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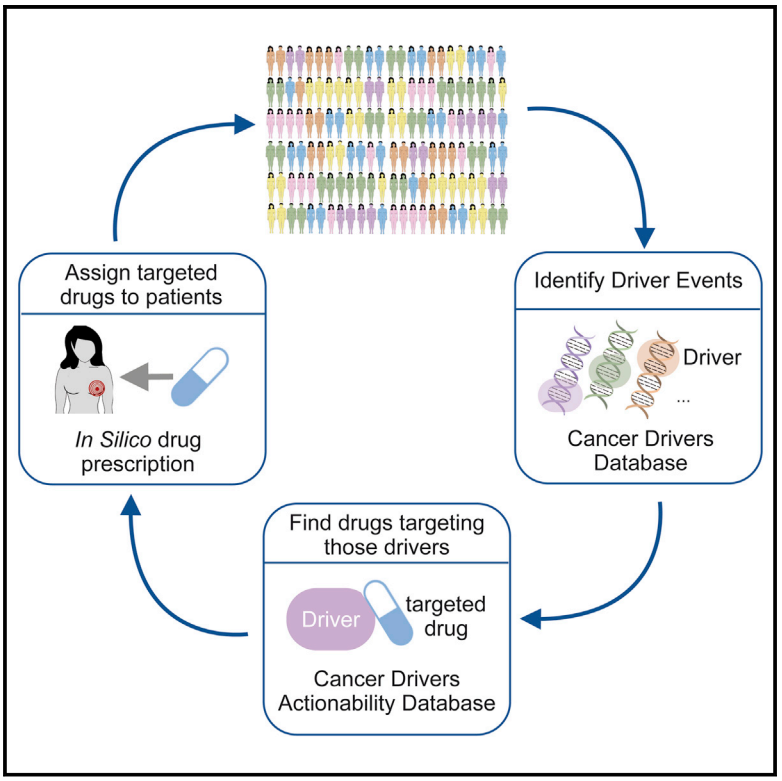
In Silico Prescription of Anticancer Drugs to Cohorts of 28 Tumor Types Reveals Targeting Opportunities

Graphical Abstract



Highlights

- Driver genes are comprehensively identified across a large pan-cancer cohort
- In silico prescription links approved or experimental targeted therapies to patients
- Up to 73.3% of patients could benefit from agents in clinical stages
- 80 therapeutically unexploited targetable cancer driver genes are identified

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In Brief

Using a large pan-cancer cohort, Rubio-Perez et al. develop an in silico drug prescription strategy based on driver alterations in each tumor and their druggability options and use it to identify druggable targets and promising repurposing opportunities.

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In Silico Prescription of Anticancer Drugs to Cohorts of 28 Tumor Types Reveals Targeting Opportunities

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SUMMARY

Large efforts dedicated to detect somatic alterations across tumor genomes/exomes are expected to produce significant improvements in precision cancer medicine. However, high inter-tumor heterogeneity is a major obstacle to developing and applying therapeutic targeted agents to treat most cancer patients. Here, we offer a comprehensive assessment of the scope of targeted therapeutic agents in a large pan-cancer cohort. We developed an in silico prescription strategy based on identification of the driver alterations in each tumor and their druggability options. Although relatively few tumors are tractable by approved agents following clinical guidelines (5.9%), up to 40.2% could benefit from different repurposing options, and up to 73.3% considering treatments currently under clinical investigation. We also identified 80 therapeutically targetable cancer genes.

INTRODUCTION

Recent advances in DNA sequencing technologies provide unprecedented capacity to comprehensively identify the alterations, genes, and pathways involved in the tumorigenic process, raising the hope of extending targeted therapies against the drivers of cancer from a few successful examples to a broader personalized medicine strategy (Garraway and Lander, 2013; Stratton, 2011). However, large-scale studies confronted with the high degree of inter-tumor heterogeneity have uncovered long catalogs of cancer driver genes (Davoli et al., 2013; Kandoth et al., 2013; Lawrence et al., 2014; Tamborero et al., 2013a; Vogelstein et al., 2013). The goal of using a tailored approach to treat all tumor patients may thus require developing a vast arsenal of anticancer targeted drugs. In addition, advances in our ability to precisely assign the most effective targeted therapy to each patient based on the genomic events driving the tumor are urgently needed. The present study offers a comprehensive assessment of the potential scope of targeted drugs in a large pan-cancer cohort. To pursue this goal, we developed a three-step in silico drug prescription strategy (Figure 1), which included identifying the driver events acting across the cohort, collecting all therapeutic agents targeting them, and connecting each patient to all targeted therapies that could benefit them, thus producing a landscape of the scope of targeted therapeutic agents in the cohort.

Significance

The development of therapies targeting altered driver proteins holds the promise of selectively and efficiently eliminating cancer cells. Nevertheless, the extent of applicability of available anticancer targeted agents is unclear. Exploiting a large pan-cancer therapeutic landscape covering 6,792 tumors, we found that the prescription of approved therapeutic agents following their clinical guidelines could provide treatment only to a small fraction of tumor patients. Nevertheless, we also uncovered promising repurposing opportunities and found that agents in clinical trials could benefit an important fraction of cancer patients upon approval. Furthermore, we identified additional target genes for therapeutic development.