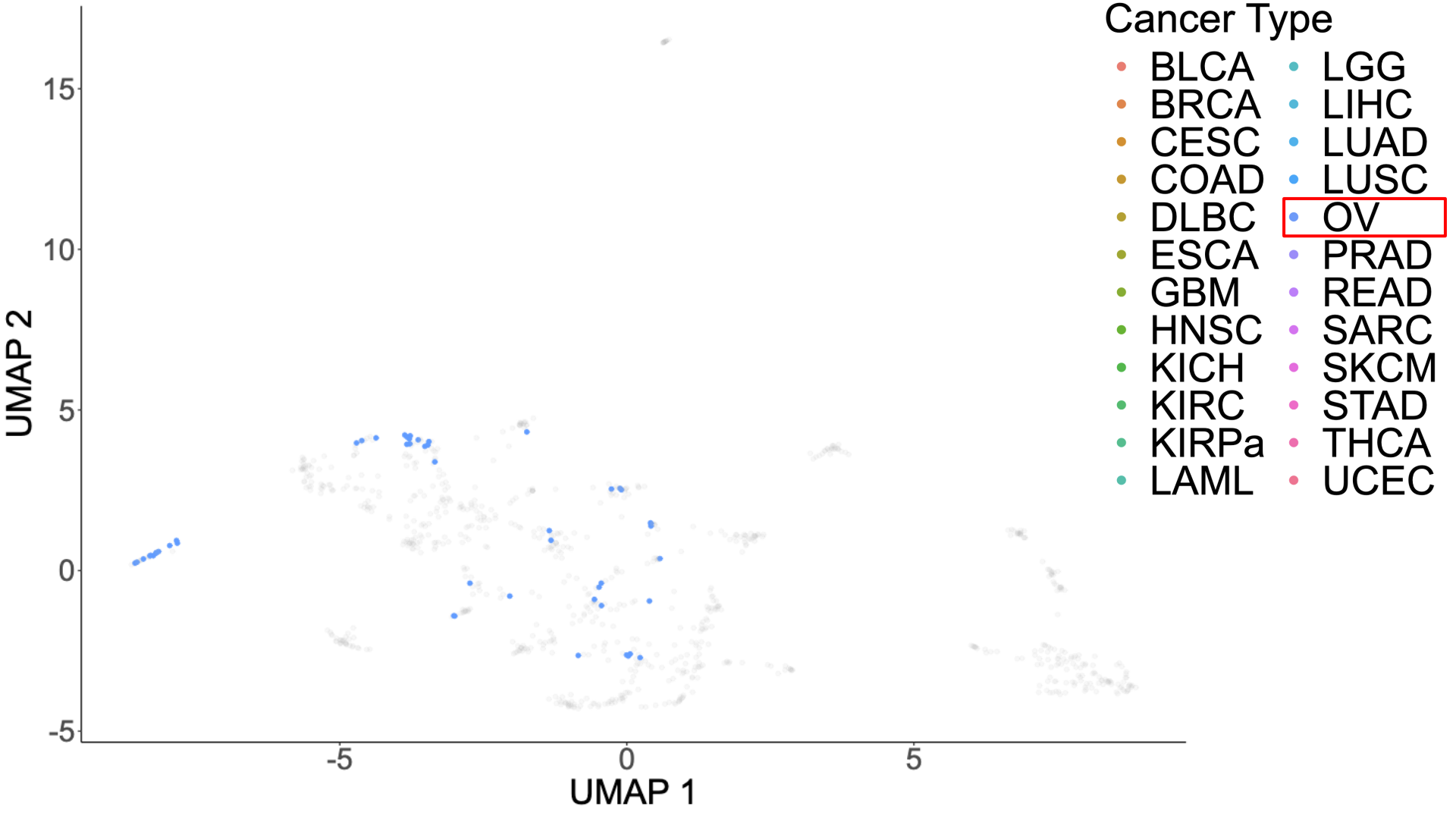
-5
-5
0
5
UMAP 1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UMAP 2
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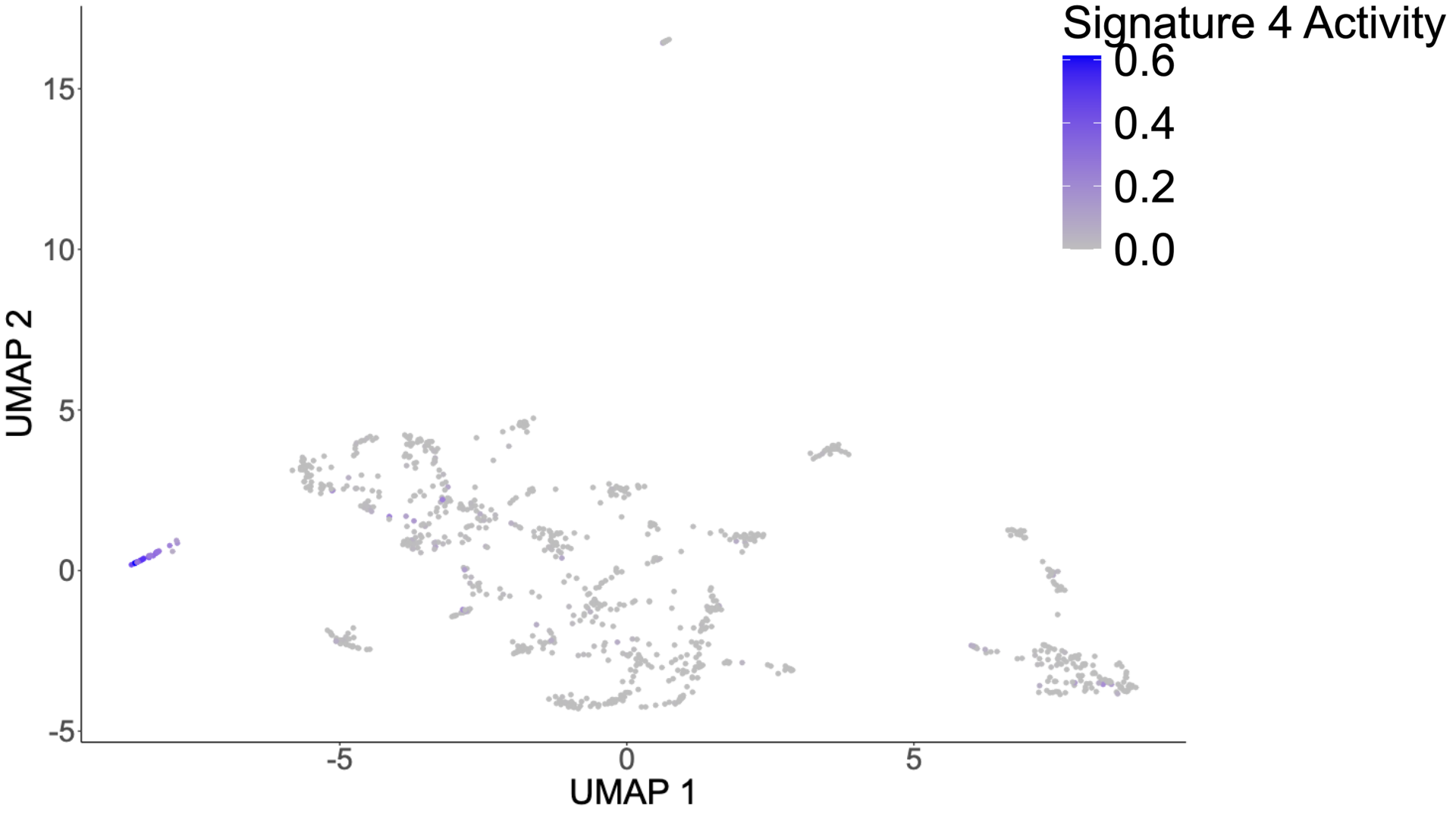
UMAP 1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10
5
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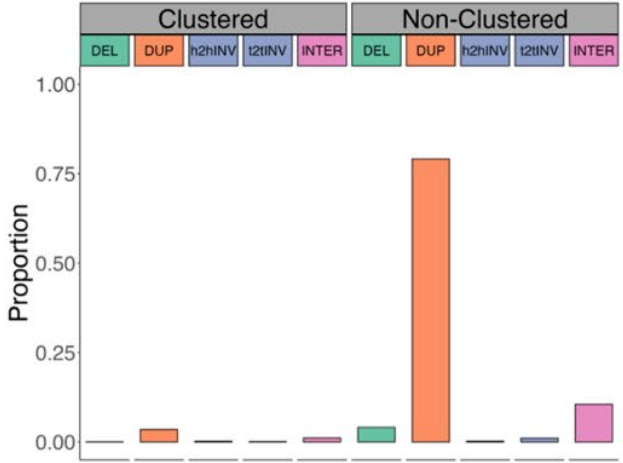
-5
UMAP 2
-5
0
5
UMAP 1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Non-Clustered
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DUP
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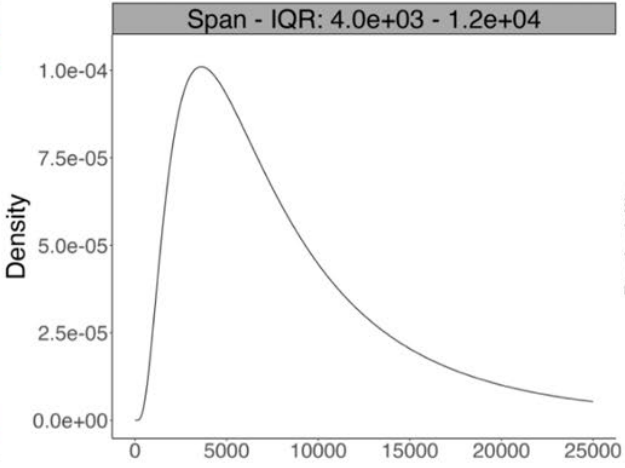
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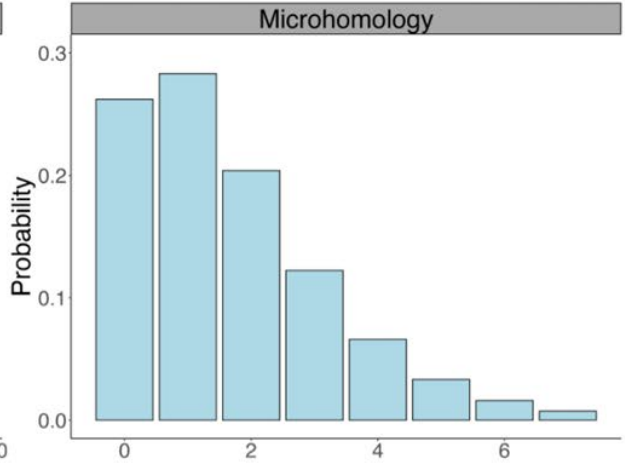
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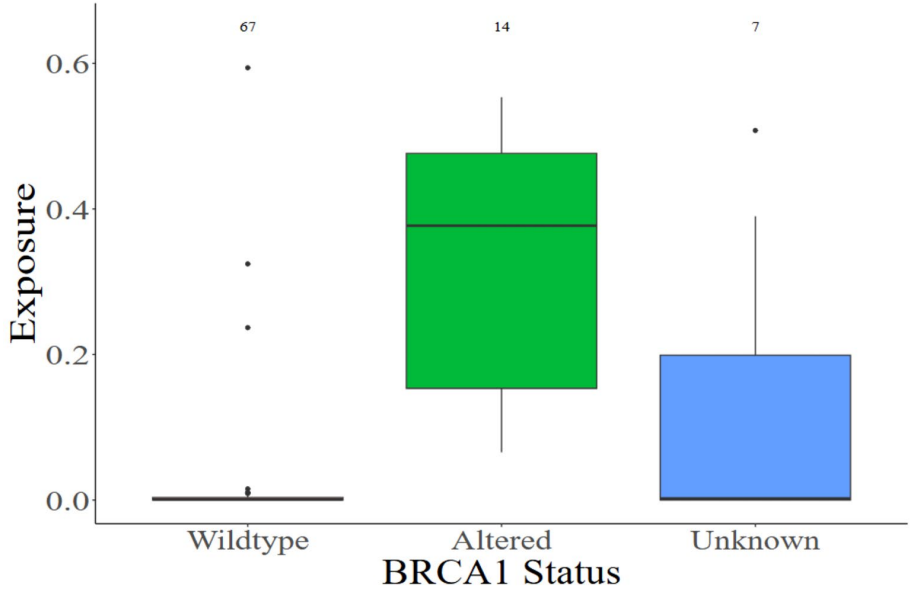
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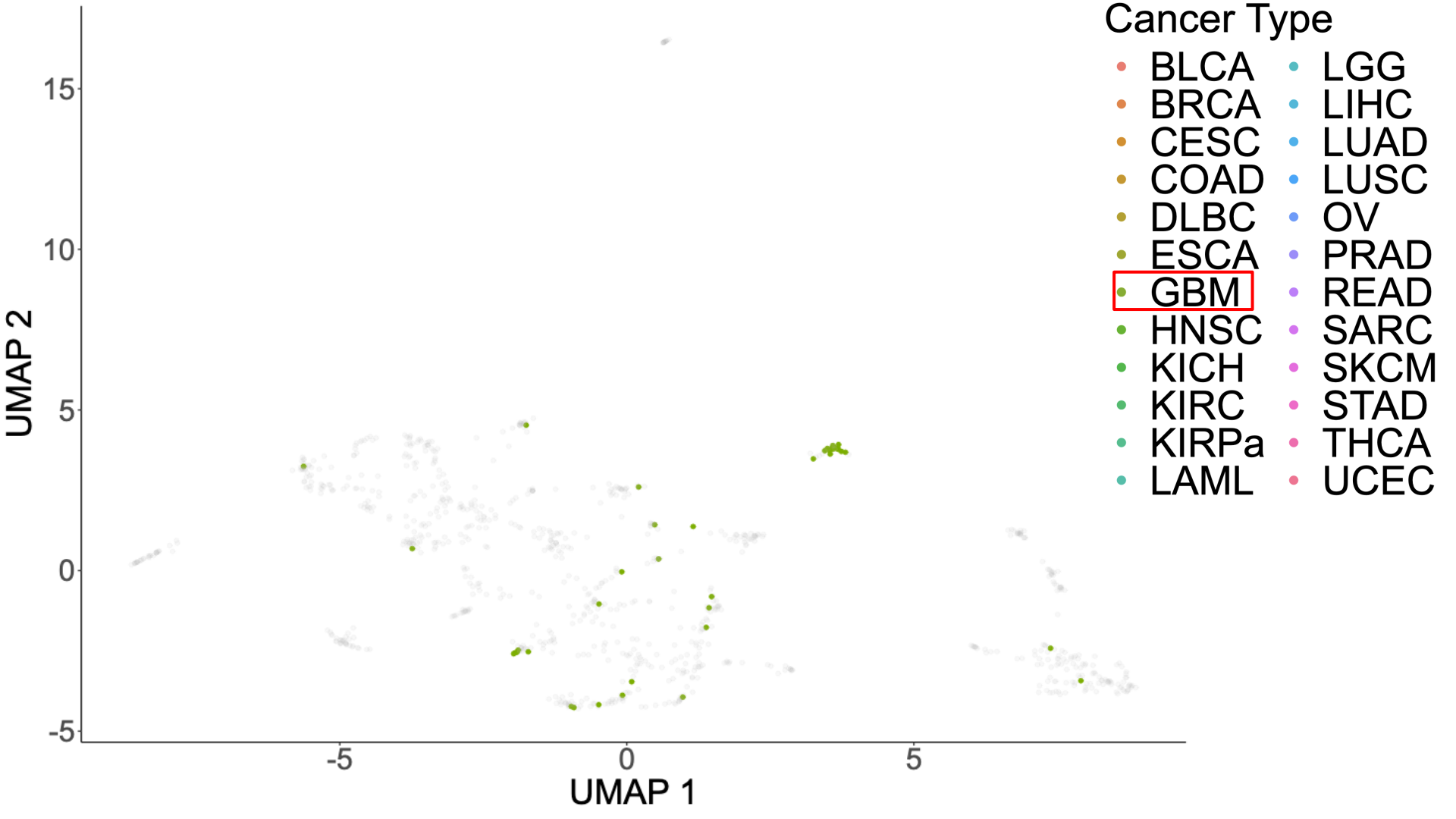
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DLBC
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LUAD
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OV
PRAD
READ
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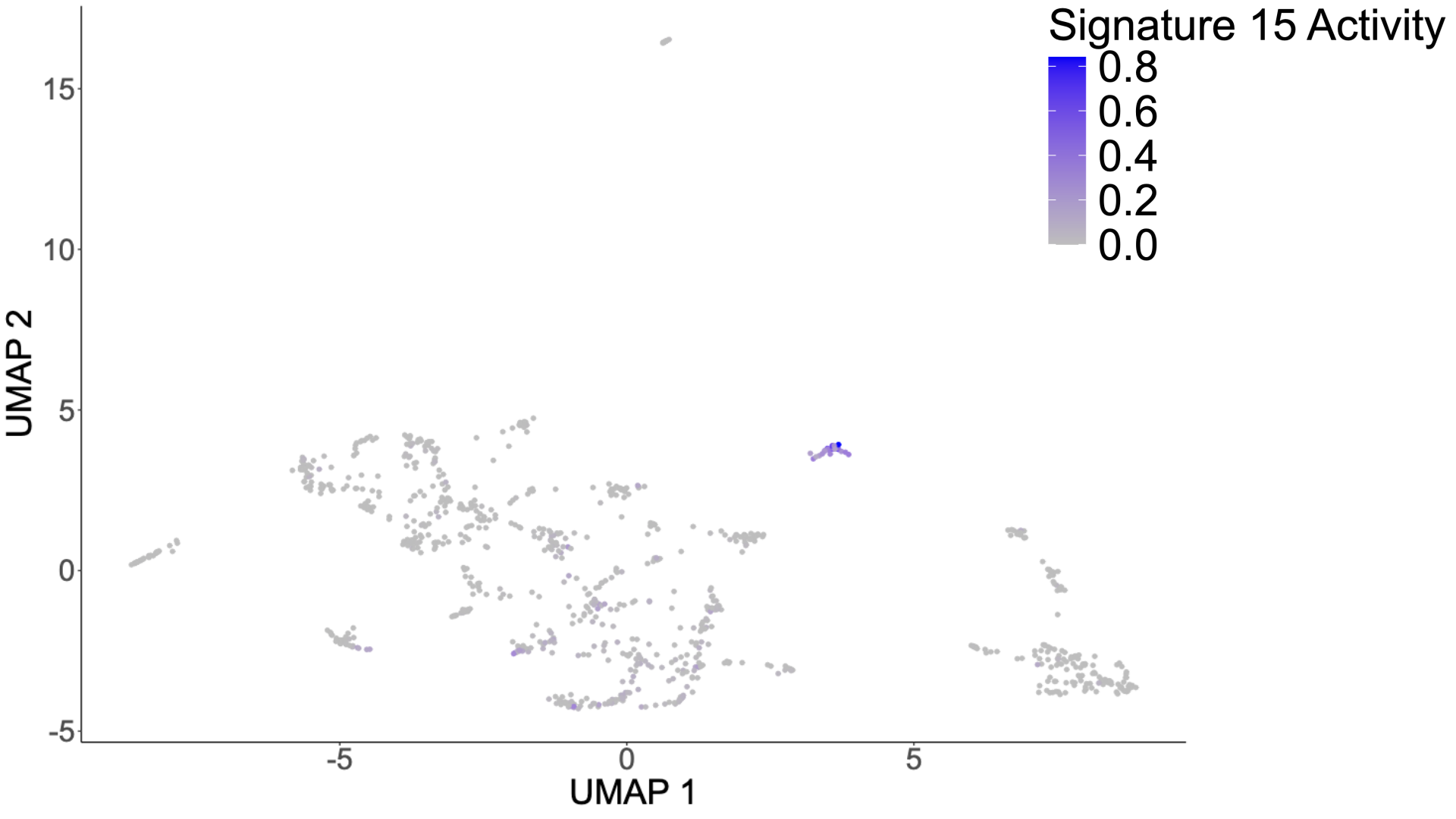
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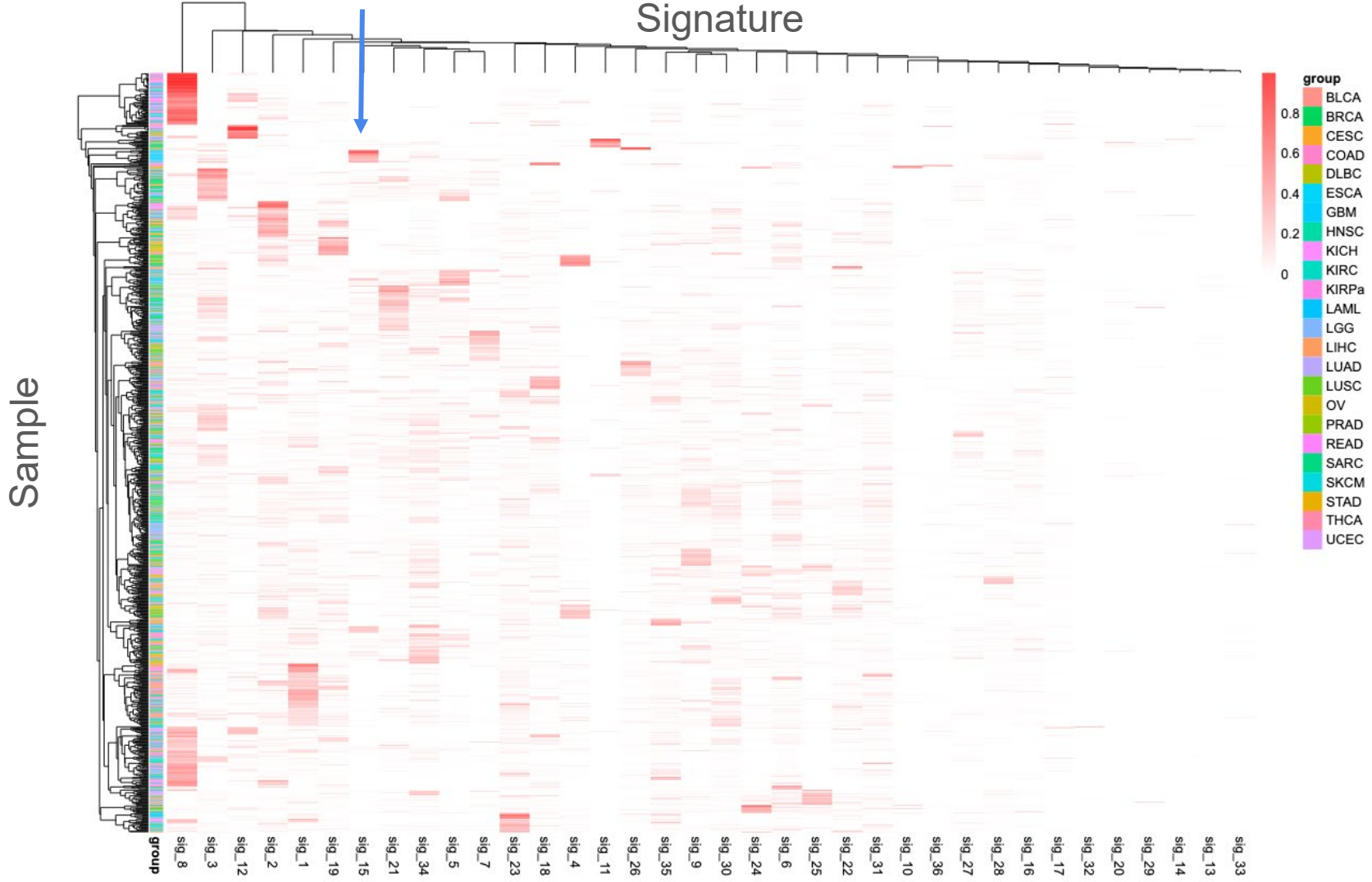
UMAP 1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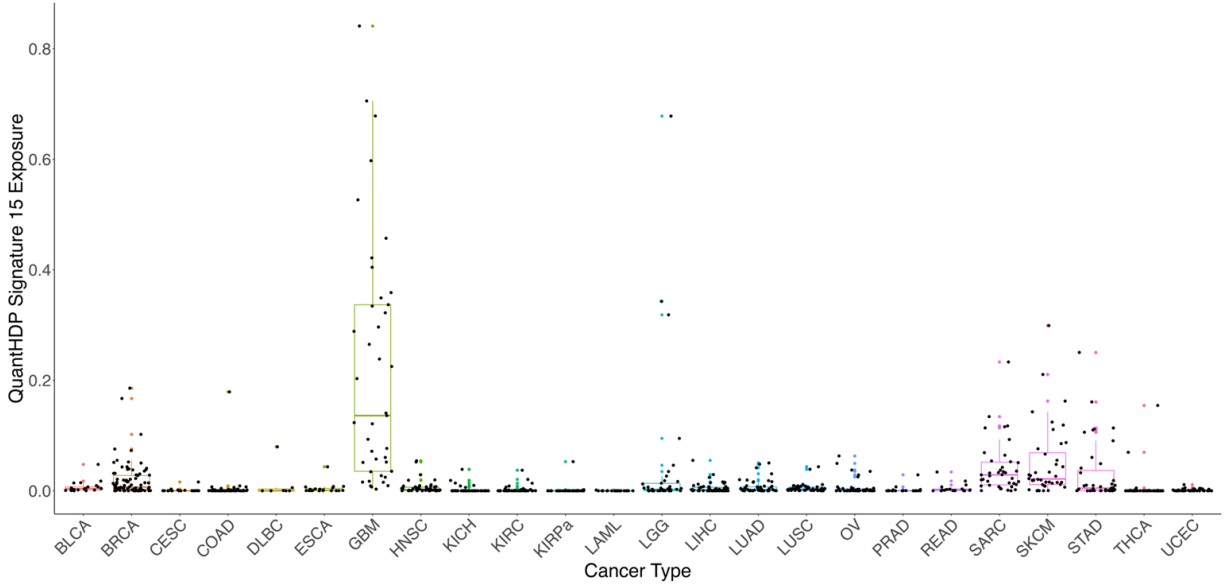
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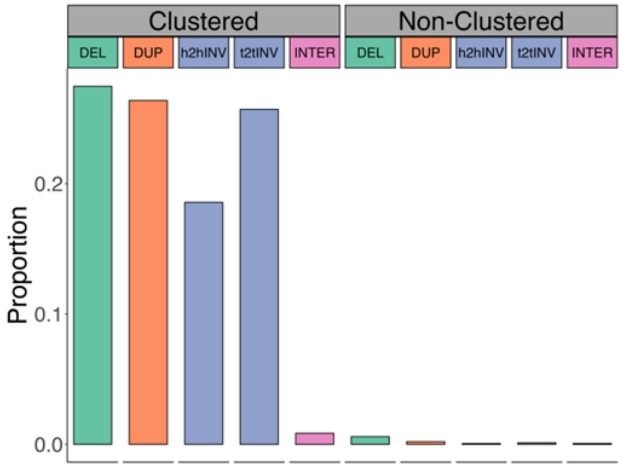
THCA
UCEC
Cancer Type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Non-Clustered
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t2tINV
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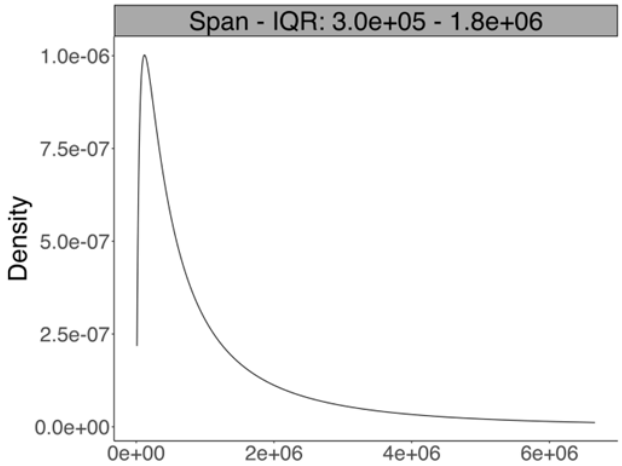
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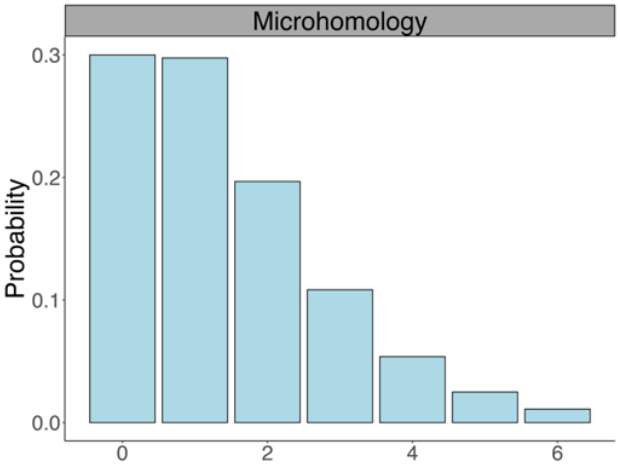
Microhomology
Probability
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0.2
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0
2
4
6

Future Directions

- Validate signatures through analysis of independent datasets, including a pan-cancer cohort of metastatic tumors from the Hartwig Medical Foundation
- Establish signature etiologies
  - Correlate signature activities with CRISPR dependencies
  - Identify up/down-regulated gene expression modules in samples with high signature activity

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- Stephen Jasina
- Jonathon Jacobs
- Noor Sohail
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