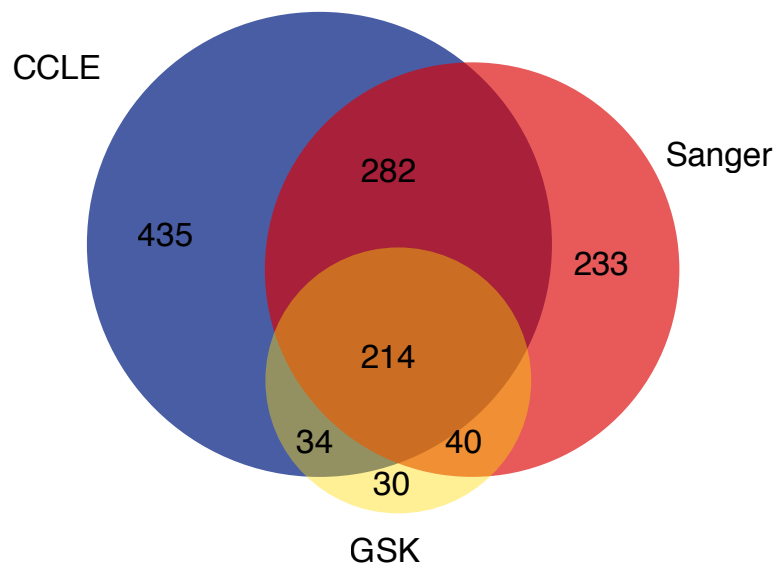
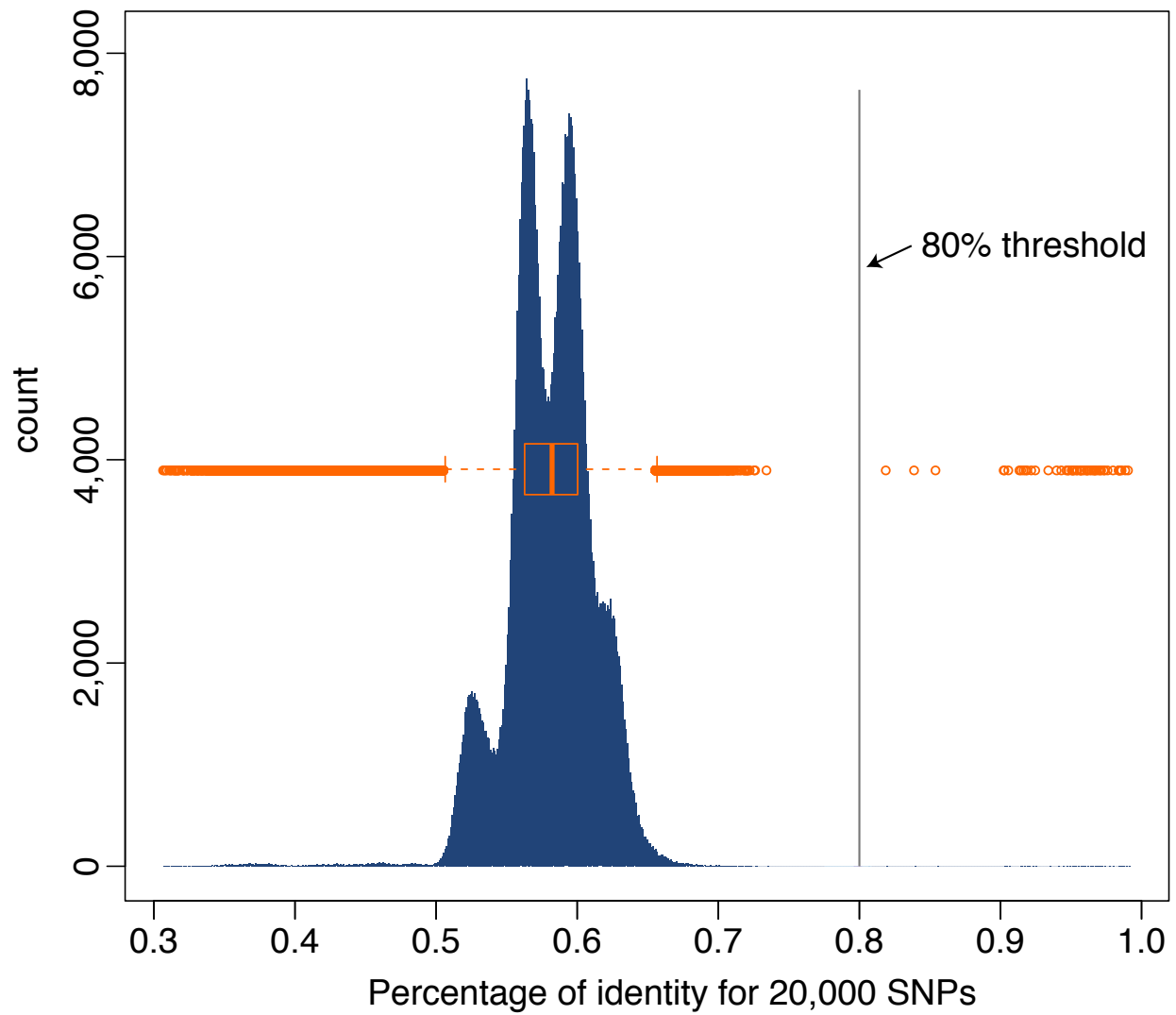


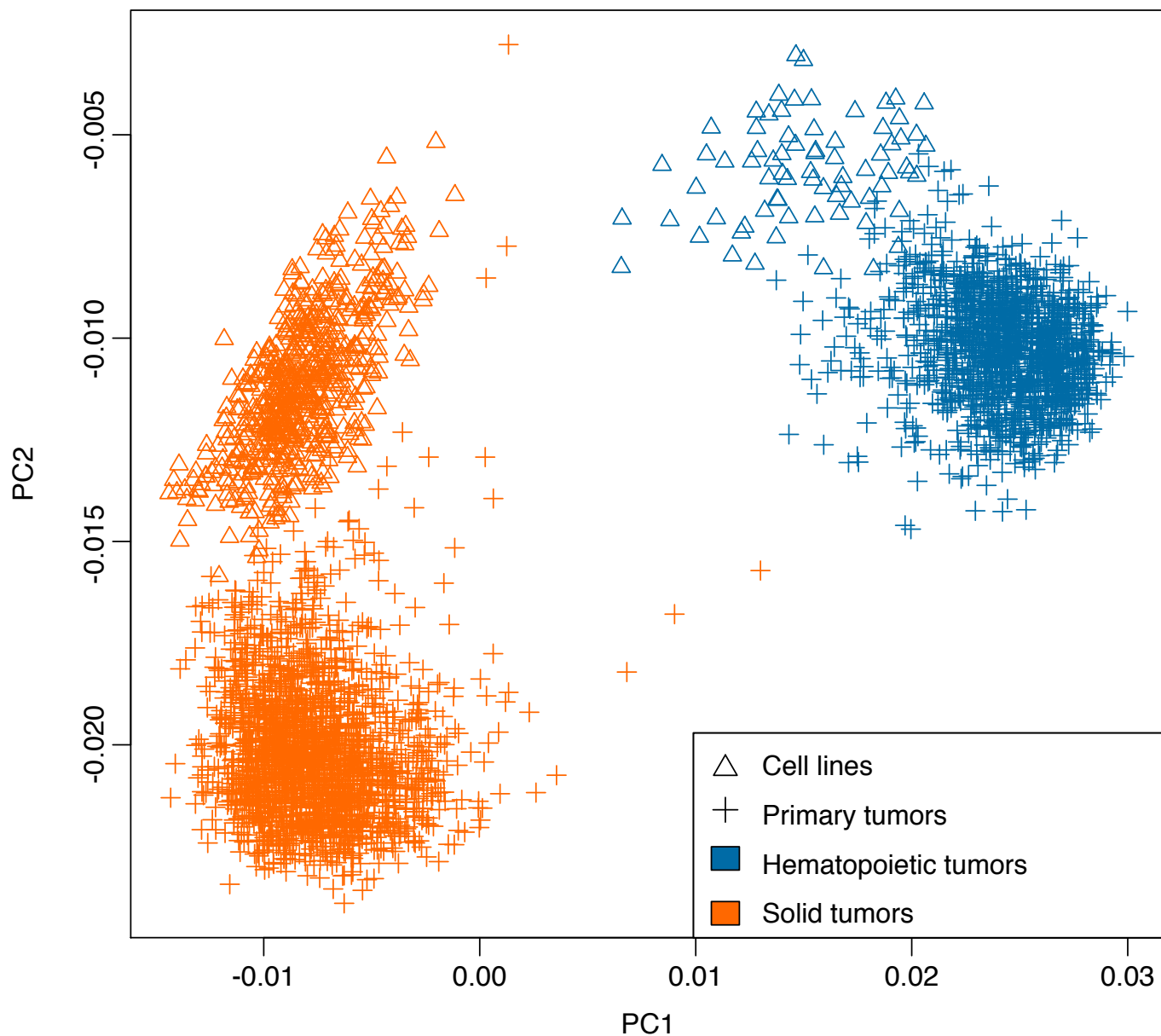
Supplementary Figure 1: Matrix-representation of point mutation data derived from hybrid capture/sequencing (a) or OncoMap analysis (b) across all CCLE cell lines. Blue bars indicate detection of at least one mutation in the relevant gene. Cell lines are sorted by lineage and cancer gene mutation frequency. The genes are sorted by mutation frequency in the hybrid capture data.



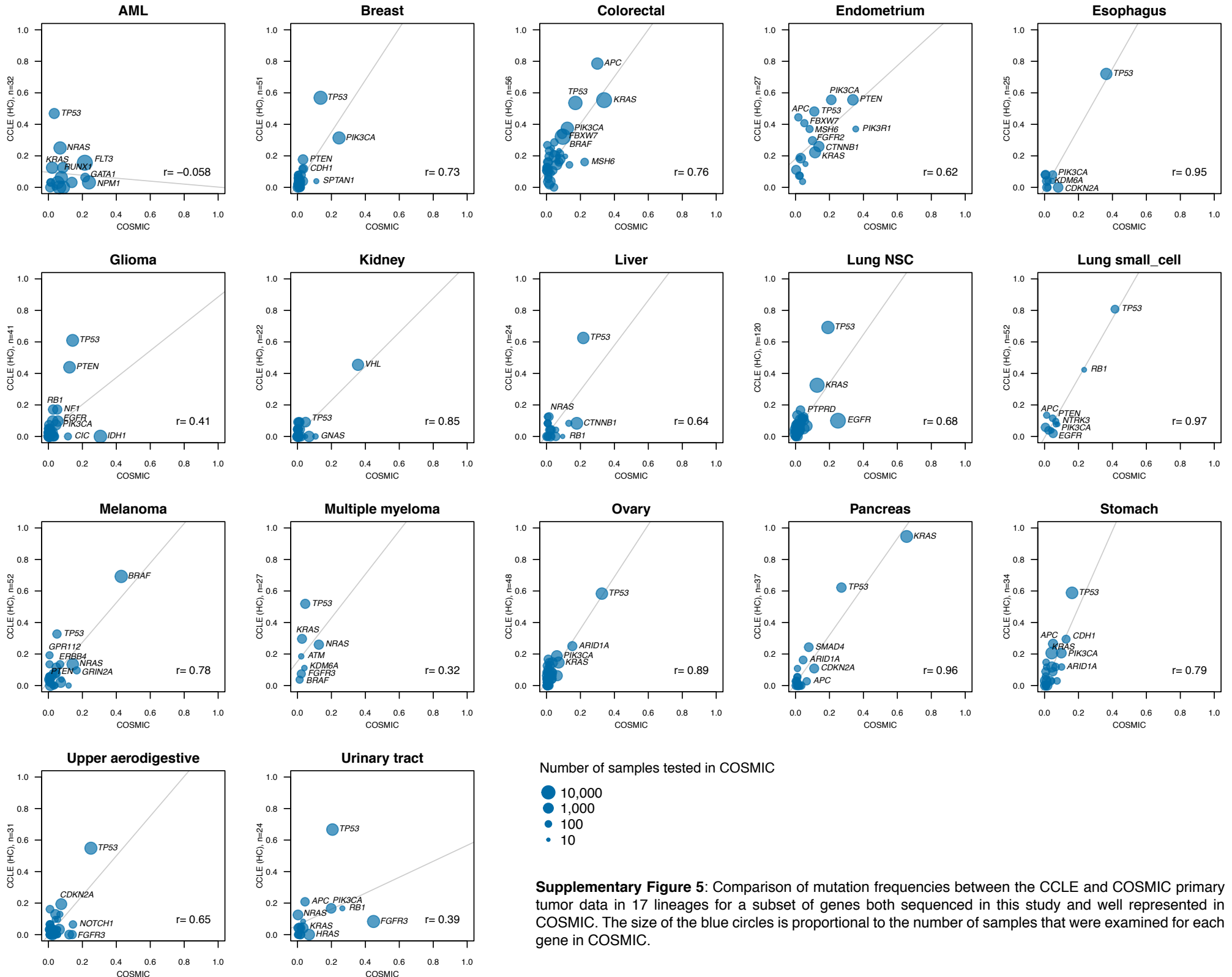
Supplementary Figure 2: Venn diagram of overlap between the cell lines in the CCLE, the Sanger Institute's Cancer Cell Line Project (<http://www.sanger.ac.uk/genetics/CGP/CellLines/>) and the GlaxoSmithKline (GSK) Cancer Cell Line Genomic Profiling dataset (https://cabig.nci.nih.gov/caArray_GSKdata/).

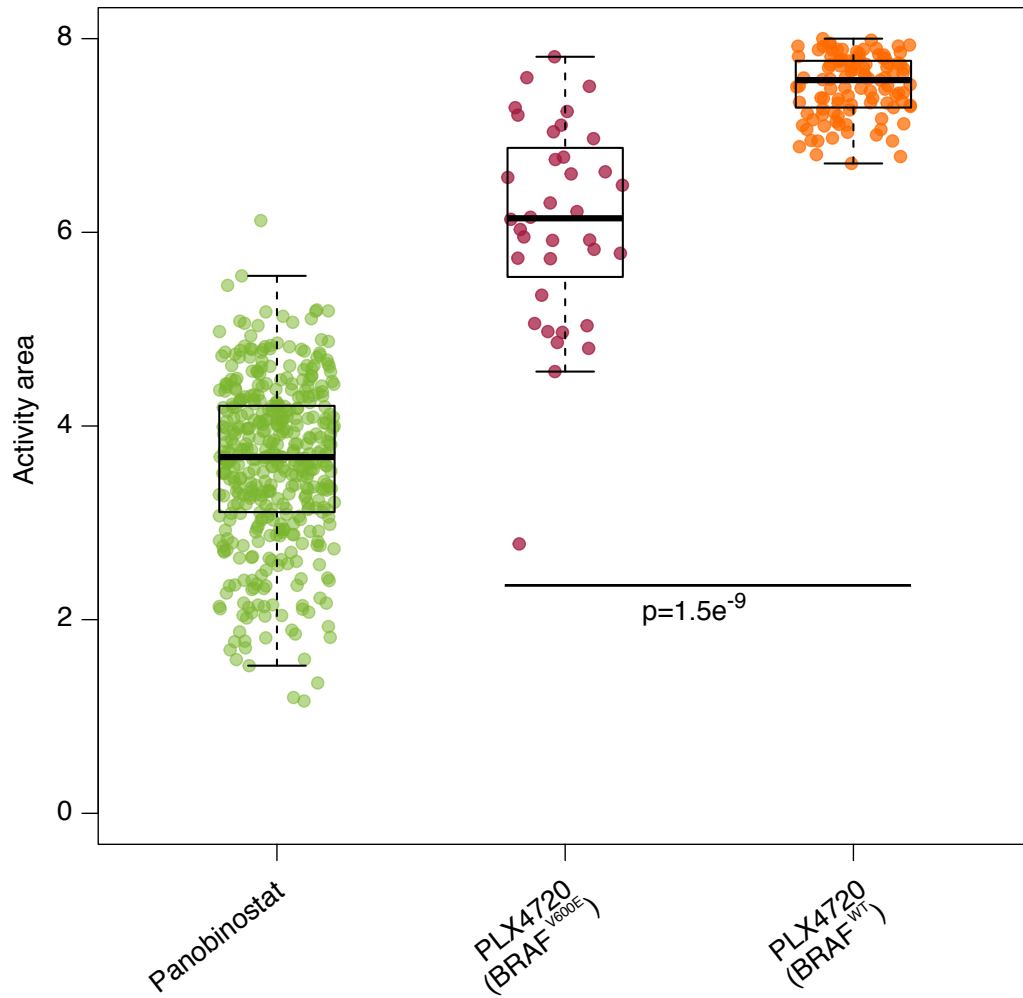


Supplementary Figure 3: Distribution of the percentages of SNP identity across cell lines. The boxplot (orange) corresponds to the same values shown as a histogram in blue. Values above 80% identity denote cell line pairs presumed to derive from the same individual.

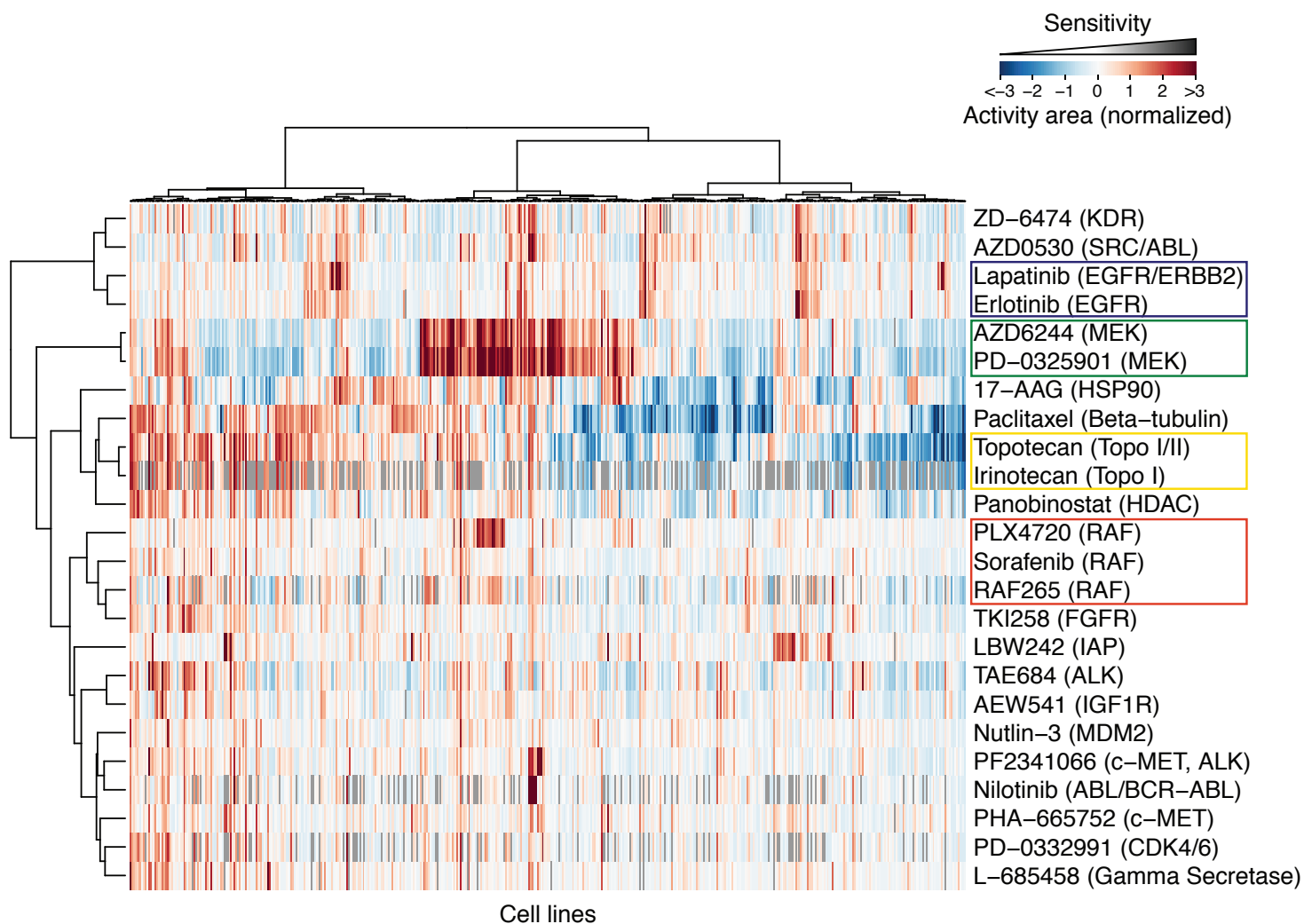


Supplementary Figure 4: Principal component analysis of expression data from cell lines and primary tumors, for the 1,000 most varying genes. Those derived from solid tumors are shown in orange, and those corresponding to hematopoietic lineages are shown in blue. This figure indicates that there was no cross-contamination between hematopoietic and solid tumor-derived cell lines. Expression data was also used to ascertain the original lineage of certain cell lines.



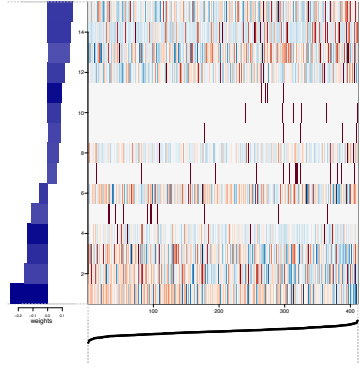


Supplementary Figure 6: Drug responses for Panobinostat (green) and PLX4720 (orange/purple), as measured by the activity area.



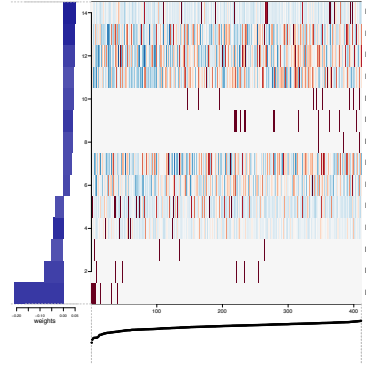
Supplementary Figure 7: Clustered response profiles across all cell lines for all the tested compounds, based on the activity area between the response curve and the zero dose effect level, up to the top tested concentration of 8 μ M. Each row was median-normalized. Colored boxes denote compounds with similar targets that cluster together.

17-AAG



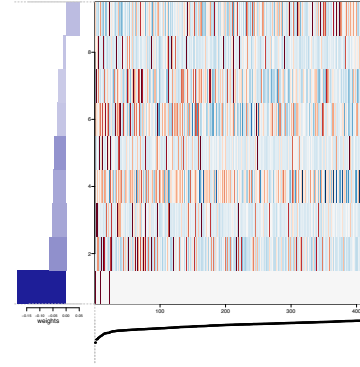
- Expr MSI1 (0.86)
- Expr ATP10A (0.87)
- Expr TM2D2 (0.8)
- Expr LHFP1 (0.86)
- Mut nmMS NRP2 (0.96)
- Mut nmMS DAPK2 (0.86)
- Mut nmMS FBNP1 (0.84)
- Expr CDHR3 (0.83)
- Mut LOF-nmMS AKAP6 (0.81)
- Expr C12orf57 (0.86)
- Mut nmMS MAMDC4 (0.82)
- Expr NM1 (0.98)
- Expr CSNK1E (0.9)
- Expr CYCS (0.84)
- Expr NOD1 (1)

AEW541



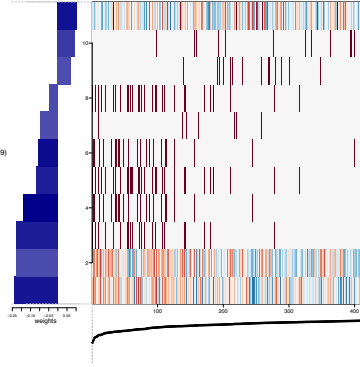
- Expr TMEM204 (0.92)
- Expr APOL5 (0.91)
- Expr BARHL1 (0.84)
- Expr LOC153684 (0.8)
- Mut LOF-nmMS SULF2 (0.82)
- Mut LOF-nmMS AFF4 (0.86)
- Mut nmMS ULK4 (0.82)
- Expr SNN (0.82)
- Expr FIGLA (0.82)
- Expr TGH (0.8)
- Expr MGC4473 (0.9)
- Mut LOF-nmMS RAF1 (0.8)
- Mut nmMS RPS6KA2 (0.84)
- Lineage multiple_myeloma (0.86)

AZD0530



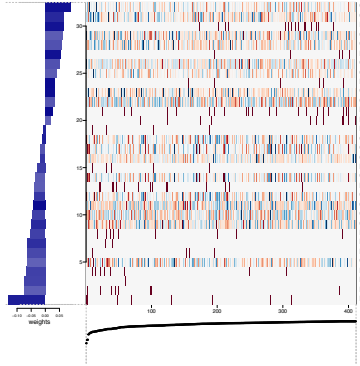
- GeneSet RIBOFLAVIN_METABOLISM (0.4)
- Expr KCAC1 (0.36)
- Expr EFNB1 (0.32)
- Expr CCL25 (0.36)
- GeneSet COT2_activated_geneo_transac (0.59)
- Expr CNM2 (0.51)
- Expr C1orf161 (0.52)
- Expr BTC (0.6)
- Lineage leukemia_CML (0.93)

AZD6244



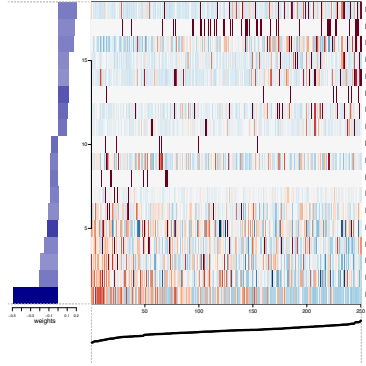
- Expr TMEM146 (0.96)
- Mut LOF-nmMS SULF2 (0.86)
- Mut LOF-nmMS ITIH5L (0.81)
- Mut nmMS BRAF (0.82)
- Mut nmMS CCDC1 (0.81)
- Mut nmMS NRAS (0.98)
- Mut LOF-nmMS BRAF (0.93)
- Mut cosmicMS NRAS (1)
- Mut cosmicMS BRAF (0.94)
- Expr S100A4 (0.82)
- Expr SPRY2 (0.95)

Erlotinib



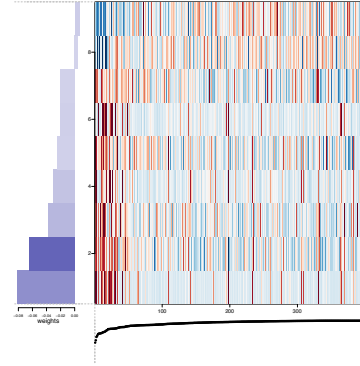
- CN SCNA (0.96)
- CN CNTN6 (0.9)
- Lineage glioma (0.96)
- CN LOC100126098 (0.77)
- CN FAM85CP (0.9)
- Mut LOF-nmMS THRAP3 (0.96)
- CN PHACTR3 (0.8)
- CN FBXL17 (0.77)
- Mut LOF-nmMS CYBBR4 (0.98)
- CN EYA1 (0.97)
- CN GSTM1 (0.78)
- Mut nmMS FBN1 (0.86)
- Mut LOF-nmMS PPP3CA (0.75)
- Mut nmMS RAF1 (0.92)
- CN TMEM170B (0.93)
- CN RARGF4 (0.79)
- CN GRID2 (0.88)
- Mut LOF-nmMS RAF1 (0.86)
- CN ZAK (0.77)
- Mut nmMS MKNB (0.76)
- CN C6orf105 (0.87)
- CN PPP3CA (0.88)
- CN TMHE (0.84)
- CN JAK2 (0.9)
- Mut nmMS BMRP2 (0.84)
- Mut LOF-NTCH1 (0.89)
- Mut nmMS PPP3C2 (0.82)
- CN FAM157B (0.76)
- Mut nmMS RHCA (0.84)
- Mut nmMS GATC2 (0.84)
- Mut nmMS EXT2 (0.76)
- Mut cosmicMS EGFR (0.93)

Irinotecan



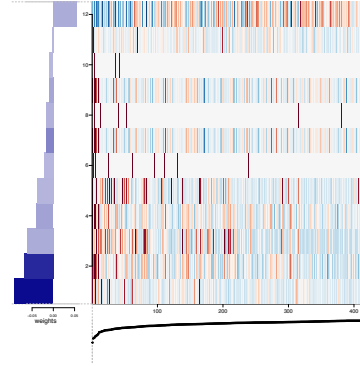
- Expr RRAD (0.66)
- Mut nmMS CSM3 (0.64)
- Expr LOC100269168 (0.66)
- Expr FAM81 (0.62)
- Expr GPR64 (0.6)
- Mut LOF-nmMS ULK4 (0.78)
- Expr TMEM908 (0.73)
- Expr SPOCK3 (0.7)
- Mut nmMS SEPT9 (0.72)
- Expr DMXB1 (0.66)
- Mut LOF-nmMS DNMT1 (0.7)
- Expr LGI1 (0.66)
- Expr ACO12 (0.62)
- Expr NF1 (0.85)
- Expr C10orf85 (0.64)
- Expr ATP2A1 (0.6)
- Expr CCNB1P1 (0.68)
- Expr SLFN11 (1)

L-685458



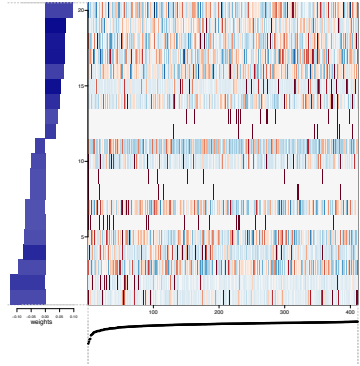
- Expr GSS (0.3)
- Expr WDR54 (0.25)
- Expr EF4EBP2 (0.27)
- Expr SELPLG (0.28)
- Expr ZCCHC7 (0.28)
- Expr ARL11 (0.37)
- Expr SPCS2 (0.44)
- Expr MSL2 (0.74)
- Expr PKOXC (0.6)

Lapatinib



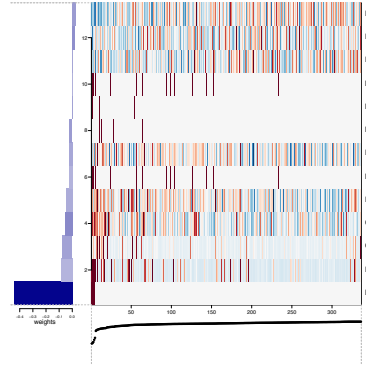
- Expr API1 (0.48)
- Expr CD34 (0.44)
- Mut LOF-nmMS TMPD (0.43)
- CN PGAP3 (0.32)
- Mut nmMS RHGA (0.46)
- CN PHMT (0.64)
- Mut LOF-nmMS STAF5B (0.44)
- Expr TPRXL (0.45)
- Expr PGAP3 (0.53)
- GeneSet GLI1_inhibited_geneo_transac (0.48)
- Expr ERBB2 (0.9)
- GeneSet MYB_inhibited_geneo_transac (0.98)

LBW242



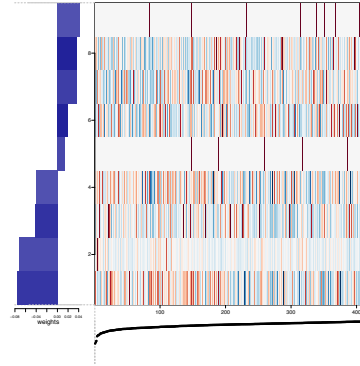
- Expr CHML (0.84)
- Expr CARTPT (0.86)
- Expr C15orf51 (0.94)
- Expr TAS2R90 (0.95)
- CN BNC2 (0.84)
- Expr FLG (0.96)
- Expr HSPA6 (0.89)
- Mut LOF-nmMS MCM3AP (0.82)
- Mut LOF-nmMS LMTK2 (0.86)
- Expr ZNF415 (0.84)
- Expr PDE7B (0.82)
- Lineage soft_tissue (0.8)
- Mut nmMS AIM1 (0.8)
- Expr LACT (0.9)
- Mut LOF-nmMS MAMDC4 (0.8)
- Expr PLACL1 (0.81)
- Expr TSPN18 (0.9)
- Expr CSR2 (0.82)
- Expr CD96 (0.86)
- Expr CNTN4 (0.82)

Nilotinib



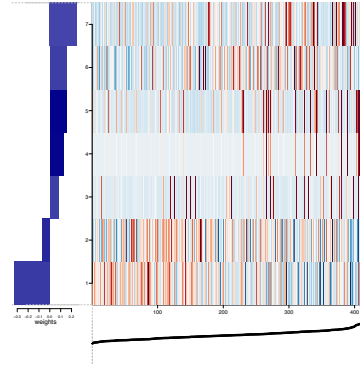
- Expr LOC100288752 (0.56)
- Expr CROCCL2 (0.6)
- Expr DRD4 (0.52)
- Mut nmMS NUP153 (0.46)
- Mut nmMS IKKB (0.53)
- Mut nmMS RAF1 (0.56)
- Expr ITM2C (0.51)
- Mut LOF-nmMS NUP153 (0.46)
- Expr SRBD1 (0.48)
- GeneSet G_protein_signaling_Rap2B (0.62)
- GeneSet RELB_activated_geneo (0.53)
- Expr ITM2A (0.45)
- Lineage leukemia_CML (0.99)

Nutlin-3

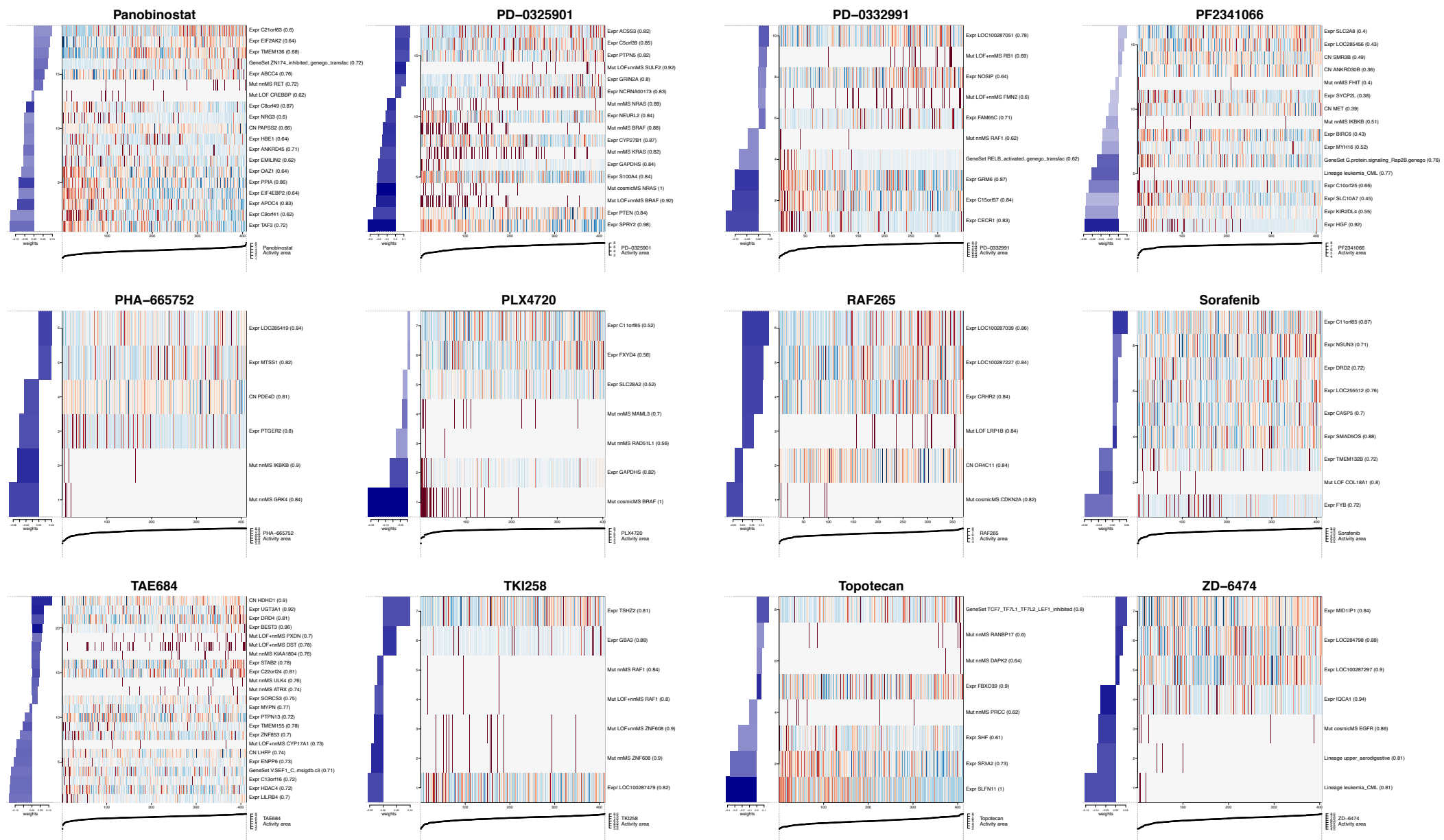


- Mut nmMS RNASEL (0.8)
- Expr CASB (0.92)
- Expr C20orf79 (0.85)
- Expr CROCCL2 (0.92)
- Mut nmMS ITGAV (0.82)
- Expr KIF11N (0.8)
- Expr LOC100289096 (0.88)
- Expr DPYS (0.82)
- Expr DDB2 (0.87)

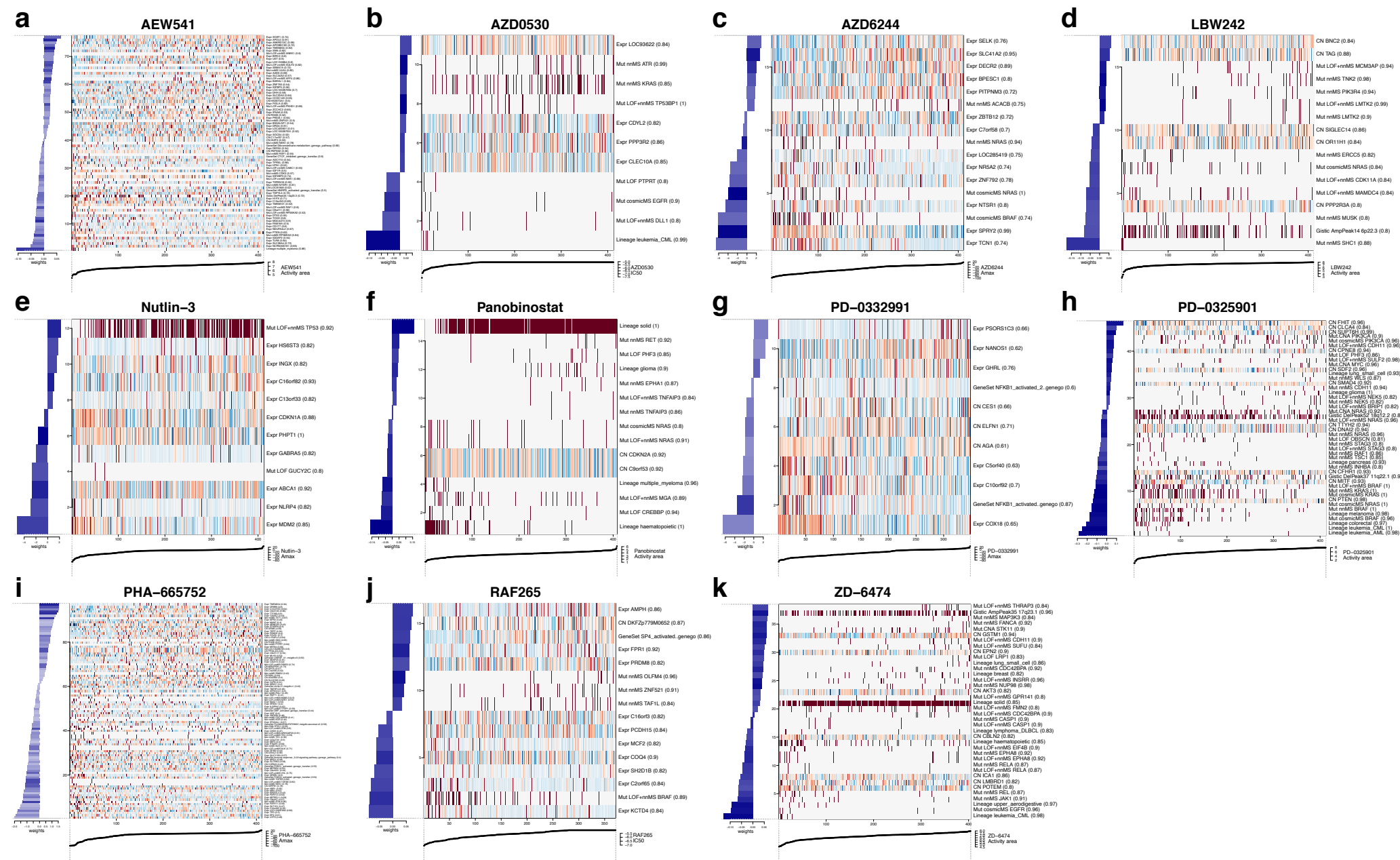
Paclitaxel

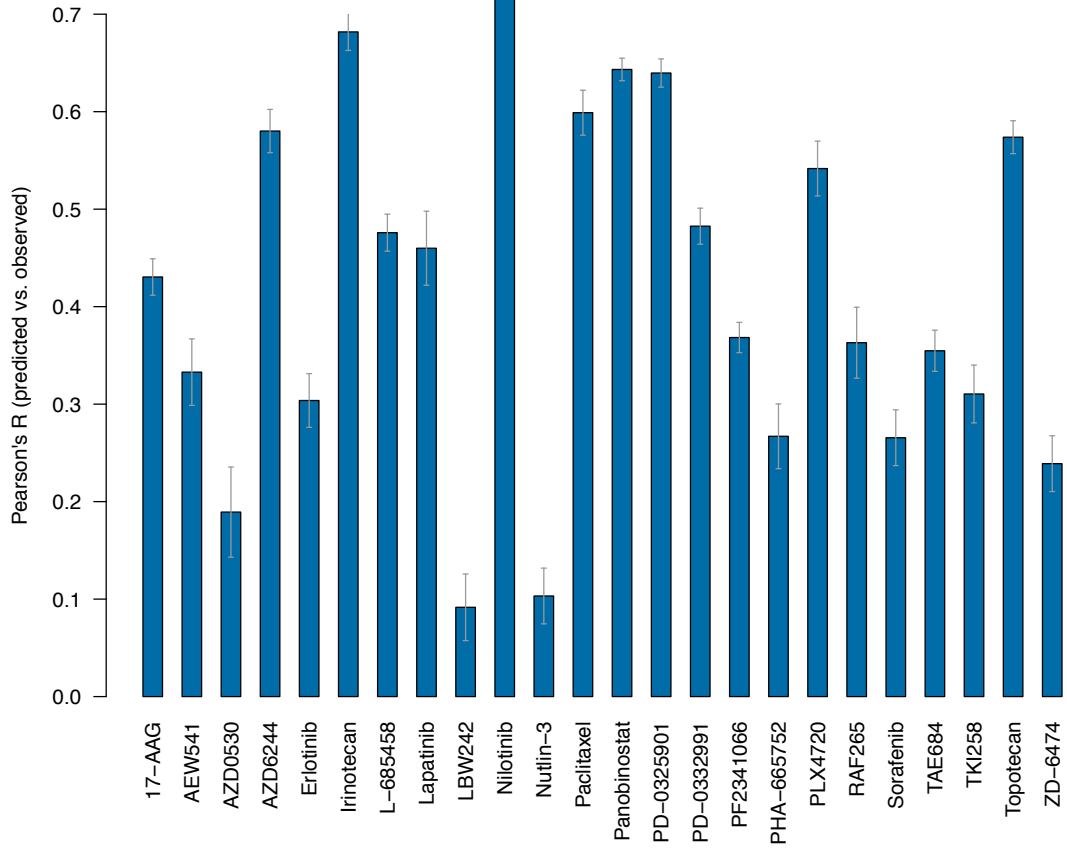


- Expr SHANK2 (0.84)
- Expr LOC100126784 (0.85)
- Expr ABCB1 (1)
- GeneSet RSP1_activated_geneo (0.99)
- Expr CADPS (0.85)
- Expr PSMG3 (0.9)
- Expr SSRP1 (0.86)

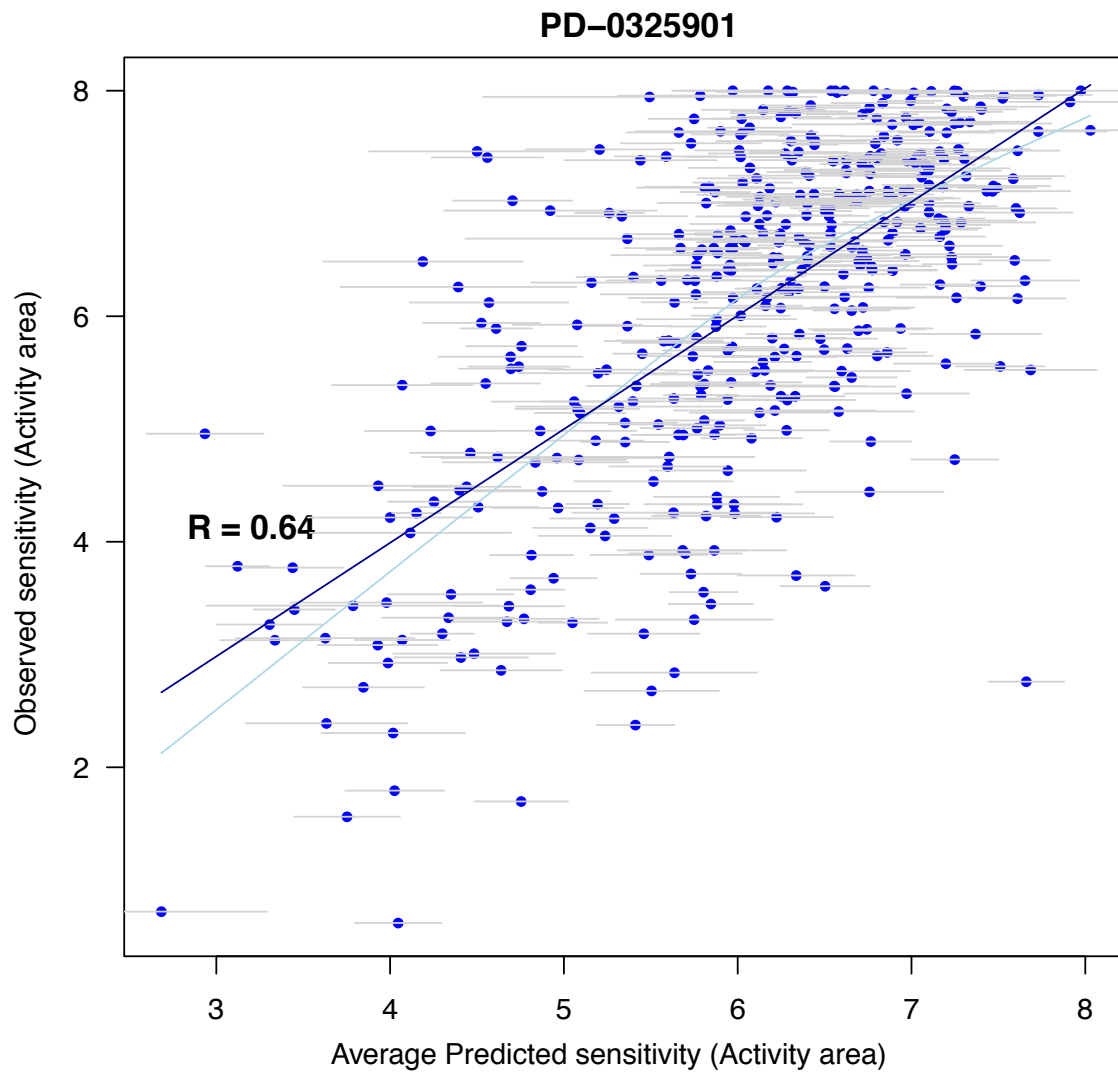


Supplementary Figure 8: Elastic net-based predictive modeling results for 24 compounds using all features as input and activity area as the sensitivity metric. In this figure (and some panels in supplementary figure 9), $\beta - \text{activity area}$ was used as the vector of response values, so that low values correspond to sensitive cell lines and are located towards the left of the heatmap, to keep consistent with other sensitivity metrics (IC_{50} , A_{max}). The frequency of each feature in the models is indicated in parenthesis next to the feature name and the shades of blue in the barplot next to the heatmap are proportional to that value. The cutoff for the bootstrapping frequency was 80% unless it would yield to a model with less than 5 features.

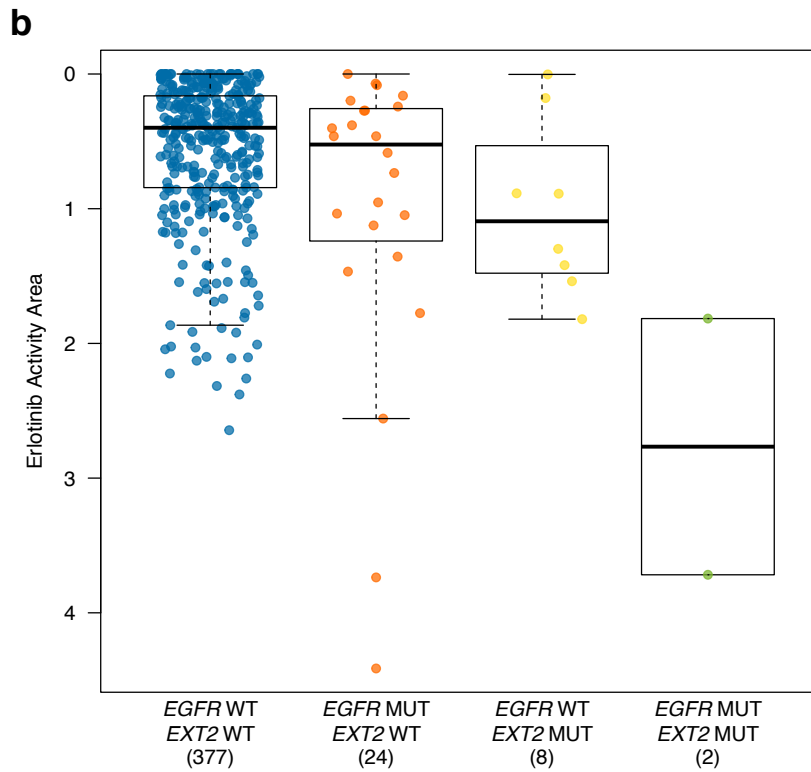
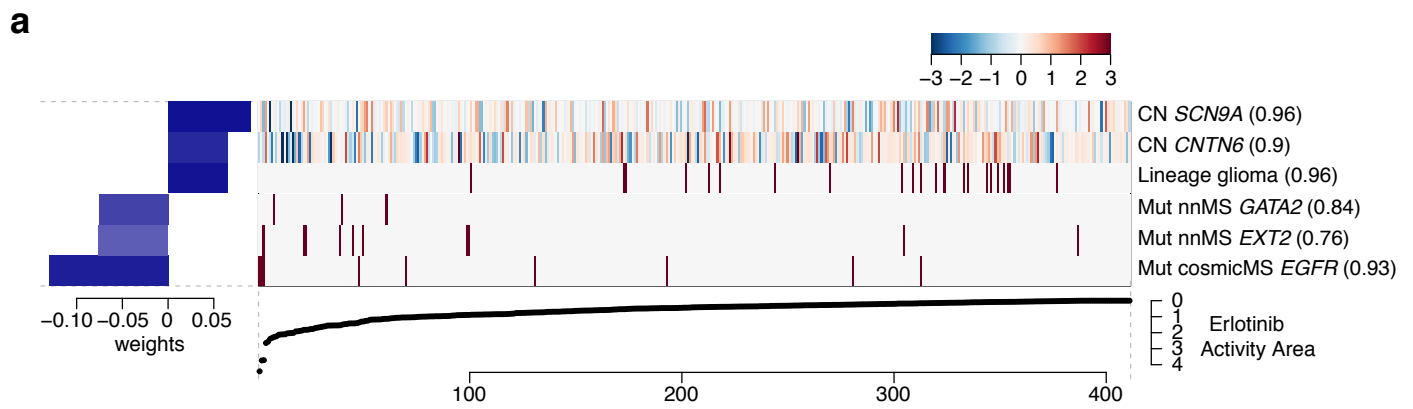




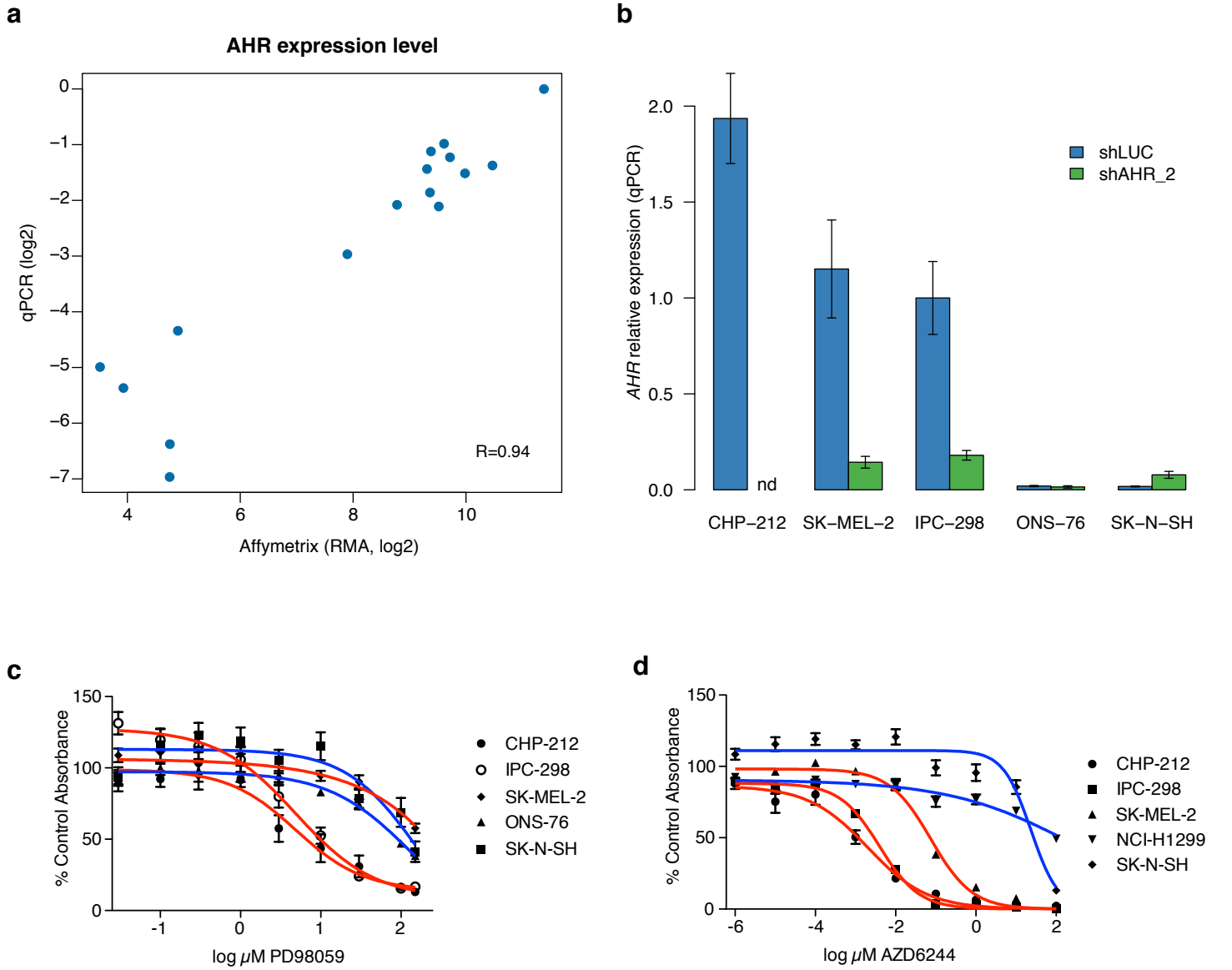
Supplementary Figure 10: Performance of the predictive models in Supplementary Figure 8 as measured by Pearson's correlation coefficients between observed and predicted sensitivity values (mean of 10 iterations of 10-fold cross-validations).



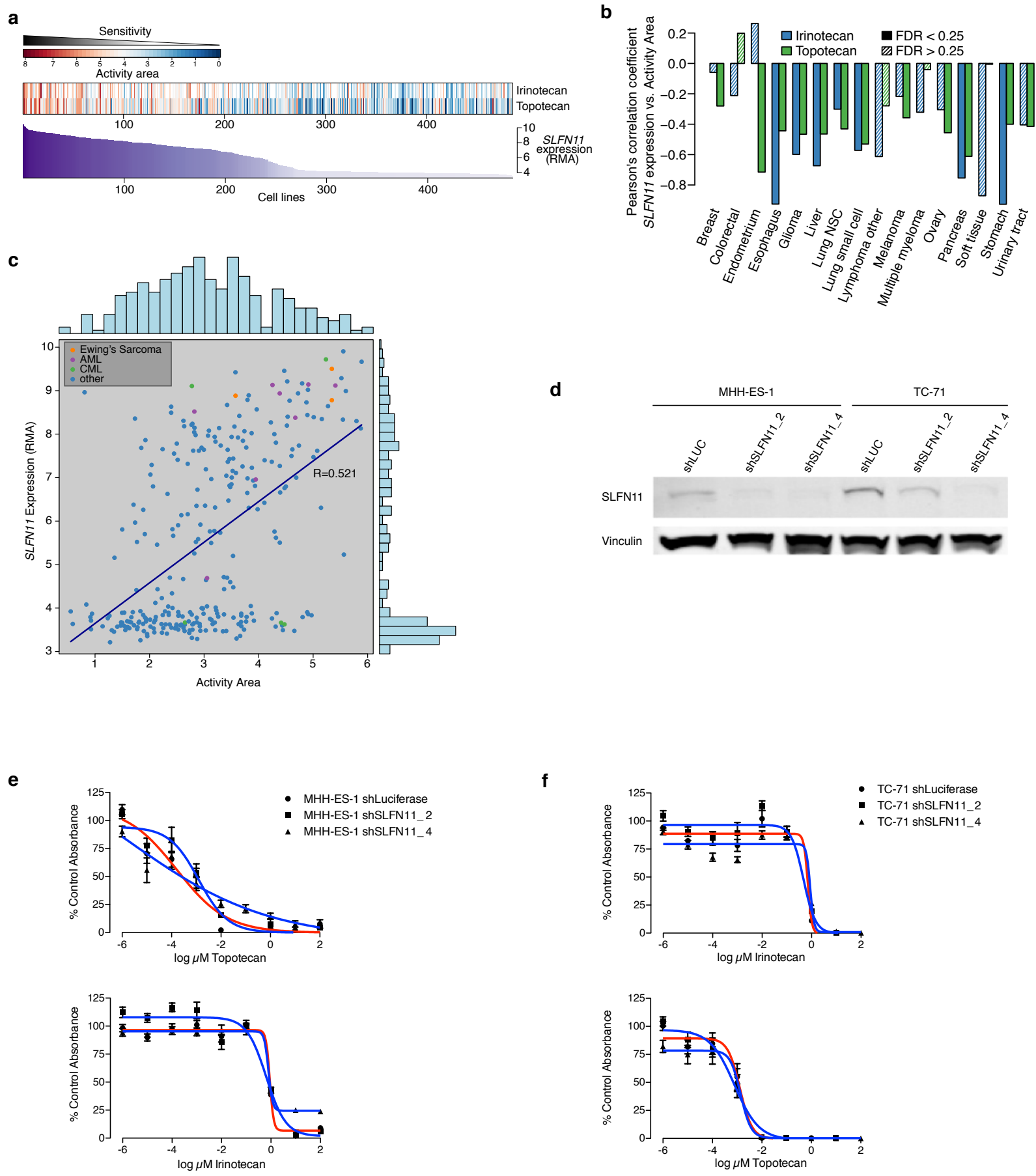
Supplementary Figure 11: Predicted sensitivity values for PD-0325901 (Activity area), versus observed sensitivities. Horizontal grey bars represent the standard deviation of the predicted values across 10 iterations of cross-validation.



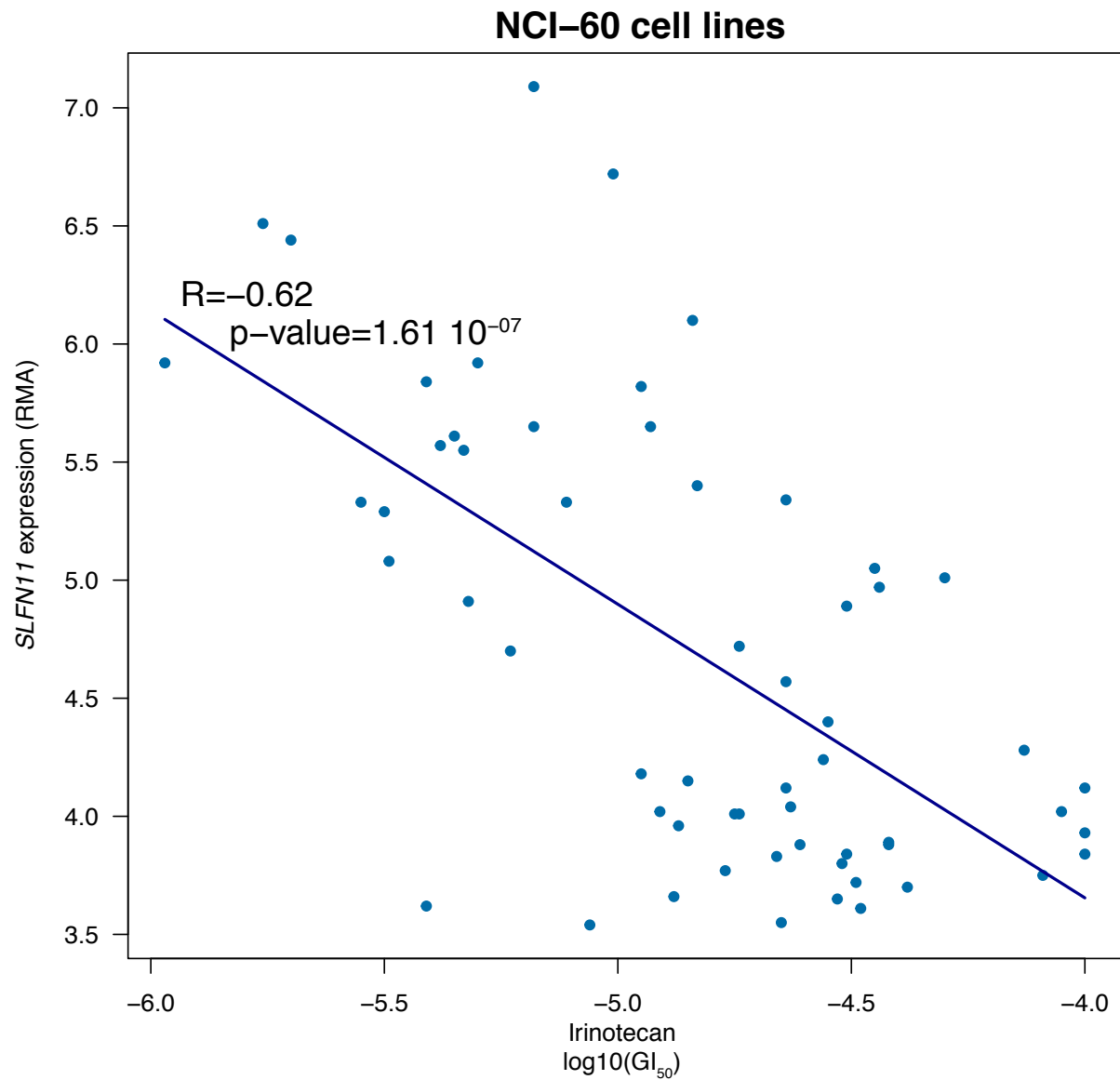
Supplementary Figure 12: *EXT2* variations may enrich for sensitivity to EGFR inhibitors. **a.** Elastic net-based predictive modeling results for Erlotinib using DNA copy number, mutations and lineages as input, and activity area as the sensitivity metric. *EGFR* mutations at or near recurrent COSMIC sites and *EXT2* missenses are the top two predictive features. (The top 3 predictive features for sensitivity and top 3 predictive features for insensitivity are shown. Bootstrapping cutoff: 75%) **b.** Drug response for Erlotinib (activity area) segregated by mutation status for *EGFR* and *EXT2* (all non-polymorphic missenses, supplemented by missenses reported by the COSMIC CGP project).



Supplementary Figure 13: *AHR* expression measurements correlates with sensitivity to MEK inhibitors in selected *NRAS*-mutant cell lines. **a.** Correlation between *AHR* expression measured by microarray analysis (X axis) or quantitative RT-PCR (Y axis). **b.** Mean *AHR* expression in five cell lines after shRNA knockdown using lentiviral constructs targeting luciferase control (shLUC; blue) or *AHR* (shAHR_2; green). Expression levels are relative to IPC-298 cells expressing shLUC. nd: not detected. (Measurement of *AHR* knockdown in the CHP-212 cell line was not possible due to the very low number of surviving cells). Error bars: standard deviation between replicates (n=3). **c, d.** Pharmacologic growth inhibition curves for selected *NRAS*-mutant cell lines using the MEK inhibitor PD-98059 (b) or AZD-6244 (c). Cell lines with high (red) or low (blue) *AHR* expression are indicated. Error bars: standard deviation between replicates (n=6).



Supplementary Figure 14: **a.** Heatmap of irinotecan and topotecan sensitivity ranked according to *SLFN11* expression. **b.** Correlation between *SLFN11* mRNA expression and topoisomerase inhibitor sensitivity (activity area) across 16 lineages with sufficient representation (>10 cell lines). **c.** Scatter plot of *SLFN11* expression versus irinotecan sensitivity. Ewing's sarcoma, AML and CML cell lines are depicted as colored dots. **d.** Anti-*SLFN11* and anti-vinculin control immunoblots of lysates from MHH-ES-1 and TC-71 cells expressing shRNA against *SLFN11* (shSLFN11_2 and shSLFN11_4) or luciferase (shLUC) as control. **e-f.** Pharmacologic growth inhibition curves for MHH-ES-1 (d) and TC-71 (e) cells expressing shRNA against *SLFN11* (shSLFN11_2 and shSLFN11_4, blue lines) or luciferase (shLUC, red lines) as control. Error bars: standard deviation between replicates (n=6).



Supplementary Figure 15: Correlation between SLFN11 expression levels across NCI-60 cell lines (Affymetrix U-133 arrays normalized with RMA) and sensitivity to irinotecan (GI₅₀). Data were obtained using the CellMiner database⁴¹. As evidenced by the significant inverse correlation between irinotecan GI₅₀ and SLFN11 expression ($R = -0.62$), SLFN11 remains predictive of the sensitivity to irinotecan in independent datasets.