Researchers develop data-driven methods for analyzing off-label drug use

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(Medical Xpress)—Physicians often prescribe drugs for unapproved indications, but current methods of tracking these off-label uses are limited in scope.

Now, a study by researchers at the Stanford University School of Medicine describes a way to extract and sort valuable information about off-label uses from electronic medical records. The study's authors hope their findings will help to jump-start research into off-label uses that are promising, low-risk and low-cost, as well as flag potentially risky uses for further review.

Drugs prescribed for unapproved conditions, dosages or age groups account for 21 percent of all U.S. prescriptions, according to a 2006 investigation published in the *Archives of Internal Medicine*. But only 27 percent of such uses are supported by robust science.

These statistics are not as alarming as they seem at first glance. The lengthy, costly drug-approval process makes a certain amount of off-label drug use inevitable. Off-label prescriptions are legal in most cases and can be an important source of innovation to accelerate new uses for drugs.

Nigam Shah, MBBS, PhD, assistant professor of medicine and senior author of the new study, believes better tracking and investigation of off-label use can help patients, physicians and regulators, but should also appeal to drug companies, who will benefit from new approved uses for

their products. "Just as detection of abnormal spending is now a routine feature of credit card services, someday off-label use detection could be a routine part of health-care systems," Shah said.

The National Disease and Therapeutic Index relies on physician surveys to monitor off-label prescriptions, but the index is far from comprehensive. "We wanted to describe the whole universe of off-label use," said Kenneth Jung, a graduate student in biomedical informatics and the lead author of the study, published Feb. 19 in *PLOS ONE*.

For an extensive view of off-label drug use, Jung, Shah and their colleagues turned to STRIDE, the Stanford Translational Research Integrated Data Environment, which hosts a comprehensive warehouse of de-identified clinical notes, diagnoses and prescriptions for nearly 2 million patients treated since 1994 at Stanford Hospital & Clinics and Lucile Packard Children's Hospital Stanford.

The researchers built a program to run 9.5 million clinical notes from the STRIDE warehouse through the National Center for Biomedical Ontology Annotator, a tool funded by the NIH and designed to pick out names of drugs, diseases and medical conditions from any text. After filtering their results and checking them for scientific support in the medical literature, they generated a final list of 403 off-label drug uses.

To prioritize these uses for further study, the researchers took into account the cost of each drug and its risk of causing adverse reactions. They used these two parameters to rank each drug use. "Then we placed them into good and bad buckets," Shah said. The "bad bucket" of high-cost, high-risk uses should raise red flags that prompt re-evaluation by physicians and regulators.

For indications in the "good bucket," Shah hopes to expedite tests in cell lines and mouse models. Positive results from these experiments may

ultimately lead to clinical trials and new approvals. "The combination of electronic health records and molecular evidence can make a stronger argument for agencies to fund clinical trials," said Shah, who is also a member of the Stanford Center for Biomedical Informatics Research.

Among the highest-risk drugs were immunosuppressants and anti-tumor agents. One of these was rituximab, an antibody that destroys the B cells of the immune system. It's approved for leukemia and lymphoma, but records show it's also used to treat purpura, a bleeding disorder that causes red or purple patches to appear on the skin. The study suggests that the high cost and considerable risk of severe reactions warrant further study before pursuing this use of the drug.

On the other hand, folic acid appeared to be a low-risk, low-cost treatment for a range of conditions, including mental depression, diarrhea and high cholesterol. Also known as vitamin B9, folic acid is found in some fruits, vegetables and whole grains, but patients often need a supplement to get enough to treat their condition. Also in the "good bucket" was the use of megestrol for patients with non-small cell lung carcinomas; the drug has traditionally been used to relieve symptoms in breast and endometrial cancer patients.

Jung was surprised by how many of the novel uses were predictable based on prior knowledge. "A lot of it actually made sense," he said. "We should have known about some of these uses already. This gives us confidence that the method we developed works."

However, this method cannot yet detect unapproved drug uses by age, sex, dosage or other contraindications. The researchers caution that some adverse reactions to drugs and co-morbidities—patient conditions unrelated to the prescribed drug—could have muddled their results. The team members said they will gain more confidence if they see similar outcomes when they apply the same methods to analyze electronic

medical records from other hospitals.

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