"Systematic pan-cancer analysis of mutation-treatment interactions using large real-world clinico-genomics data"

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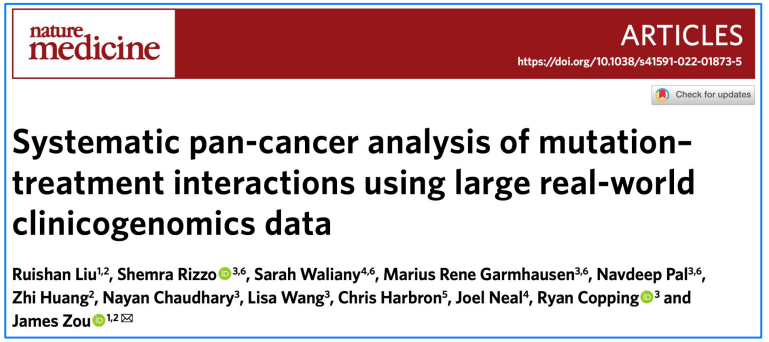

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01873-5

Check for updates

Systematic pan-cancer analysis of mutation–treatment interactions using large real-world clinicogenomics data

Ruishan Liu[1,2], Shemra Rizzo[3,6], Sarah Waliany[4,6], Marius Rene Garmhausen[3,6], Navdeep Pal[3,6], Zhi Huang[2], Nayan Chaudhary[3], Lisa Wang[3], Chris Harbron[5], Joel Neal[4], Ryan Copping[3] and James Zou[1,2]

RESEARCH ARTICLE

Theme: Applications of Machine Learning and AI to Drug Discovery, Development, and Regulations

Check for updates

Machine Learning Prediction of Clinical Trial Operational Efficiency

Kevin Wu[1] · Eric Wu[2] · Michael DAndrea[3] · Nandini Chitale[3] · Melody Lim[3] · Marek Dabrowski[4] · Klaudia Kantor[4] · Hanoor Rangi[5] · Ruishan Liu[2] · Marius Garmhausen[6] · Navdeep Pal[3] · Chris Harbron[7] · Shemra Rizzo[3] · Ryan Copping[3] · James Zou[1,2]

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Article

Evaluating eligibility criteria of oncology trials using real-world data and AI

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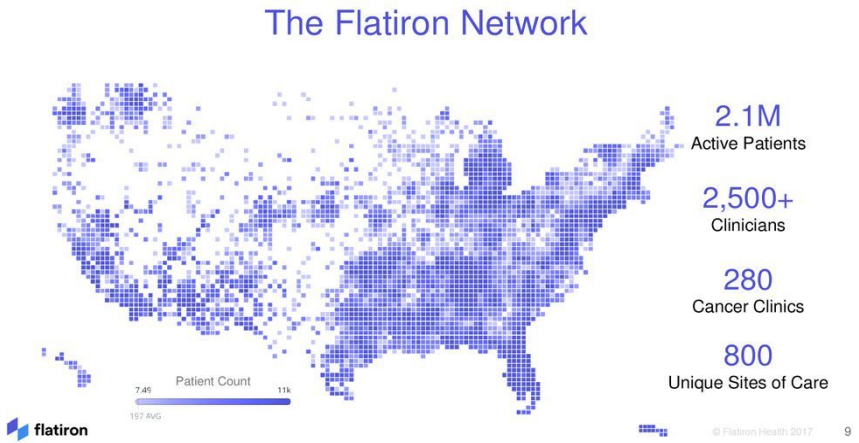
Ruishan Liu[1], Shemra Rizzo[2], Samuel Whipple[2], Navdeep Pal[2], Arturo Lopez Pineda[2], Michael Lu[2], Brandon Arnieri[2], Ying Lu[3], William Capra[2], Ryan Copping[2] & James Zou[1,3,4,5]

Clinicogenomics - Real World Data

Clinicogenomics database

Scaling up on cancer



+

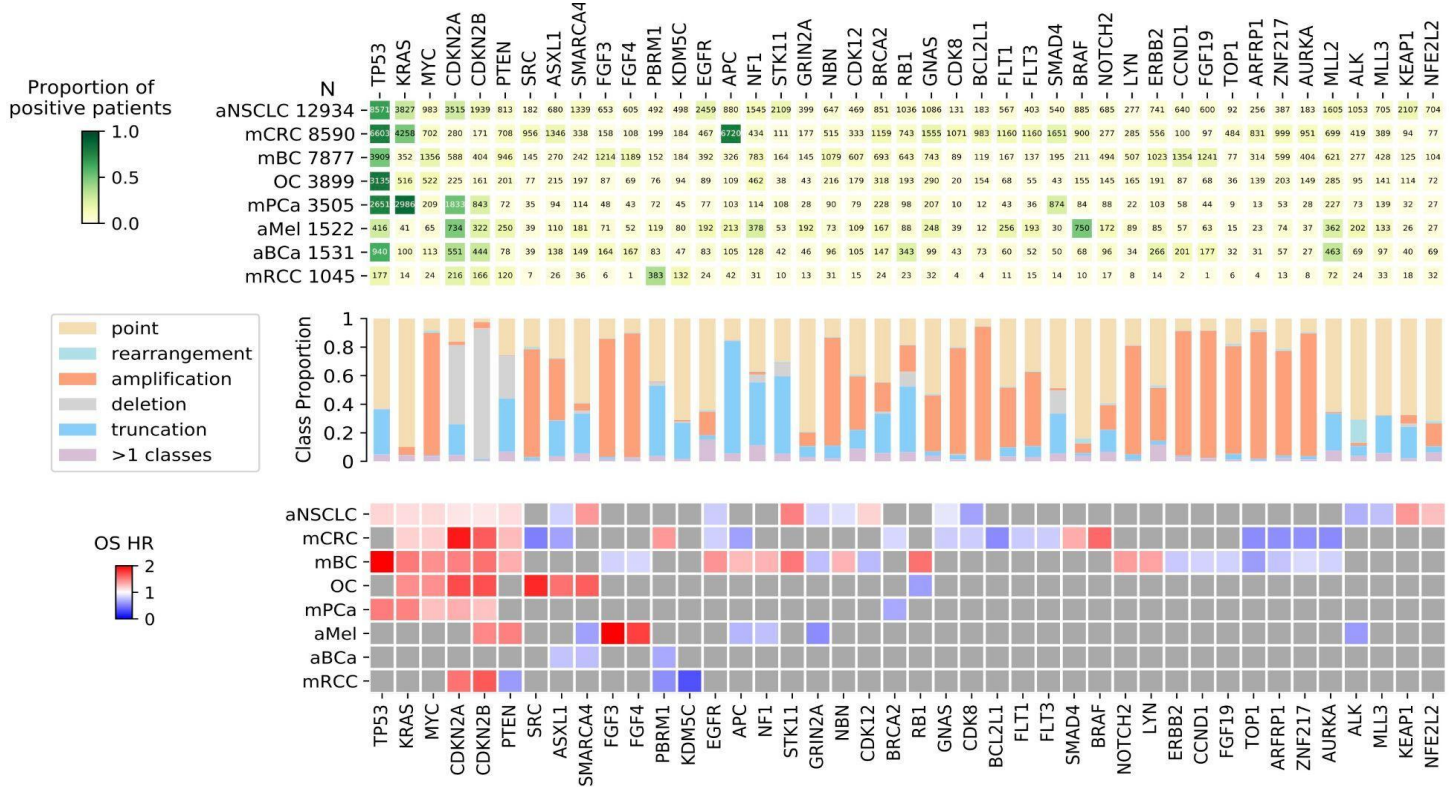
FOUNDATION MEDICINE

NGS for 500+ driver genes

>40k cancer patients with mutation profiles and treatment outcomes

AACR GENIE BPC data could be leveraged to validate some of our findings

Significant[1] prognostic markers



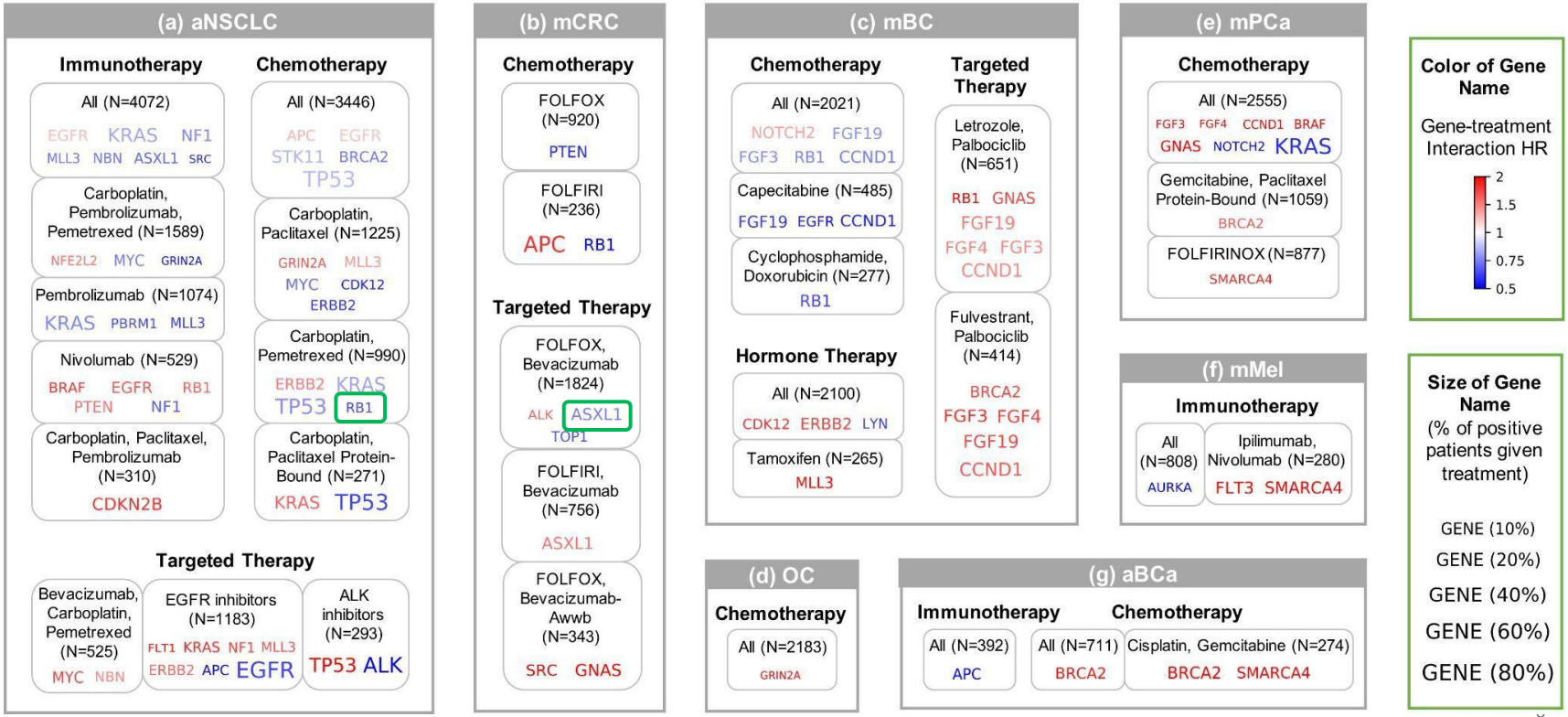
[1] OS HR p-value < 0.001, FDR < 0.05

(Liu et al. Nat. Med. 2022)

Mutation-Treatment Interactions

458 mutation-treatment interactions

Only <60 interactions were previously known (our FDR < 5%)



Validated using AACR GENIE BPC data

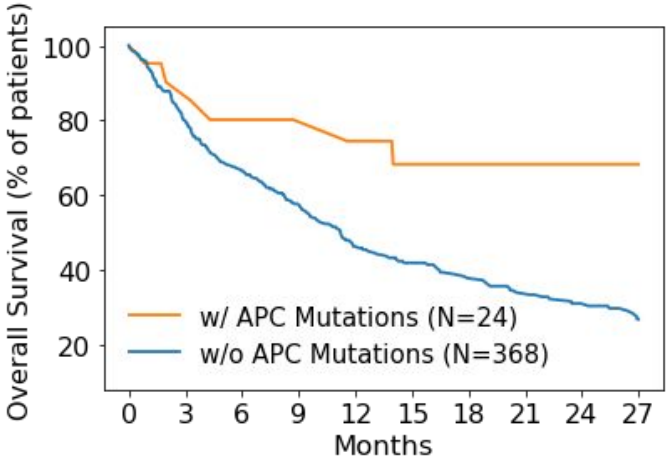
(Liu et al. Nat. Med. 2022)

Example: APC in advanced bladder cancer

Example: APC mutation

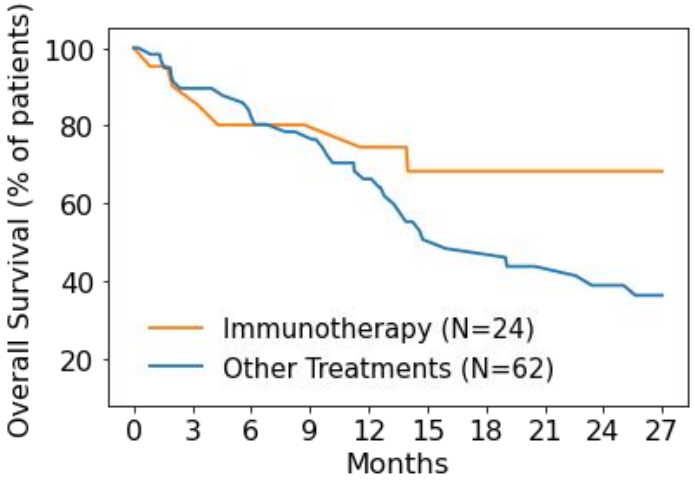
Better immunotherapy response in bladder cancer patients

patients on immunotherapy



APC is a tumor suppressor

patients w/ APC mutation



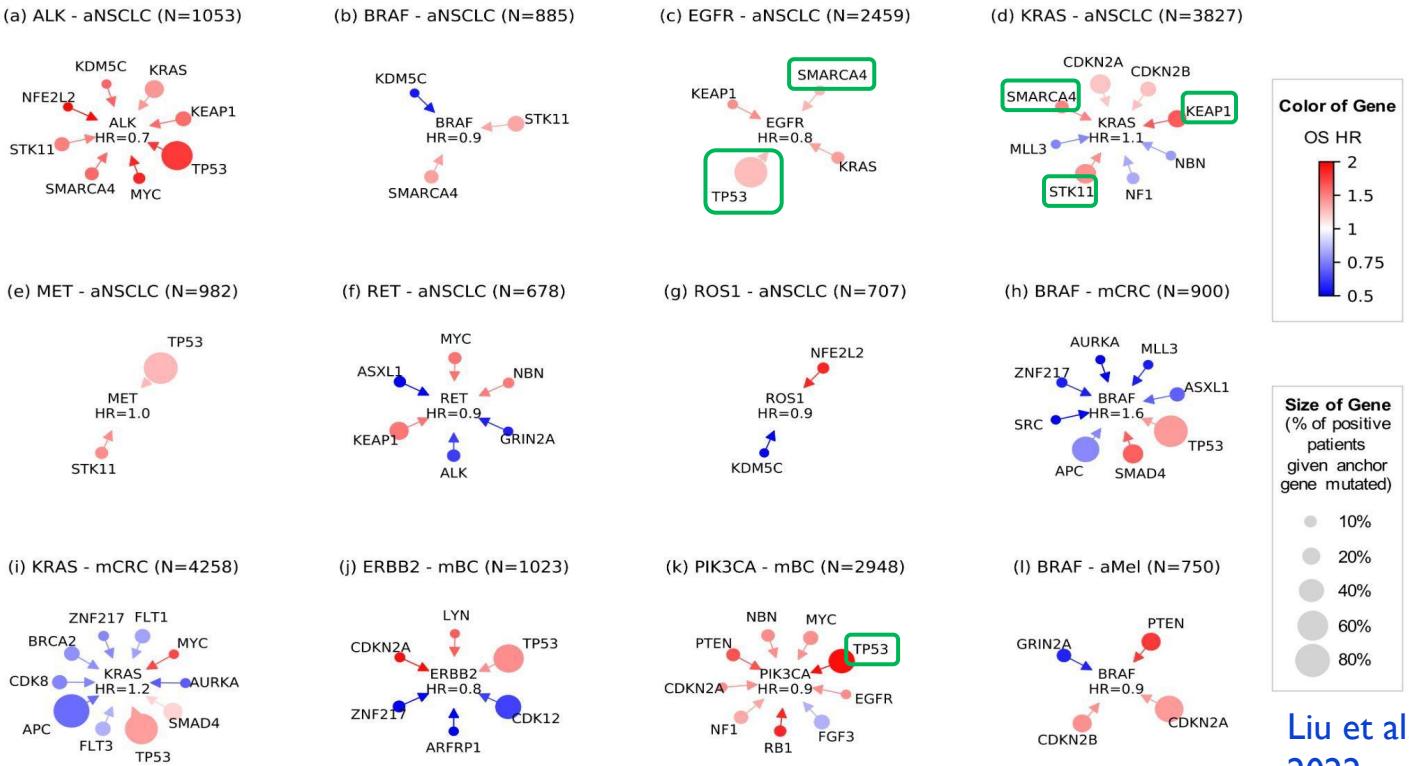
interaction effect

$$\text{Survival} \sim \beta_0 \cdot \text{confounders} + \beta_g \cdot \text{genotype} + \beta_t \cdot \text{treatment} + \beta \cdot \text{genotype} \cdot \text{treatment}$$

Gene-gene interactions

Gene-gene interactions

Modifying the effects of targeted therapies



Validated using AACR GENIE BPC data

Liu et al. *Nat. Med.* 2022

www.precision-cancer.org

Our results can be easily accessed

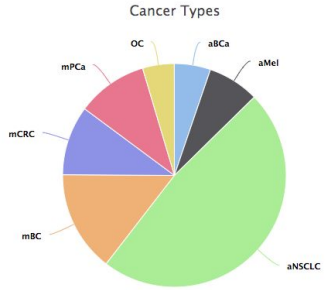
Precision Cancer

MAIN

- Introduction
- Statistics
- Mutation-Treatment
- Mutation-Mutation

Mutation-Treatment Interactions

Overall survival associated with all 458 predictive genes based on first-line therapies received. All of the drug-gene interactions with p value < 0.05, with at least 200 patients in the treatment group and at least 20 patients with the gene mutated in the treatment group are reported. Overall survival is measured from the start date of the first-line treatment to death. The overall false discovery rate (FDR) is < 0.05 based on Benjamini–Hochberg procedure.



Show 10 entries

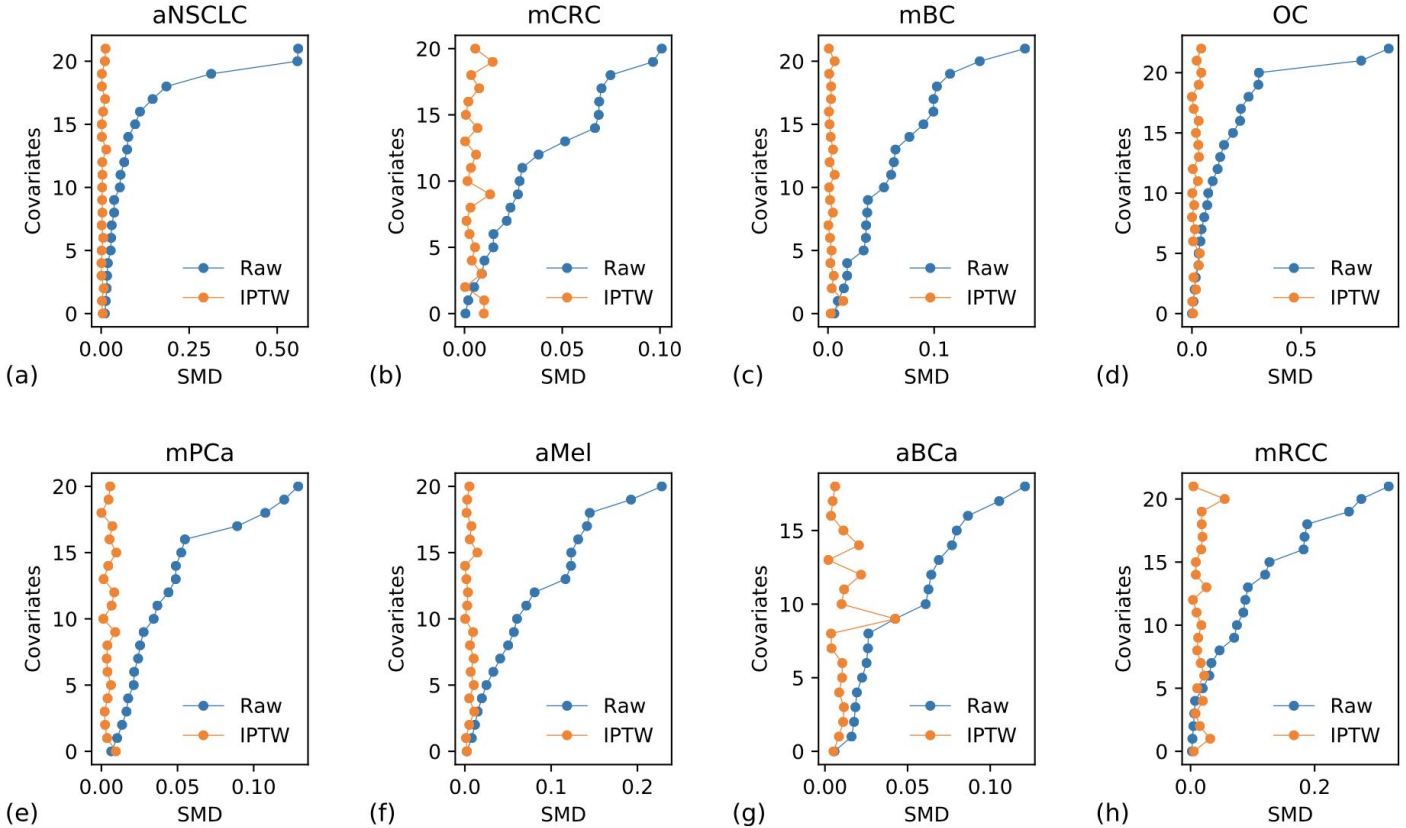
Search:

Cancer	Treatment class	Treatment	Gene	N - given drug	Interaction: exp(coef)	HR for gene mutation	HR for absence of gene mutation	Mutation subtype with strongest treatment interaction	HR for that subtype of mutations	HR given drug	HR given other drugs
aBCa	Chemotherapy	Carboplatin, Gemcitabine	MDM2	30 (11.3%)	0.46 (0.26, 0.83)	0.64 (0.37, 1.12)	1.32 (1.06, 1.64)	amplification (86.7%)	0.68 (0.39, 1.17)	0.70 (0.40, 1.24)	1.36 (1.00, 1.85)
aBCa	Chemotherapy	Carboplatin, Gemcitabine	MTAP	29 (10.9%)	0.44 (0.21, 0.94)	0.60 (0.31, 1.18)	1.31 (1.06, 1.62)	deletion (96.6%)	0.61 (0.31, 1.18)	0.44 (0.22, 0.88)	1.02 (0.66, 1.57)
aBCa	Chemotherapy	Chemotherapy	TRRAP	25 (3.5%)	4.56 (1.33, 15.6)	5.78 (1.91, 17.4)	0.96 (0.81, 1.15)	point (80.0%)	5.04 (1.29, 19.5)	1.71 (1.04, 2.81)	0.33 (0.12, 0.89)
aBCa	Chemotherapy	Chemotherapy	EPHA5	20 (2.8%)	3.66 (1.01, 13.2)	4.02 (1.09, 14.7)	0.97 (0.81, 1.15)	point (95.0%)	4.52 (0.99, 20.5)	1.50 (0.87, 2.57)	0.36 (0.10, 1.21)
aBCa	Chemotherapy	Chemotherapy	AKT2	31 (4.4%)	3.47 (1.15, 10.4)	3.34 (1.04, 10.6)	0.97 (0.82, 1.16)	amplification (83.9%)	6.23 (1.25, 31.0)	1.17 (0.76, 1.80)	0.34 (0.13, 0.90)
aBCa	Chemotherapy	Chemotherapy	LRP1B	55 (7.7%)	2.35 (1.26, 4.39)	2.52 (1.48, 4.28)	0.93 (0.78, 1.11)	point (81.8%)	2.53 (1.38, 4.64)	1.77 (1.09, 2.86)	0.72 (0.48, 1.08)

Summary

- The ability to predict the most effective treatment based on mutational profiles could be transformative for cancer care
- Large scale real world clinico-genomics data let us investigate mutation-treatment and even co-mutational effects on targeted treatments
- RWD is a powerful way to approach this question. Inherent biases require state-of-the-art statistical methods (e.g. propensity score matching and left-truncation aware survival models) to deal with confounders
- We could identify 42 altered genes across 8 cancer types with significant prognostic effect on overall-survival
- 458 significant mutation-treatment interactions were found, the majority of which are yet undescribed and might be a valuable starting point for further research
- Patients receiving targeted treatments might benefit from further comprehensive genomic profiling in future
- Still, the reasons for not being able to identify other or known interactions in RWD are plenty. E.g. rare mutations/treatments, exclusive combinations and biases complicate their identification

Doing now what patients need next



Extended Data Fig. 6 | Balance assessment between experiment and control cohorts for baseline covariates. Here we use the analysis of the prognostic effect of TP53 mutation on overall survival as an example; similar results are seen for other genes. For each cancer, we plot the standardized mean difference (SMD) for every baseline covariate between the experiment cohort (patients with TP53 mutation) and control cohort (patients without TP53 mutation). SMD close to 0 represents that the two cohorts are balanced. The inverse propensity weighting used in our analysis (IPTW) effectively balances the two cohorts. Raw corresponds to the unadjusted cohorts.