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Taking a predictive approach to identifying adverse drug reactions

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In a move aimed at bolstering current systems for assessing and monitoring drug safety, researchers at Children's Hospital Boston have created a new method that combines multiple forms of widely available data to predict adverse drug reactions. Unlike current approaches, which rely on detecting evidence of drug safety issues as they accumulate over time in clinical databases, this new method may be able to identify issues years in advance.

This study, led by Aurel Cami, PhD, and Ben Reis, PhD, of Children's Hospital Boston's Informatics Program (CHIP), appeared online December 21 in Science Translational Medicine.

The safety of drugs in the market is currently assessed through a combination of adverse drug event (ADE) reporting and data mining tools designed to detect previously unrecognized drug-ADEs relationships. While generally effective, these methods may not be able to flag the presence of certain types of ADEs until patients have been on the drug for some time.

Because of these limitations, it can take years before physicians and regulators accumulate enough data to recognize serious safety problems with a particular drug and take appropriate action.

To help address these delays and the public health risks associated with them, Reis and Cami set out to create a mathematical model for predicting drug-ADE relationships that might likely appear within a few

years of a drug's entry into the market.

"This approach allows us to make the important transition from detection to prediction," said Reis, who leads the Predictive Medicine Group within CHIP. "We can potentially identify a dangerous drug side effect early on, instead of having to wait for sufficiently many patients to be affected by it in order to allow for detection."

"Given the myriad of entities and complex relationships that exist in the pharmacological domain, we felt that a network-based approach would be a promising way to try to predict unforeseen but likely adverse events ," said Cami, an instructor in CHIP. "For the approach to be properly validated, though, we knew we needed to use historical and current data on drug ADEs."

To test the network, Reis and Cami integrated information from a commercially available drug safety database from Lexicomp with data on drug chemistry and information on drug and ADE taxonomy. They then took a snapshot of 809 drugs and 852 kinds of adverse events associated with those drugs in the Lexicomp data in 2005. Using the network model, they generated a list of predicted drug-ADE relationships and compared that list to a second snapshot of the Lexicomp database from 2010.

The researchers found the network model to be quite effective at predicting drug-ADE relationships that were absent in the 2005 snapshot but present in that from 2010. For instance, based only on data available in 2005, the model correctly identified 42 percent of the drug-ADE relationships that were subsequently discovered between 2006 and 2010, while correctly recognizing as false 95 percent of drug-ADE pairs that in the 2010 data were categorized as having no association.

"We think the approach holds real promise for strengthening efforts to

identify and manage drug risks by helping drug safety practitioners predict high likelihood events and guide efforts to understand, avoid, and alleviate those events before they start appearing in patients," Cami said. "We're now working to extend these methods to incorporate additional sources of drug safety data and to promote their adoption in clinical drug safety practice."

"Today we rely mainly on post-marketing surveillance to identify unknown drug ADEs, especially with novel drug classes," said Shannon Manzi, PharmD, a pharmacist in the Children's Hospital Boston's Emergency Department and co-author on the study. "It would be impossible for drug companies to test every possible drug-ADE combination, so many unknown relationships surface only after the drug is introduced in the market."

"Being able to predict a potential relationship that was not previously considered," she continued, "will improve the safety of drugs as they come to market, benefiting both drug companies and patients."

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