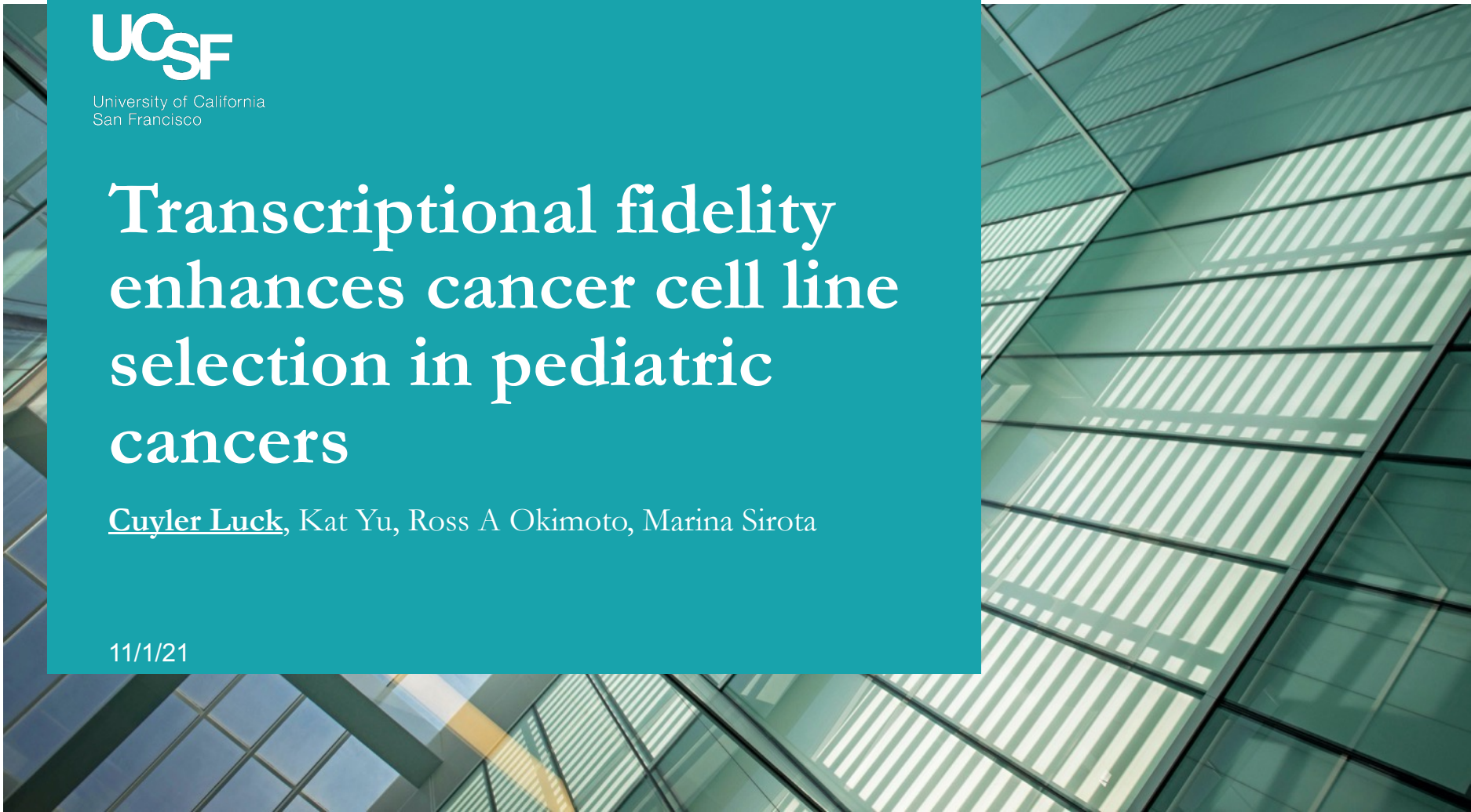


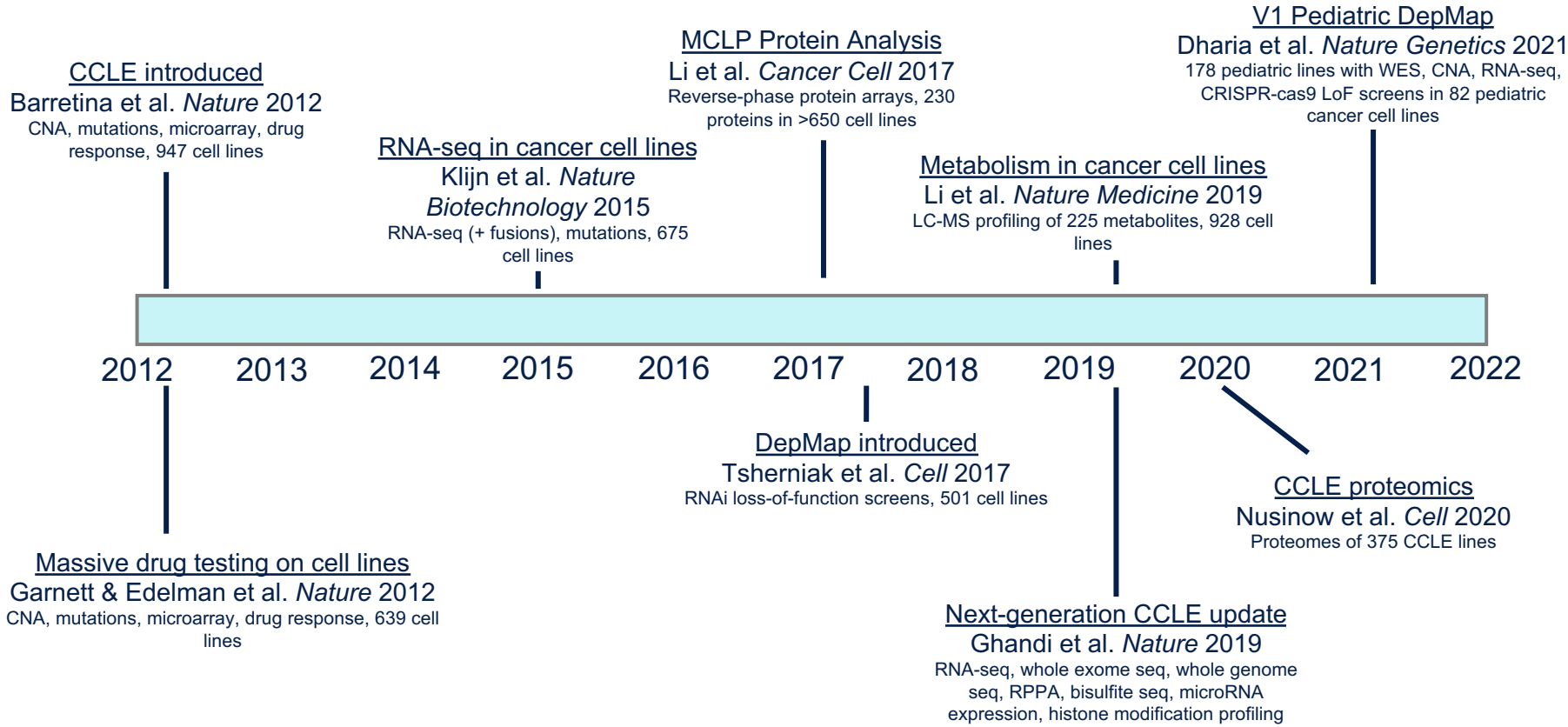
University of California
San Francisco

Transcriptional fidelity enhances cancer cell line selection in pediatric cancers

Cuyler Luck, Kat Yu, Ross A Okimoto, Marina Sirota

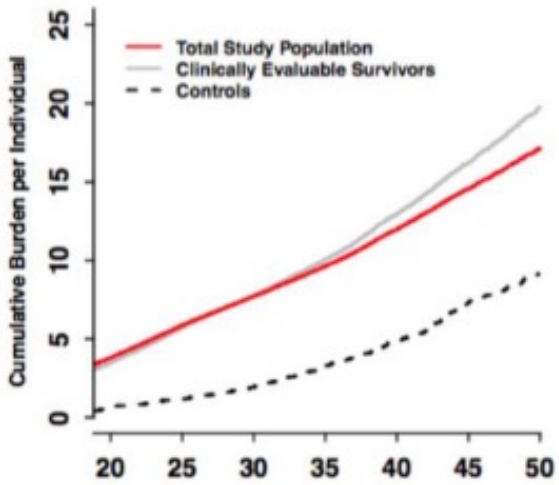
11/1/21

Characterization of Cancer Cell Lines



Current Outlook of Childhood Cancers

Chase Center
Seats 18,604



>11,000 est. 2021 cases, >1,200 est. 2021 deaths among children & adolescents

~86% 5-year relative survival all cancers, children/adolescents

Siegel et al. *CA CANCER J CLIN* 2021

Chronic health conditions (low and high grade) ~2x higher than community controls

Bhakta et al. *The Lancet* 2017

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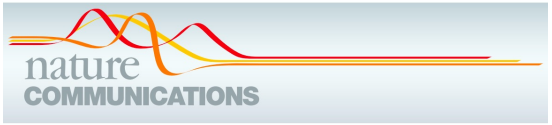
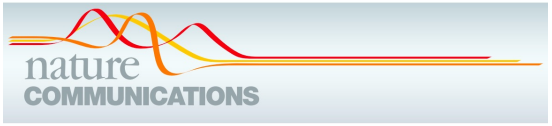
Previous Work – Mostly Adult or Broad Pediatrics



https://doi.org/10.1038/s41467-020-20294-x OPEN

Global computational alignment of tumor and cell line transcriptional profiles

Allison Warren[1], Yejia Chen[1], Andrew Jones[1], Tsukasa Shibue[1], William C. Hahn[1,2,3], Jesse S. Boehm[1], Francisca Vazquez[1], Aviad Tsherniak[1,4] & James M. McFarland[1,4]✉



https://doi.org/10.1038/s41467-019-11415-2 OPEN

Comprehensive transcriptomic analysis of cell lines as models of primary tumors across 22 tumor types

K. Yu[1,2], B. Chen[3,4], D. Aran[1], J. Charalel[5], C. Yau[6,7], D.M. Wolf[7], L.J. van 't Veer[8], A.J. Butte[1,2], T. Goldstein[1] & M. Sirota[1,2]

A first-generation pediatric cancer dependency map

Neekesh V. Dharia[1,2,3,4], Guillaume Kugener[3,7], Lillian M. Guenther[1,2,3,4], Clare F. Malone[1,2,3,4], Adam D. Durbin[1,2,3,4,8], Andrew L. Hong[1,2,3,4,9], Thomas P. Howard[1,2,3,4,5], Pratiti Bandopadhayay[1,2,3,4], Caroline S. Wechsler[1,2,3,4], Iris Fung[3], Allison C. Warren[3], Joshua M. Dempster[3], John M. Krill-Burger[3], Brenton R. Paolella[3], Phoebe Moh[3,10], Nishant Jha[3], Andrew Tang[3], Philip Montgomery[3], Jesse S. Boehm[3], William C. Hahn[3,4,5], Charles W. M. Roberts[6], James M. McFarland[3], Aviad Tsherniak[3], Todd R. Golub[1,2,3,4], Francisca Vazquez[3,5]✉ and Kimberly Stegmaier[1,2,3,4]✉

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Goal: to create a public resource for pediatric cancer researchers to choose cell lines based on transcriptomic similarity to primary tumor samples

Transcriptional fidelity enhances cancer cell line selection in pediatric cancers

https://comphealth.ucsf.edu/app/pecan

Cuyler Luck, Katharine Yu, Ross A. Okimoto, Marina Sirota

doi: https://doi.org/10.1101/2021.10.01.462682

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Data Overview

Treehouse CHILDHOOD CANCER INITIATIVE

12,747 tumor samples

912 cell lines

All RNA-seq processed with Toil pipeline

age_at_dx <= 18

Use CCLE annotations file for cell line disease information

1,655 tumor samples spanning 12 tumor types

799 cell lines spanning 29 TCGA codes

Integrate data for correlation analysis

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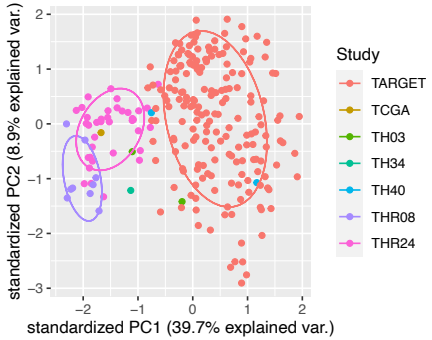
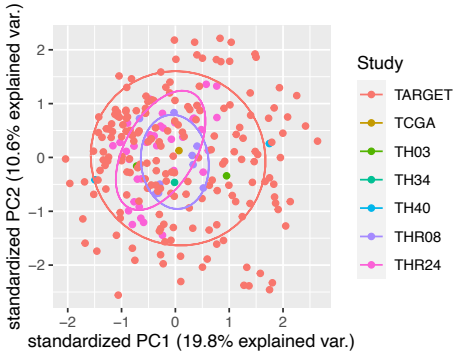
Data Analysis



Acute myeloid leukemia

ComBat

batch = study of origin

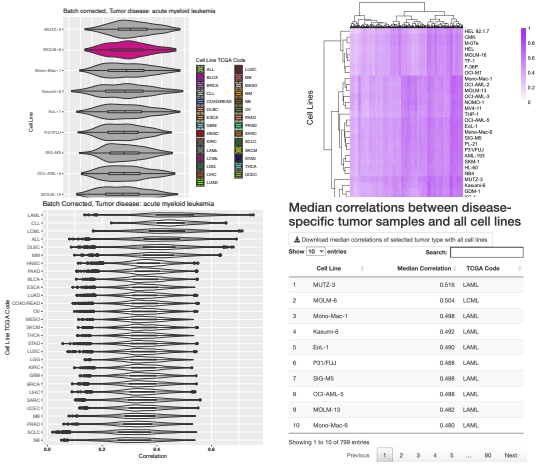


Acute myeloid leukemia

Cell line expression data

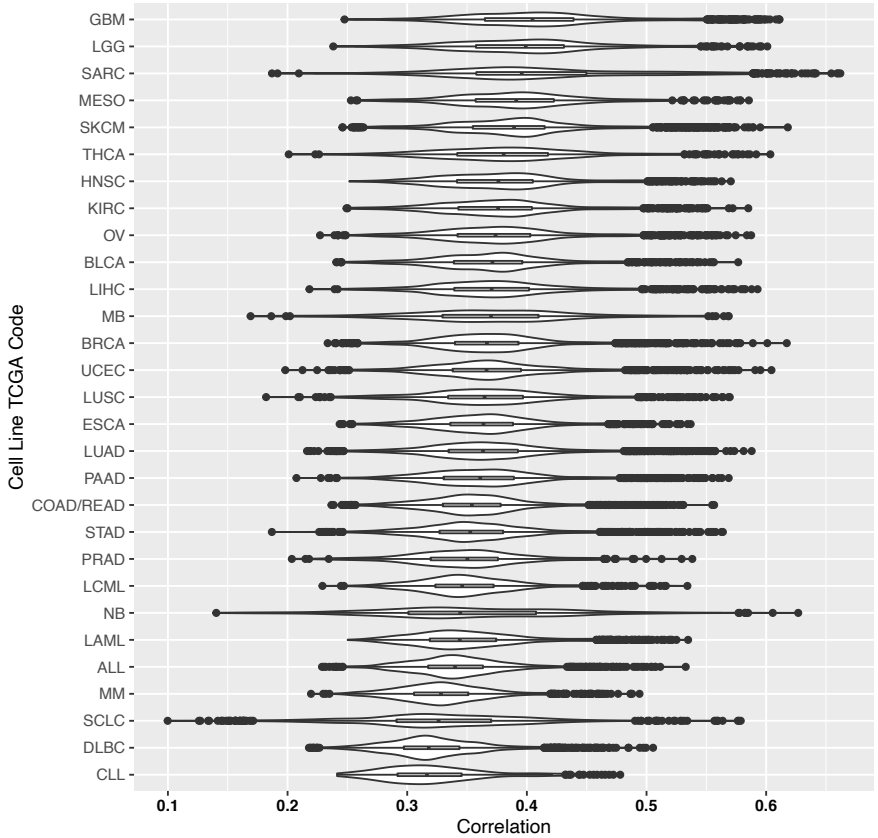
Merge with cell line data

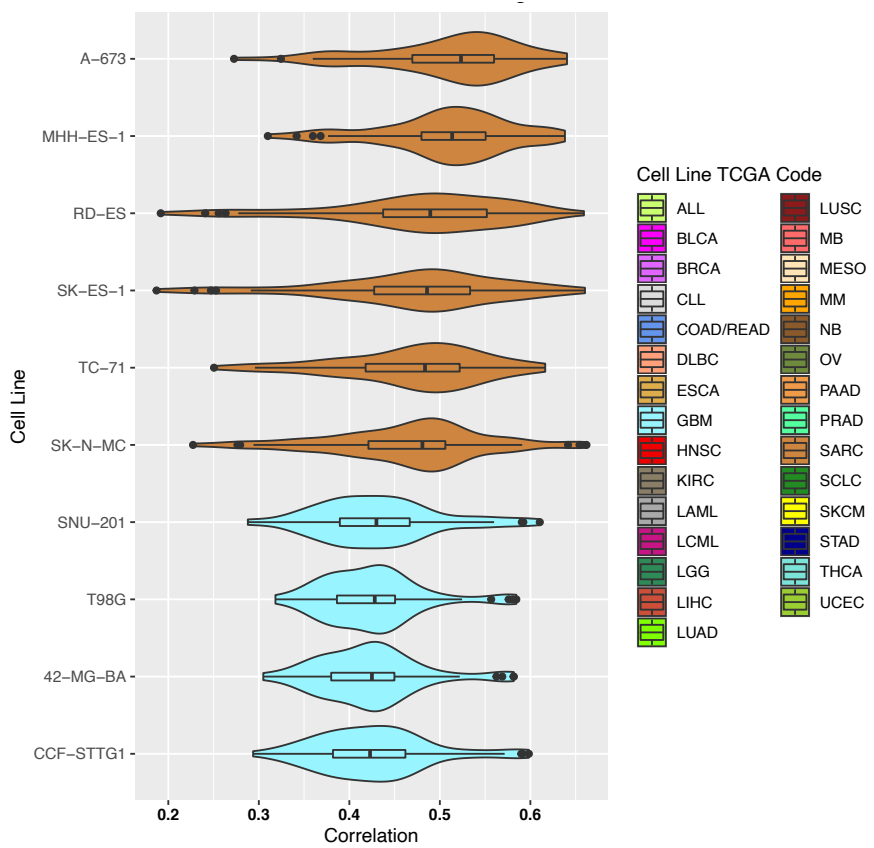
Calculate Spearman correlation coefficients



https://pecanexplorer.org

Case Study: Ewing Sarcoma





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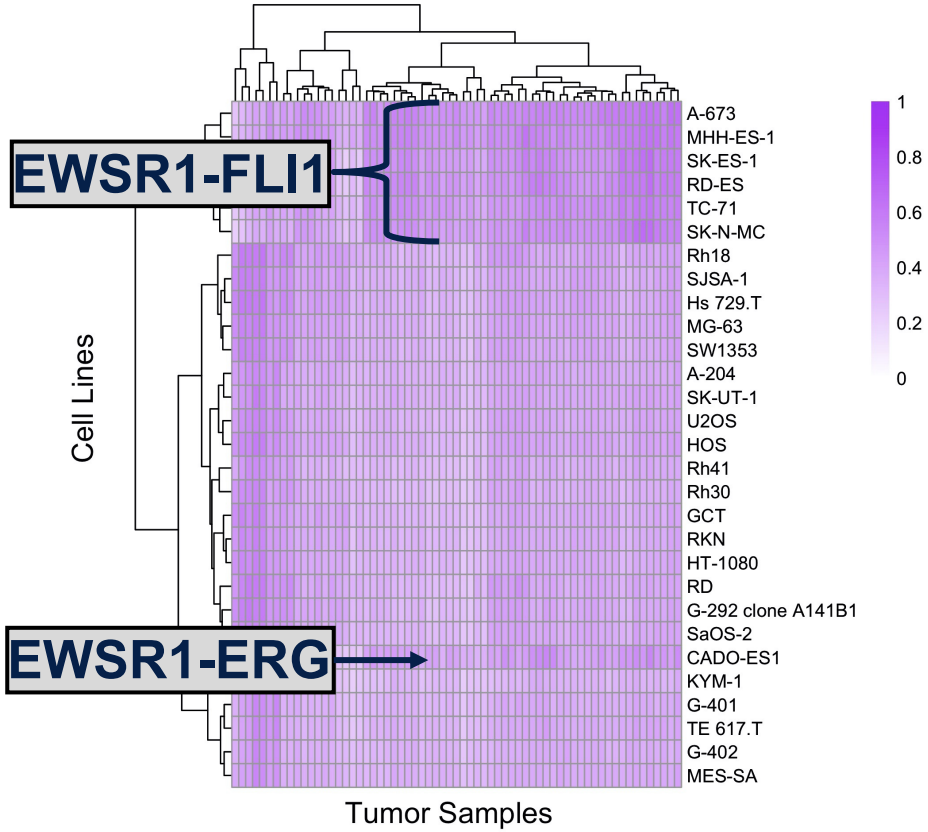
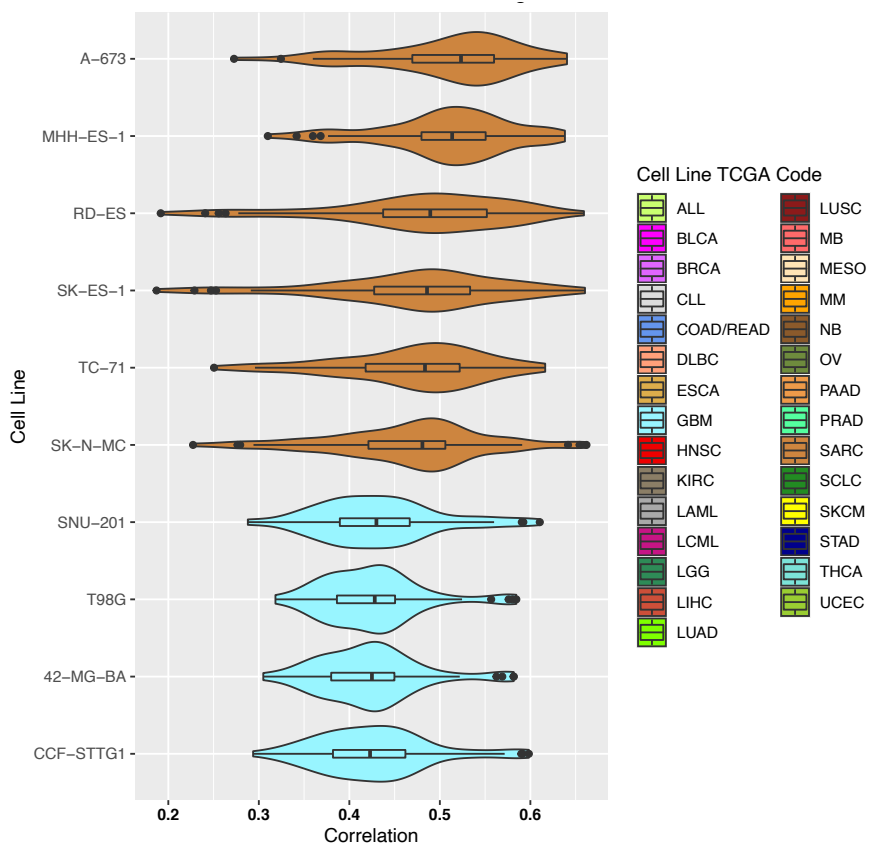
Case Study: Ewing Sarcoma





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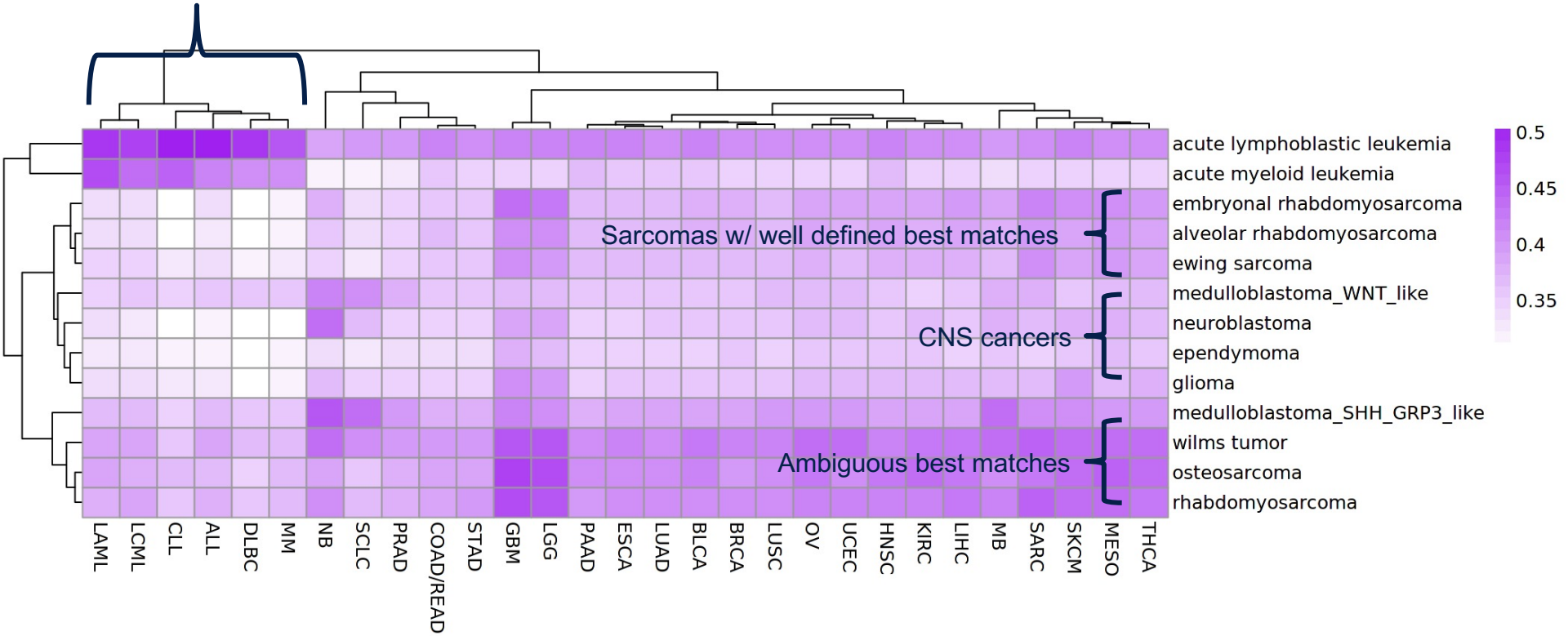
Global Overview

Blood cancers



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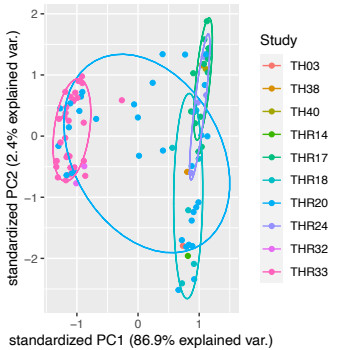
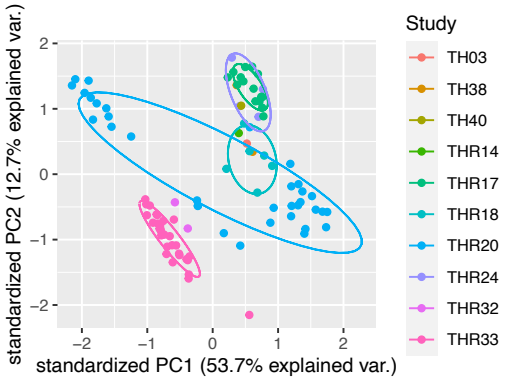
Medulloblastoma data – bad or interesting?

TPM

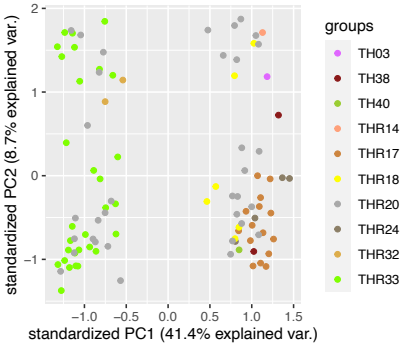


ComBat

batch = study of origin

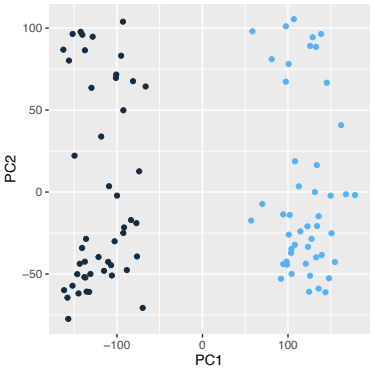


Expected counts



K-means

K=2



edgeR
DGE Analysis

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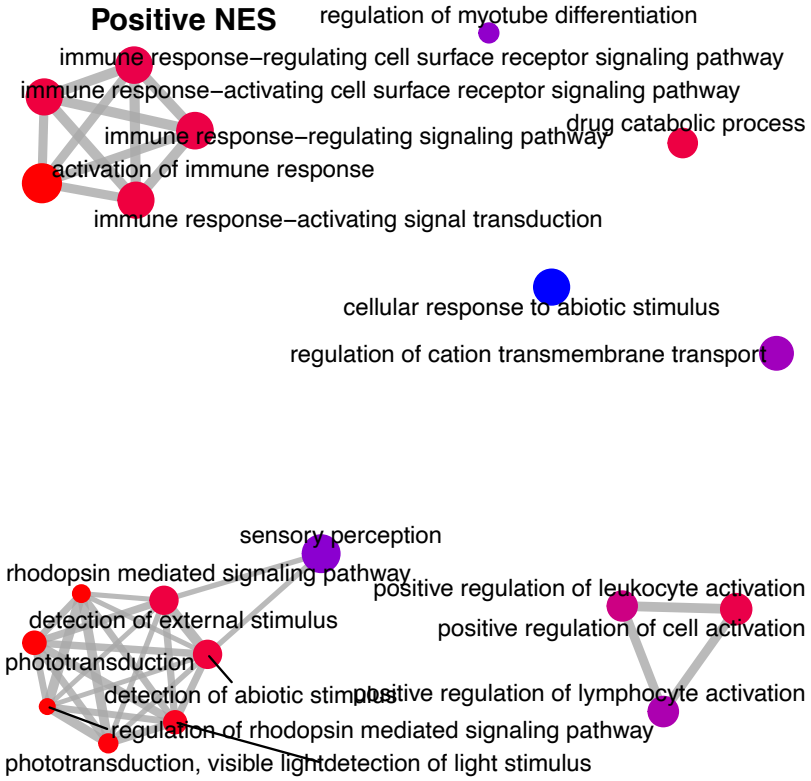
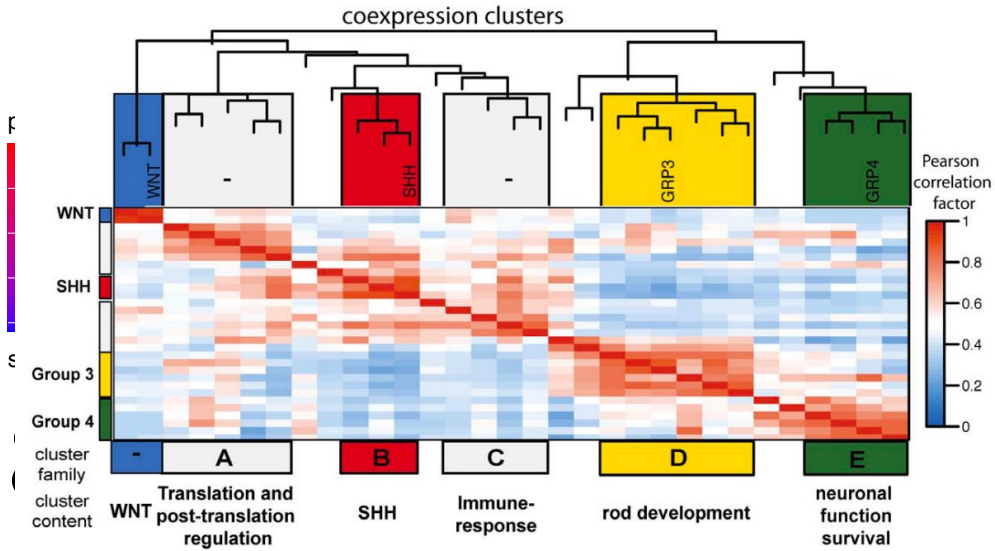
Inference of MB molecular subtypes





Hooper et al. *PLoS ONE* 2014

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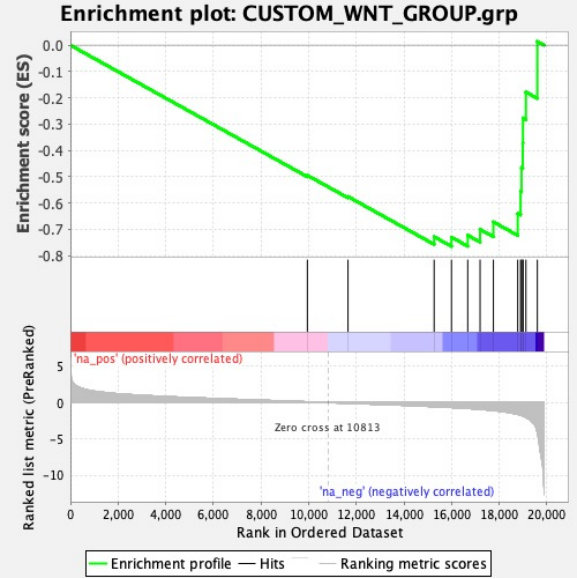
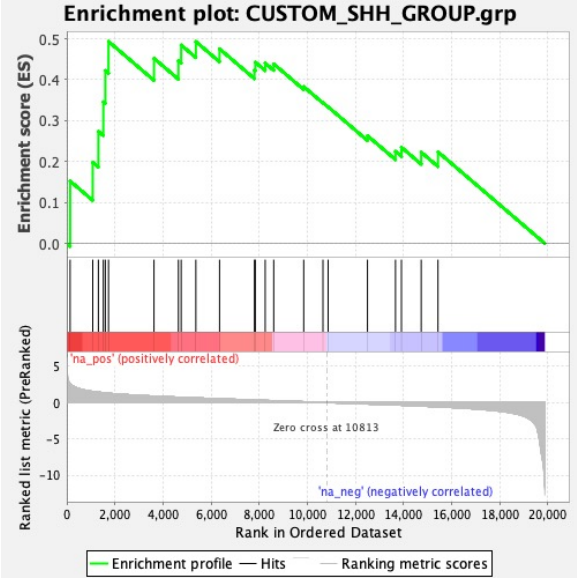
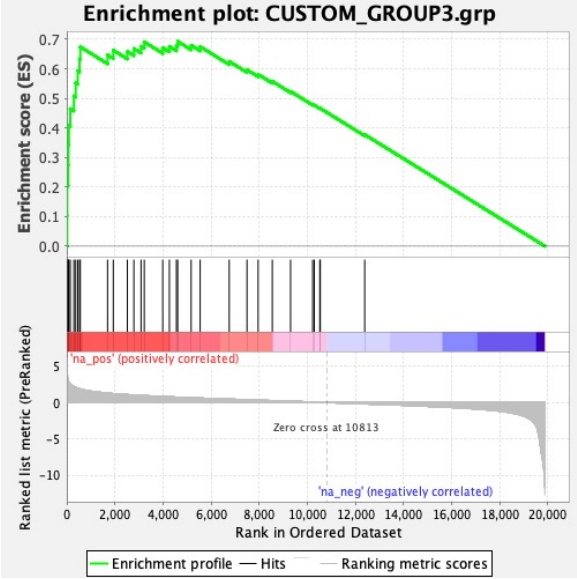
WNT, SHH, and Group 3 MB gene expression signatures are enriched in DGE groups







Group 4: no significant enrichment

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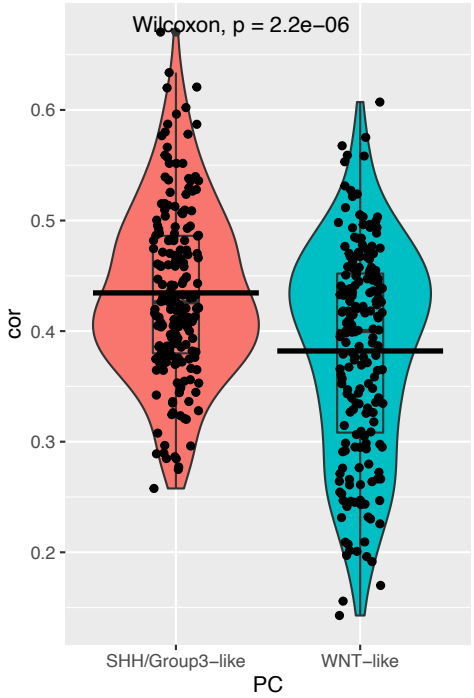
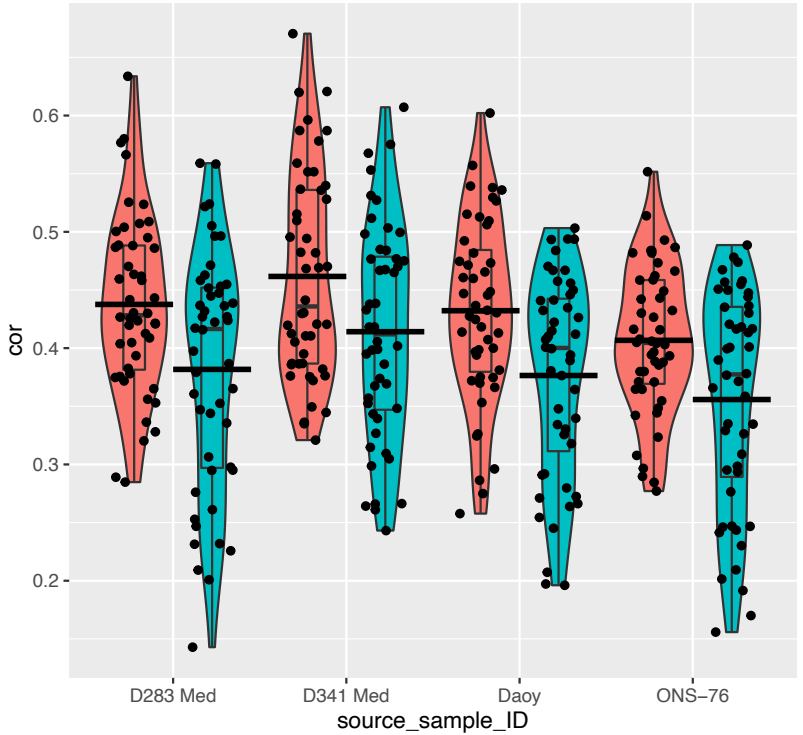
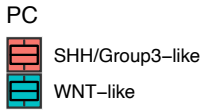
Impact of MB subtype on correlations with MB lines



All Wilcoxon FDR p < 0.05





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Conclusions

- Created an interactive public resource to guide cell line selection for pediatric cancer researchers
  - https://pecanexplorer.org

- Showed that molecular subtype can influence representation by cell lines
  - We add to the call for more WNT/Group 4 MB cell lines

Thank you!

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