Molecularly informed prediction of treatment efficacy in GDSC cell line data using computational reasoning

Abstract #2719

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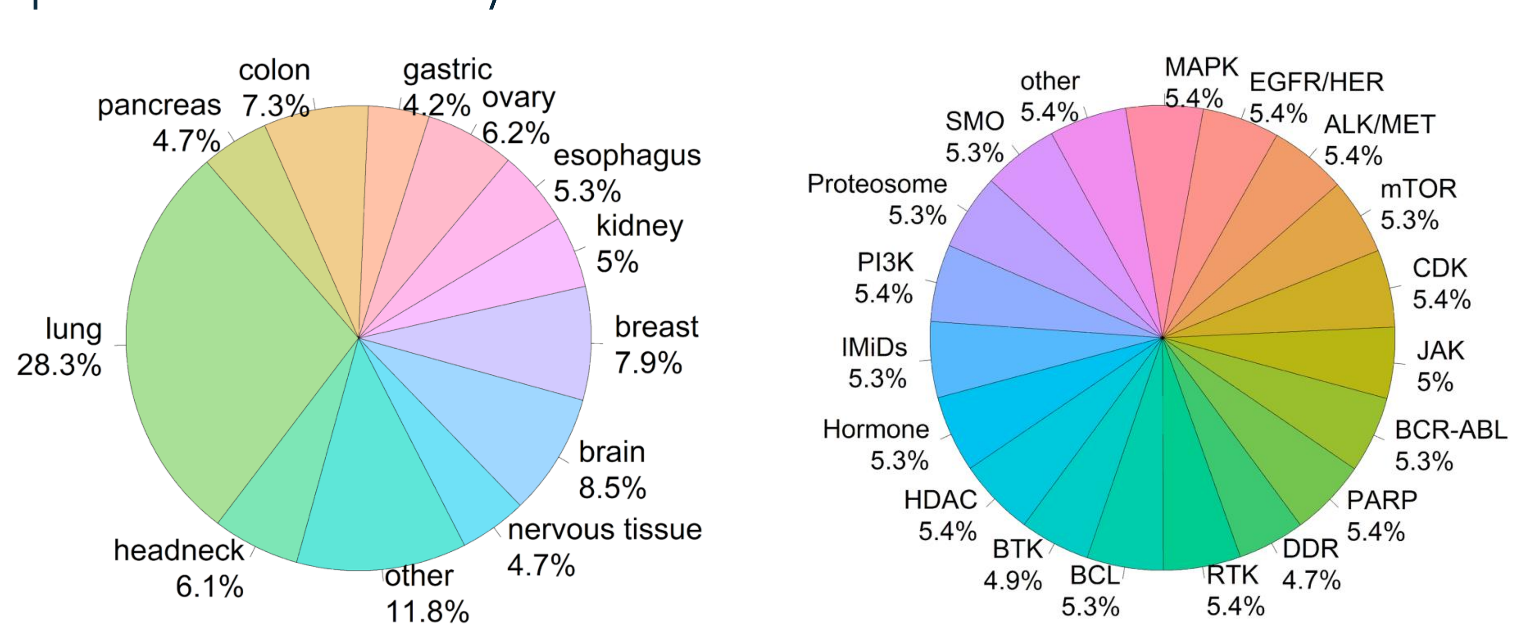
INTRODUCTION

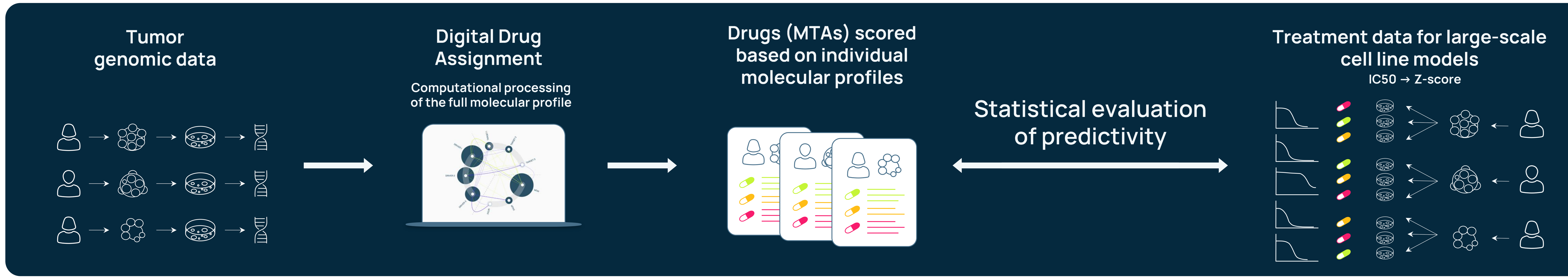
Interpretation of complex molecular profiles in clinical practice can be challenging and subjective. **The Digital Drug Assignment (DDA) system is a knowledge-graph-based computational method that automates reasoning at the patient level and scores molecularly targeted agents (MTAs) based on the full tumor genomic data.** This approach was predictive of relative benefit of the agents as used in the SHIVA01 trial (1).

METHODS

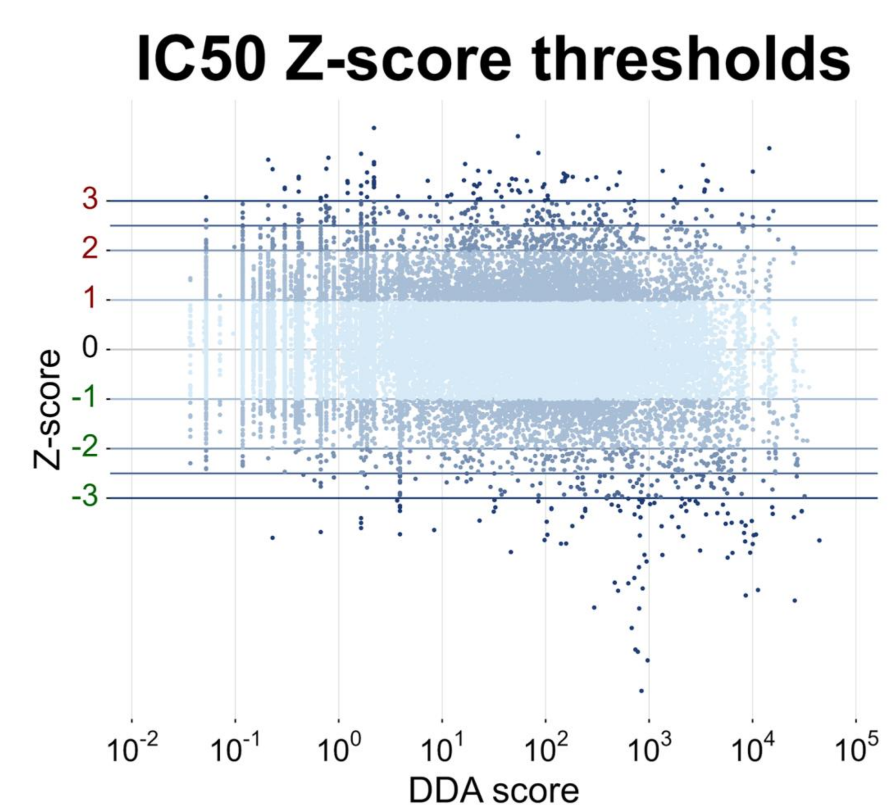
In this study we analyzed large-scale cancer cell line data from the Genomics of Drug Sensitivity in Cancer (GDSC) database (2), using data from 659 cell lines derived from solid tumors. Corresponding drug sensitivity data were available for 34,713 treatment datapoints involving 87 types of MTAs. All tumor genomic profiles were processed using DDA, which scores MTAs according to predicted efficacy. Consequently, the same MTA can receive different drug scores across tumors, depending on their individual molecular profiles. **Treatments were then ranked for each tumor based on their DDA scores**, resulting in 72 treatment groups defined by ranking positions (i.e., drugs ranked at the same position across tumors formed one treatment group). Alternatively, **treatment datapoints were classified into ten decimal bins** in decreasing ranking order. Sensitivity to treatment was determined using Z-scores of IC50 values. The association between drug efficacy and DDA ranking was assessed by the Cochran–Armitage (CA) trend test for categorical and Monotone Shape-Constrained Additive Model (SCAM) for quantitative efficacy data.

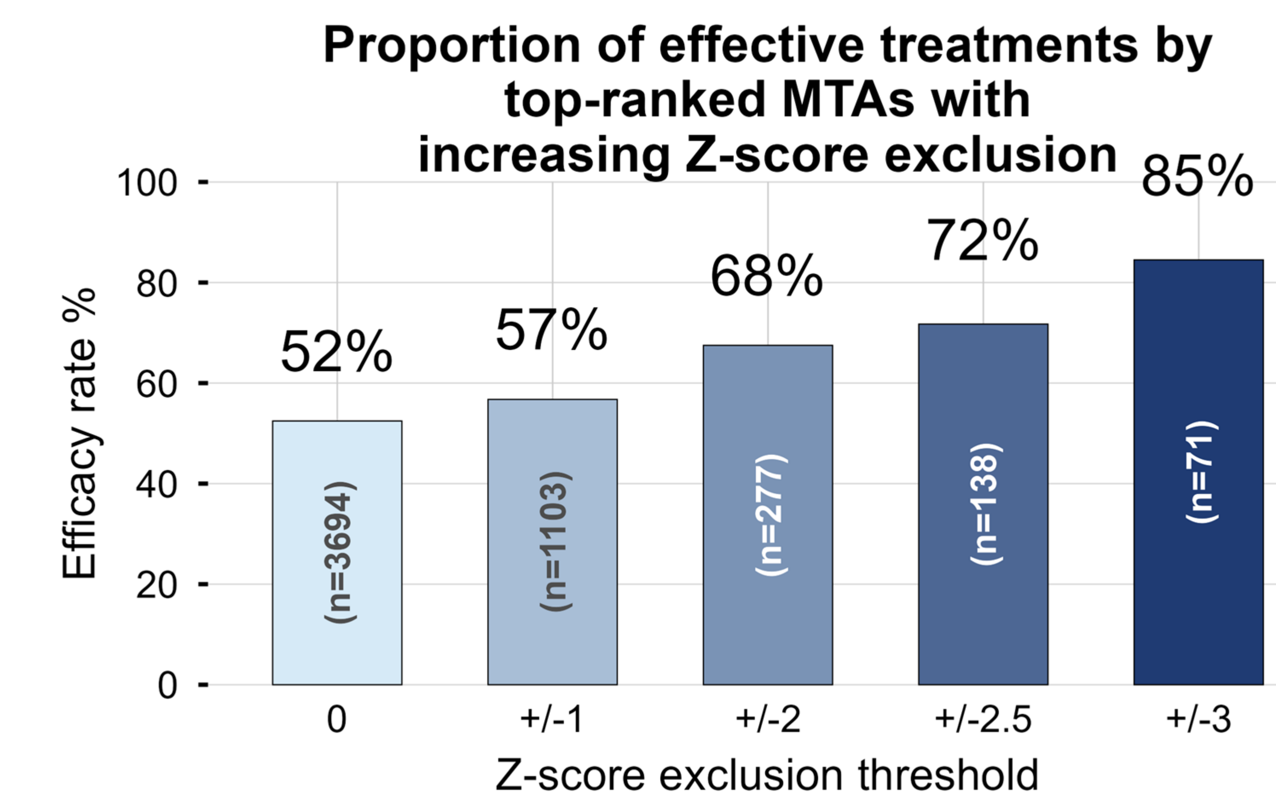


Distribution of the 659 solid tumor-derived cell lines by primary tumor site (left) and the 87 MTAs applied (right).

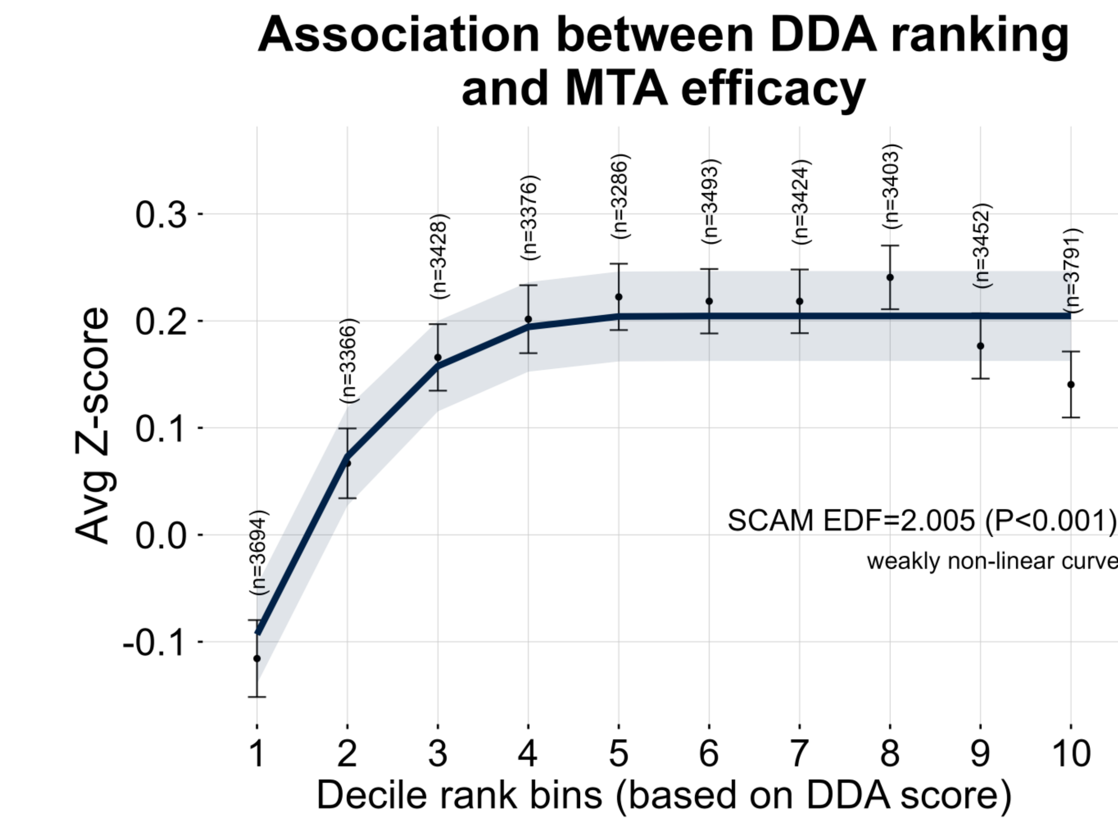


RESULTS





Treatments with negative Z-scores were classified as sensitive. Increased confidence in drug response classification was achieved by excluding treatments around the median (Z-score = 0) with progressively larger absolute IC50 Z-score thresholds (left), resulting in increasing efficacy of top-ranked drugs (right). Efficacy gradually decreased across lower-ranking groups and reaching 0% in the bottom group. Linear trend across ranking positions was confirmed by CA trend test: Z-values ranged from -8.33 to -4.68 with increasing exclusion thresholds (all p < 0.001).



SCAM regression model demonstrated a saturation-like pattern: sudden increase in median Z-score (i.e., less effective treatments) from the top decimal downwards, reaching a saturation around decimal group four.

CONCLUSIONS

- Our results demonstrate the predictive power of DDA-score-based treatment ranking across solid tumors and MTAs, with **top-ranked drugs having the greatest efficacy**.
- DDA can serve as a practical and economic in silico avatar system for treatment planning and can potentially address challenges with complex molecular profiles in routine clinical settings.
- The predictive power of DDA indicates that this method can potentially be utilized for trial enrichment purposes due to its speed and scalability.

REFERENCES

(1) Petak et al., NPJ Precis Oncol. 2021 5:59
(2) Iorio et al., Cell. 2016 166:740-54

DDA

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