

An AI model can help predict adverse events from new drug combinations

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Preliminary data from an artificial intelligence model could potentially predict side effects resulting from new combination therapies, according to results presented at the AACR Annual Meeting 2022, held April 8-13.



"Clinicians are challenged by the real-world problem that new combination therapies could lead to unpredictable outcomes," said Bart Westerman, Ph.D., senior author of the study and an associate professor at the Cancer Center Amsterdam. "Our approach can help us understand the relationship between the effects of different drugs in relation to the disease context."

Many cancer types are increasingly being treated with combination therapies, through which clinicians attempt to maximize efficacy and minimize the chances of treatment resistance. However, such combination therapies can add multiple drugs at once to a patient's already complicated list of medications. Clinical trials that test new drugs or combinations rarely account for other medications a patient may take outside of the tested treatment regimen.

"Patients seeking treatment commonly use four to six medicines daily, making it difficult to decide whether a new combination <u>therapy</u> would risk their health," Westerman said. "It can be hard to assess whether the positive effect of a combination therapy will justify its negative side effects for a certain patient."

Westerman and colleagues—including graduate student Ash Küçükosmanoğlu, who presented the study—sought to use machine learning to better predict the adverse events resulting from new drug combinations. They collected data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), a database containing over 15 million records of adverse events. Using a method called dimensional reduction, they grouped together events that frequently co-occur in order to simplify the analysis and strengthen the associations between a drug and its side-effect profile.

The researchers then fed the data into a convolutional neural network algorithm, a type of machine learning that mimics the way <u>human brains</u>



make associations between data. Adverse events for individual therapies were then used to train the algorithm, which identified common patterns between drugs and their side effects. The recognized patterns were encoded into a so-called "latent space" that simplifies calculations by representing each adverse event profile as a string of 225 numbers between 0 and 1, which can be decoded back to the original profile.

To test their model, the researchers provided unseen adverse event profiles of combination therapies to their model, called the "adverse events atlas," to see whether it could recognize these new profiles and properly decode them using the latent space descriptors. This showed that the model could recognize these new patterns, demonstrating that measured combined profiles could be converted back into those of each drug in the combination therapy.

This, Westerman said, demonstrated that the adverse effects of <u>combination therapy</u> could be easily predicted. "We were able to determine the sum of individual therapy effects through simple algebraic calculation of the latent space descriptors," he explained. "Since this approach reduces noise in the data because the algorithm is trained to recognize global patterns, it can accurately capture the side effects of combination therapies."

Westerman and colleagues further validated their model by comparing the predicted adverse event profiles of combination therapies to those observed in the clinic. Using data from FAERS and the U.S. <u>clinical</u> <u>trials database</u>, the researchers showed that the model could accurately recapitulate adverse event profiles for certain commonly used combination therapies.

One complicating factor of combination therapies is the new, potentially unforeseen side effects that may arise when drugs are combined. Using additive patterns as identified by the model, the researchers were able to



differentiate additive side effects from synergistic side effects of drug combinations. This, Westerman said, may help them better understand what could happen when complex adverse event profiles intertwine.

The researchers are developing a statistical approach to quantify the accuracy of their model. "Given that the landscape of <u>drug</u> interactions is highly complex and involves many molecular, macromolecular, cellular, and organ processes, it is unlikely that our approach will lead to black-and-white decisions," Westerman said. "The adverse events atlas is still in the proof-of-concept phase, but the most important finding is that we were able to get snapshots of the interplay of drugs, diseases, and the <u>human body</u> as described by millions of patients."

Limitations of this study include potential difficulties in comparing these data with more sparse data, as well as the limited application of the <u>model</u> to <u>clinical practice</u> until further validation is provided.

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More information: www.aacr.org/meeting/aacr-annual-meeting-2022/

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