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Predicting patient treatment response and resistance via single-cell transcriptomics of their tumors.

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Background: Tailoring the best treatments to cancer patients is an important open challenge. Here, we build a precision oncology data science and software framework for PERsonalized single-Cell Expression-based Planning for Treatments In Oncology (PERCEPTION). **Methods:** Our approach capitalizes on recently published matched bulk and single-cell transcriptome profiles of large-scale cell-line drug screens to build treatment response models from patients' single-cell (SC) tumor transcriptomics. Our approach is a two-step process: first, the prediction models are trained on large-scale bulk-expression profiles of cancer cell lines and then, in a second step, the models' performance is further optimized by training on SC-expression profiles of cancer cell lines. **Results:** First, we show that PERCEPTION successfully predicts the response to monotherapy and combination treatments in screens performed in cancer and patient-tumor-derived primary cells based on SC-expression profiles. Second, it successfully stratifies responders to combination therapy based on the patients' tumor's SC-expression in two very recent multiple myeloma and breast cancer clinical trials. Thirdly, it captures the development of clinical resistance to five standard tyrosine kinase inhibitors using tumor SC-expression profiles obtained during treatment in a lung cancer patients' cohort. Notably, PERCEPTION outperforms state-of-the-art bulk expression-based predictors in all three clinical cohorts. **Conclusions:** In sum, this study provides a first-of-its-kind conceptual and computational method that is predictive of response to therapy in patients, based on the clonal SC gene expression of their tumors. Research Sponsor: U.S. National Institutes of Health.