Upgraded computational tool boosts search for cancer vulnerabilities

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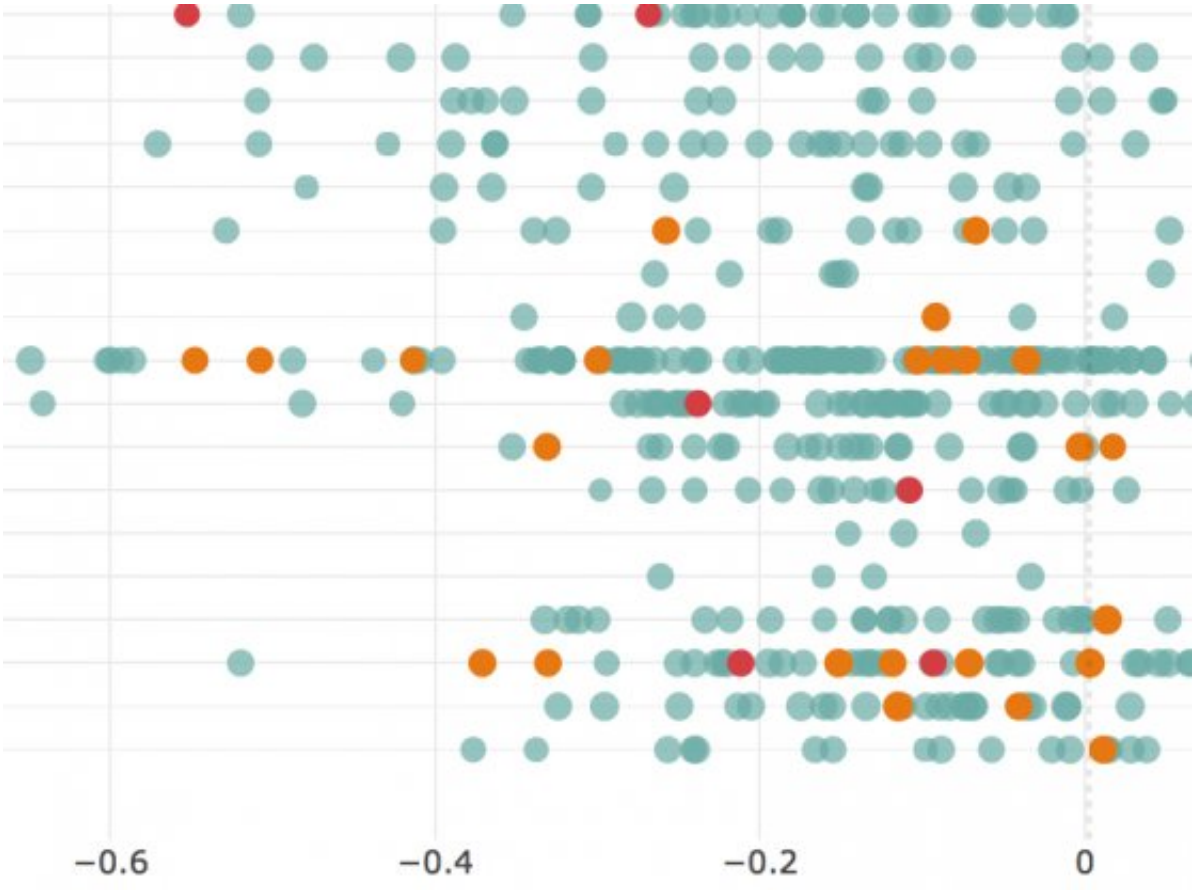

Credit: Broad Institute of MIT and Harvard

Researchers on the Broad Institute's Cancer Dependency Map (DepMap) team have released DEMETER2, an upgraded version of an open source software tool that identifies cancer cells' genetic dependencies (genes

they need in order to survive).

The tool is fueled by data from genome-scale RNA-interference (RNAi) screens, which allow researchers to individually suppress thousands of genes and measure the effects on cancer cells' survival. This approach can help researchers locate key vulnerabilities in the cancer genome, insights that may reveal new drug targets and drug development opportunities.

Writing in *Nature Communications*, DepMap team members led by James McFarland and Zandra Ho of the Broad's Cancer Data Science (CDS) group and CDS associate director Aviad Tsherniak also announced the release of the largest cancer dependency dataset compiled to date, covering 712 cancer cell lines and 54 types of cancer.

RNAi can provide valuable biological insights and can complement CRISPR-based screens. While CRISPR knocks out a gene out completely, RNAi can decrease a gene's activities by degrees. The two approaches can thus affect a cancer cell's survival in different ways.

However, researchers have noted that RNAi screen data are notoriously noisy, often muddled by false-positive results. In 2017, the DepMap team released DEMETER, a computational model that corrects for the false-positives in large-scale RNAi datasets. DEMETER laid the foundation for a major DepMap study, published that summer in Cell, that mapped gene dependencies within more than 500 cancer cell lines.

DEMETER2 improves on the original DEMETER model in three significant ways:

1. It controls for technical differences between screening experiments, which otherwise complicate efforts to merge data across cell lines and different screening datasets.

2. It provides metrics for assessing the confidence of identified genetic dependencies.
3. Instead of grading each gene's dependency scores on a curve (relative to other cell lines for each gene), it reports them in absolute terms that can be more readily compared.

Those improvements together make it easier to combine data from different RNAi screening efforts from different institutions, allowing more comprehensive assessment of dependencies across cancer types and cell lines. And indeed, the team has used DEMETER2 to integrate data from three large-scale RNAi dependency efforts into the largest such dataset in existence: the Broad Cancer Program's Project Achilles, Novartis's Project DRIVE, and a 76-line breast cancer screen conducted by a team at the University of Toronto.

The unified dataset is openly available to the cancer research community via the DepMap portal. The code for DEMETER2 is available on GitHub.

More information: James M. McFarland et al. Improved estimation of cancer dependencies from large-scale RNAi screens using model-based normalization and data integration, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06916-5

Provided by Broad Institute of MIT and Harvard