Chicago Tribune

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On phone, 25-year-old killed by stray bullet

Dad's hope: Tragedy can help end violence

By Megan Crepeau and Carlos Sadovi
Chicago Tribune

As she sat in her car in the Heart of Chicago neighborhood, talking by telephone with her father back home in California, a bullet came seemingly from nowhere to cut Aaren O'Connor's promising life short.

The stray bullet — police would tell family later that someone was running down the street, firing at someone chasing them — took the 25-year-old San Diego native's life, adding her name to dozens killed in violence in Chicago so far this year.

Her father, who listened to her confusion and anguish in the moments after that bullet struck her, wants her death to be a wake-up call for the city.

"People need to know what's going on and what kind of loss is taking place here," said David O'Connor, who is helping raise money in his daughter's name for at-risk children in Chicago. "I want her name and her voice to be the impetus for bringing all this violence to an end. I know that's

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GOFUNDME

Aaren O'Connor was shot in the Heart of Chicago neighborhood.

EXCLUSIVE

President talks race, conflict in Illinois visit

Obama catches up with old pals from legislature

By Christi Parsons
Tribune Newspapers

SPRINGFIELD — He had just given an hourlong speech calling for comity in politics, and President Barack Obama craved a few moments with a few friends who remember when he was not a polarizing figure but an effectively bipartisan one — his poker buddies from his eight years in the Illinois Senate.

The three retired state senators, two Democrats and a Republican, were still laughing about Obama's warmly received address to the Illinois General Assembly when he sat down Wednesday to join them for an interview with Tribune Newspapers about the legislative gridlock in Washington and his role in it.

In a free-wheeling exchange, Obama said that he doesn't think his race explains the Republican fortress against his agenda or that having lawmakers over for drinks or to watch football every weekend would have made a difference

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TRIBUNE WATCHDOG

E. JASON WAMBSGANS/CHICAGO TRIBUNE

Algorithms cover a glass wall at Columbia University in New York, where data scientist Nick Tatonetti, center, and his team used novel techniques in signal detection to identify potentially harmful drug interactions hidden in a vast database.

The hunt for dangerous doses

In a unique collaboration, the Tribune and top scientists uncovered drug combinations linked to an increased risk of a serious heart condition. By mining the universe of big data, then testing in a lab, the team created a new model to protect people from hidden drug interactions.

By Sam Roe and Karisa King | Chicago Tribune

The experiment began with thousands of patient files, millions of prescription orders, billions of clinical measurements and a single question: Could big data be used to discover deadly drug combinations?

For decades, scientists have wrestled with the problem that trusted prescription medications can combine in dangerous ways, often placing Americans at risk when they take more than one drug. Sometimes the dangers are well-documented. In other cases, they remain hidden from everyone: doctors, pharmacists, drugmakers and patients.

But in recent years a new era of data analysis has dawned. Across fields as varied as medicine and finance, researchers are developing powerful new mathematical formulas to reveal patterns within patterns and clues within clues.

The Chicago Tribune, in a unique collaboration with data scientists, pharmacologists and cellular researchers at Columbia University Medical Center, set out to see if these same novel techniques could be used in the hunt for risky drug pairs.

Two years later, the results are in: The team has identified four drug combinations associated with a heart condition that can lead to a potentially fatal arrhythmia. The drugs include several widely prescribed medications, none of them linked to the cardiac condition on its own.

To find the potentially risky combinations, the Tribune enlisted the help of scientists at Columbia, who used sophisticated algorithms to analyze a massive government database of drug complaints for signs of the heart condition. The team then used 380,000 electronic hospital patient files to confirm which drug pairs were indeed associated with an increased risk.

The team next turned to Columbia cellular researchers, who tested one of the drug combinations on individual cells.

The tests found that the combination — ceftriaxone, a popular antibiotic, and lansoprazole, a former blockbuster heartburn medication best known by the brand name Prevacid — blocked an

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Thursday, February 11, 2016

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The tests found that the combination — ceftriaxone, a popular antibiotic, and lansoprazole, a former blockbuster heartburn medication best known by the brand name Prevacid — blocked an electrical channel crucial to the heart, providing a biological explanation for why these drugs might be interacting.

E. JASON WAMBSGANS/CHICAGO TRIBUNE

Algorithms cover a glass wall at Columbia University in New York, where data scientist Nick Tatonetti, center, and his team used novel techniques in signal detection to identify potentially harmful drug interactions hidden in a vast database.

The investigation is believed to be the first time anyone has discovered a potential drug interaction by searching for signals in the Food and Drug Administration's complaint archive, then confirming the findings through patient records and cellular testing.

The project is also noteworthy for how it mined the data: The team intentionally looked for evidence where none was visible.

Typically, researchers trying to spot drug interactions analyze the FDA archive and scientific literature for signs that a pair of medications is causing harm. If no patient has reported a particular interaction, there won't be any obvious clues. But that doesn't mean the problem isn't occurring, or that it can't be found.

To identify hidden interactions, the scientists working with the Tribune analyzed indirect evidence: side effects associated with the dangerous heart condition. The researchers could use the side effects to lead them to drug pairs that might be risky.

It's similar to the way astronomers infer the presence of black holes by observing their side effects, such as the gravitational pull on neighboring stars.

The Columbia scientists cautioned that the study, published Wednesday in the journal Drug Safety, does not prove cause and effect and that the results are preliminary. They said further research and, potentially, a clinical trial are needed.

But the project has demonstrated the potential of an innovative scientific model that offers a new way to protect patients and save lives.

The FDA, which is charged with protecting consumers from drug interactions, said it welcomed the new data mining effort and would look at the findings.

Drugmakers contacted by the Tribune because the study flagged their medications stressed their commitment to safety. Citing medical literature or their own research, several companies said they had seen no evidence that their drugs caused such interactions.

It's unclear how many people in the U.S. die each year of drug interactions, but researchers estimate tens of thousands are hospitalized annually. And the risks are escalating. One in 5 Americans take three or more drugs. One in 10 people take five or more — twice the percentage as in 1994.

Yet the issue has few advocates, there is little public awareness and the amount

of research is startlingly thin.

At the same time, doctors and hospitals are collecting and storing an enormous amount of data every day: prescription drug orders, lab measurements, diagnoses and patient complaints — digital information with the potential to transform the way we identify health hazards.

Joining the Tribune in the quest to make use of this new information were a creative data scientist who was determined to prove his skeptics wrong; a former medical school dean who spent years raising awareness about drug interactions but was often left frustrated; and a noted Columbia scientist who opened up his cellular research lab to see if the signals detected deep in the data were indeed real.

Something to prove

Five years ago, Nick Tatonetti fed 40 mice nothing but butter and Sprite. Every Friday he used a tiny needle to inject each mouse with insulin and then carefully nicked its tail with a razor blade to draw samples of blood.

It was a curious sight: a data scientist logging long hours in the animal lab. But Tatonetti had something to prove. Critics were skeptical about his novel approach to identifying risky drug combinations.

At the time, Tatonetti was a 27-year-old doctoral student at Stanford University, working in the growing field of biomedical informatics, or the use of data science to study medicine. Drug interactions intrigued him, and he began exploring the most complete database on the problem: an FDA archive of millions of reports from physicians, drugmakers and consumers about bad reactions to medications.

But Tatonetti thought the database had a weakness: If a bad reaction to a drug was rare, or rarely reported, researchers couldn't determine whether there was a problem. There simply wouldn't be enough complaints to analyze.

Tatonetti wondered if the concept of signal detection could be used to reveal hidden drug interactions.

Signal detection theory had been in use for years and has its roots in radar. When early radar operators looked at a screen, they had to determine whether they were seeing a real signal — an enemy plane, ship or missile — or insignificant noise.

Likewise, when scientists analyze big data, they try to distinguish between a real event — say, a health risk caused by a new drug — or random complaints one would expect by chance.

But Tatonetti wanted to take this concept one step further, using a technique he called latent signal detection.

Instead of looking for a direct signal in the FDA database, could he search for indirect evidence — the black hole approach? Could he find hidden interactions that way?

Using nothing more than his MacBook Pro, Tatonetti identified all side effects linked to drugs known to cause diabetes-related complications, such as high blood sugar. This created a side effect profile for such medications. He then scanned the FDA database for which drug pairs, when taken together, had side effects that closely matched this profile.

He made a surprising discovery. Two of the world's most prescribed drugs, the antidepressant paroxetine and the cholesterol-lowering medication pravastatin, were associated with high blood-glucose levels when administered together — a finding important to people with diabetes.

Tatonetti published his work in peer-reviewed scientific journals and was invited to speak at conferences. But invariably somebody would ask: How do you know for sure these drug combinations are harmful? Isn't this all speculative?

Tatonetti hit the animal lab to see if his findings would hold up to traditional

E. JASON WAMBSGANS/CHICAGO TRIBUNE

Data scientist Nick Tatonetti, center, and team members Tal Lorberbaum, left, and Phyllis Thangaraj work on calculations related to the project.

scientific testing. He fed his mice a high-fat, high-sugar diet until they teetered on the edge of being diabetic — a condition that would help reveal any changes in their health once Tatonetti treated them with drugs. The results: Mice given both paroxetine and pravastatin had higher blood sugar than the control groups.

He emailed his findings to the FDA, but agency officials were unimpressed. According to Tatonetti, the officials looked in their database and saw few complaints of paroxetine and pravastatin causing high blood sugar.

"That was the entire point of my work," Tatonetti said. "They didn't get it."

The FDA declined to comment.

Soon after, Columbia's medical school in New York hired Tatonetti to be an assistant professor of biomedical informatics and to run his own data lab.

The Tribune, which was investigating drug interactions, met Tatonetti the following fall, in September 2013. His office was a small, windowless room in an aging building near 168th Street and Broadway.

Tatonetti had a trim black beard and wore jeans and a sweater. A tattoo of an anatomically correct Sacred Heart was visible on his left forearm. "My mom is super Catholic," he said. "It's a little bit of my mom in it, a little bit me."

Picking up a red marker, he drew a diagram directly on the office wall — a wall he had coated with washable, whiteboard paint — and explained his work on interactions.

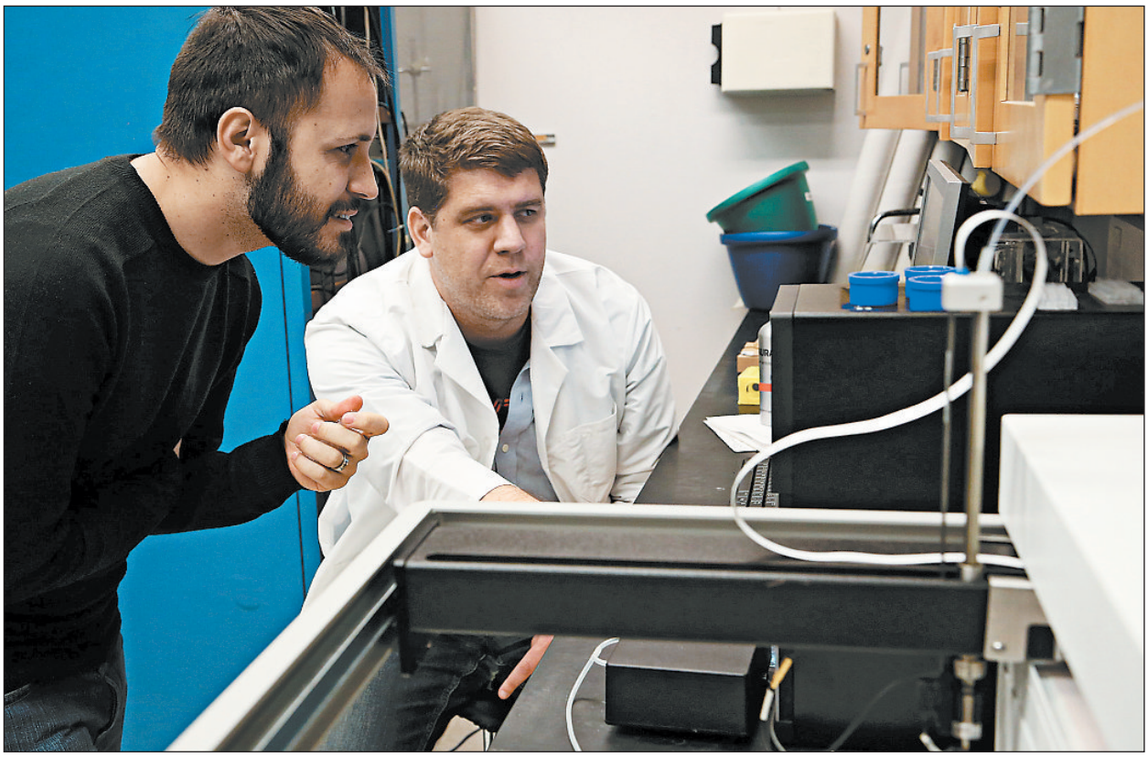
But he remained frustrated by the FDA and seemed ready to move on to other projects.

The Tribune made a proposal: Instead of looking at drug combinations that might raise blood sugar, what if he searched for drug combinations that might cause sudden death? The FDA might pay attention to those findings.

Tatonetti said he was not an expert on sudden death. The Tribune said it knew somebody who was and believed he would be willing to help.

A baffling condition

Drive north on Oracle Road out of Tucson, Ariz., and you come to the foothills of the Catalina Mountains, red granite peaks harboring rattlesnakes, bobcats and



E. JASON WAMBSGANS/CHICAGO TRIBUNE

Tatonetti, left, and cell researcher Kevin Sampson check on testing to see if a drug pair would block an electrical channel involving the heart.

hummingbirds. There, in a gated community, lives Dr. Ray Woosley, one of the nation's leading experts at uncovering dangerous drug combinations.

Back in the 1990s, when he was chairman of pharmacology at Georgetown University Medical Center, Woosley and his colleagues helped show that the popular antihistamine Seldane, when taken with certain antibiotics and antifungal drugs, could cause abnormal heart rhythms and sudden death. Unlike Tatonetti, Woosley's work got the FDA's attention; Seldane was eventually pulled from the market.

Woosley went on to become the dean of the University of Arizona's medical school but never lost interest in drug interactions. "It's a huge public health problem," he said, "but it is enormously frustrating. People are dying and the problem is ignored."

Now retired as dean, he still researches the same side effect that doomed Seldane: a baffling abnormality of the heart's electrical activity known as QT prolongation.

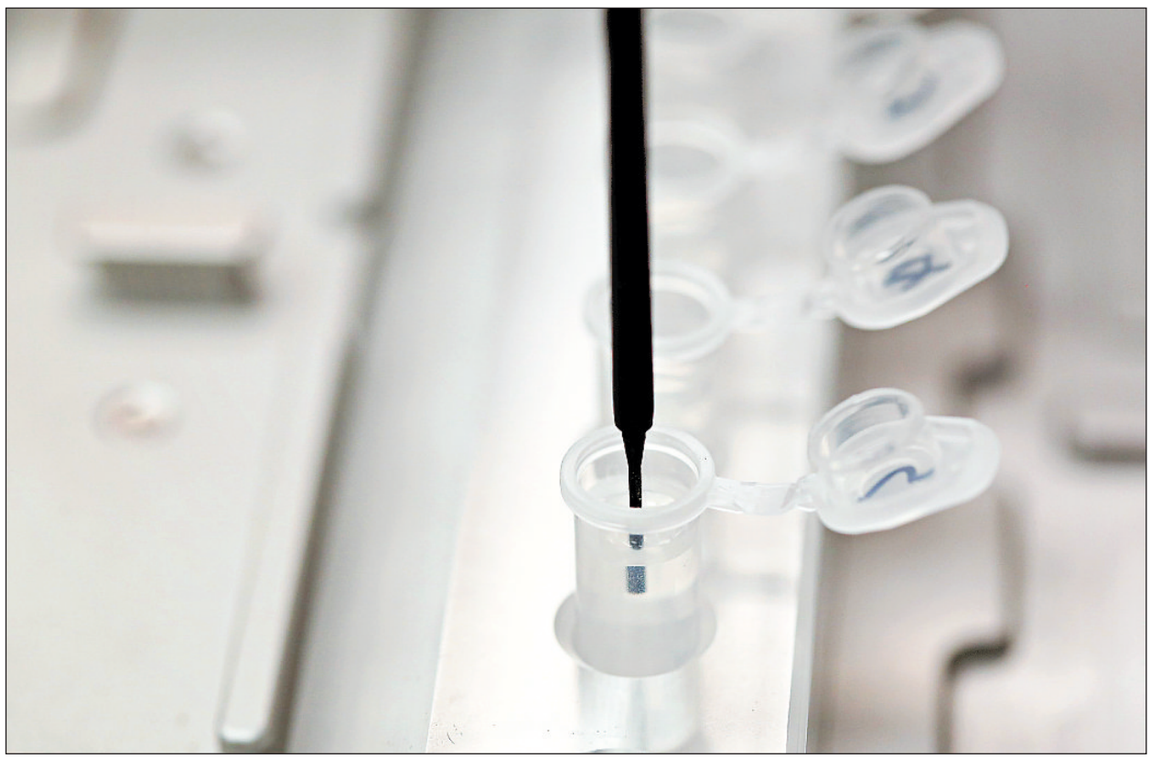
The "Q" and the "T" refer to the electrical waves on a patient's electrocardiogram. To demonstrate, Woosley makes a fist, squeezes it, relaxes it and squeezes it again, simulating a heart pumping. The time between when the heart starts squeezing to when it finishes relaxing and prepares to beat again is the QT interval.

If this interval lengthens markedly, the condition is called QT prolongation. And an increase of 50 milliseconds — faster than the blink of an eye — can trigger a potentially fatal arrhythmia. The heart starts beating so fast that it is essentially quivering and not pumping any blood. The heart's waves on the electrocardiogram resemble twisted spikes — hence, the name of this form of arrhythmia: torsades de pointes, French for "twisting of the points."

Not enough blood reaches the brain, and victims black out. "And it happens very quickly," Woosley said, "within seconds."

Some people are born with a long QT interval and are at risk of the dangerous arrhythmia, but more than 50 medications have been shown to cause both conditions. No one knows how many people have died, because unless a person is connected to an ECG monitor at the time of death, it is difficult to prove that an abnormal heart rhythm was the culprit.

Woosley and other scientists think many unexplained deaths, such as young peo-



E. JASON WAMBSGANS/CHICAGO TRIBUNE

Cells are treated with a mix of ceftriaxone, an antibiotic, and lansoprazole, a heartburn drug, to test for electrical pathway interference.

ple suffering heart attacks or good swimmers who drown, are actually cases of arrhythmia triggered by QT prolongation, perhaps brought on by prescription drugs.

The Tribune told Woosley about Tatonetti's data mining algorithms and how the news organization wanted to use them to try to find drug combinations that might be silently causing QT prolongation. Woosley agreed to help, supplying a list of drugs already known to cause the heart condition as well as related side effects. Back in New York, Tatonetti used the lists to start writing computer code to drill down on the FDA database.

Cognizant that an early coding error could sabotage the entire effort, Tatonetti carefully crafted 10 to 20 lines at a time. Computers catch most typographical mistakes, but an error in logic — typing a plus sign when a minus symbol is needed — could go undetected for weeks, if it is caught at all.

One afternoon, furious typing was followed by long stretches of silence in which Tatonetti stared at the screen and stroked his beard. At one point, he muttered, "It's still not working. Not sure why." Eventually, he found the coding bug and began to rewrite the script. Emphatically banging out the last few keystrokes, he swiveled in his chair and announced: "Awright! So! That's running!"

After weeks of tweaking his algorithm, Tatonetti had results: hundreds of drug combinations with statistically significant signals for QT prolongation. In other words, these pairs were more closely associated with the disorder's profile than one would expect by chance.

But were they truly affecting patients?

Verifying signals

Now was the time to tap into Columbia's rich patient archive — one of the largest of its kind. It contained clinical data on 4 million patients at NewYork-Presbyterian Hospital/Columbia University Medical Center going back to 1989; 20 million prescription orders; and more than 300 million lab results.

Most important, the archive had patients' QT measurements.

Using "de-identified" data that did not include patient names, Tatonetti wrote a computer script that searched for all patients who had ever been prescribed the

suspected drug combinations.

For many pairs, few patients popped up. For others, hundreds did. In those cases, Tatonetti compared the patients' QT levels in the 36 days after they were prescribed the drug combinations to levels for patients prescribed only one of the medications.

As the results slowly appeared on his computer, Tatonetti's eyes lit up. "Whoa! This is a great hit," he said. "An increase of 15 milliseconds in females and 14 in males."

In the end, the patient records validated Tatonetti's algorithm. Dozens of drug pairs were associated with increases in the QT interval in real people.

The team eventually narrowed the list to eight combinations, based largely on which pairs showed the greatest QT increases. In addition, more patients prescribed these pairs had at least one QT value over 500 milliseconds — the threshold for clinical concern — compared with those prescribed just one of the drugs.

But Tatonetti remained concerned. Would skeptics say the findings were largely speculative?

He couldn't test mice, because the hearts of mice and humans are too different. Then Woosley had an idea. One of his old friends worked at Columbia's medical center, in a building attached to Tatonetti's. His name was Robert Kass, but people called him Rocky.

Kass had the perfect background for the project. He had experience researching arrhythmia, was interested in drug interactions and — more important — ran a lab where scientists conducted cellular research.

Woosley wondered: Would Kass be willing to apply the suspected drug pairs to individual cells to see if they affected a crucial electrical channel in a way that could trigger QT prolongation? If so, it would offer a biological explanation for why these drug combinations might be causing the condition.

Tatonetti and Kass soon met in Kass' office. Kass was impressed by Tatonetti and his big data approach. Tatonetti was impressed by Kass and his spacious lab: "It's like its own wing. It has its own doors."

Kass offered more than Tatonetti expected. He agreed to have his lab conduct cellular testing on multiple drug pairs, and work could begin immediately.

Tatonetti walked away ecstatic, but he wondered if this influential figure — at the time vice dean for research at the medical center — was merely humoring him.

"I think he might think it's a little crazy," Tatonetti said.

A tricky test

At Kass' lab, electrophysiology scientist Kevin Sampson opened an incubator the size of a mini-fridge and pulled out a flask where cells are grown for testing. They were Chinese hamster ovary cells — commonly used in medical research, he said, but tricky to handle.

The cells must be fed a nutrient-rich solution or they will not multiply. Once enough are grown for testing, the cells are washed in a chemical to peel them apart. Not enough chemical and the cells stick together; too much and they burst.

And individual cells must be spherical. For the test to work, a single, perfectly shaped cell must roll into a tiny well for analysis.

Of the eight suspected drug pairs, four were determined to be the best candidates for cell testing, and the combination of ceftriaxone and lansoprazole was selected to be tested first. Both are immensely popular medications.

Ceftriaxone, an antibiotic also known by the brand name Rocephin, is sold in 110 countries and is on the World Health Organization's list of essential medicines. Lansoprazole, commonly sold as Prevacid, is a proton pump inhibitor that reduces stomach acid. The drug once generated annual sales of more than $3 billion; it's

CHRIS RICHARDS/FOR THE CHICAGO TRIBUNE

Dr. Ray Woosley, who participated in the project, helped get a risky drug pulled off shelves in the 1990s.

now also available over the counter.

The test would determine whether the drugs affected an electrical pathway in the cell called the hERG channel, which helps coordinate the beating of a heart. When drugs cause QT prolongation, it is almost always because this channel becomes blocked.

The first phase of testing went as expected. When ceftriaxone and lansoprazole by themselves were applied to the cells, the channel was not affected.

But what would happen when the drugs were added together? Several weeks later, after new cells were grown, the team gathered to find out.

Lab manager Jenny Rao handed a tube containing 2 million cells to Sampson. She said the cells appeared healthy, round and mobile. Sampson carefully poured the cells into a receptacle atop the lab's Patchliner, a $313,000 testing machine no bigger than a suitcase.

He said they had an hour to do the experiment; after that, the cells would begin to die. Tatonetti was anxious.

"There are so many ways that this can go wrong and only one way that it can go right," he said.

Sampson clicked the play button on an adjacent computer screen, and the testing machine made a high-pitched whirring sound. A pencil-thin robotic arm glided back and forth, pipetting the cell solution into tiny chambers filled with fluid. Sampson checked the computer screen and reported that seven cells had rolled into wells for testing.

The machine then applied suction to break holes in each cell. To establish a current, electrical pulses were applied to the cells every 20 seconds. Then the drugs were added, slowly flowing across the exterior of the cell membranes.

Sampson pointed to a flat line on the computer screen representing the current going through the cells. If the drugs did not affect the cells, the line would remain flat. "If something happens," he said, "you'll see a dip in that line."

At first, the line didn't budge, but Sampson said the concentration of the drugs was still extremely low. A few minutes later, when the machine added higher concentrations, the line began to stir.

Four potentially risky drug pairs flagged through data mining

Columbia scientists, in collaboration with the Tribune, identified drug pairs associated with an increased risk of QT prolongation, a heart condition that can lead to a potentially fatal arrhythmia. The results are based on public FDA records as well as patient archives at a New York hospital. The researchers stress the results are preliminary and do not show cause and effect. The team agreed that four pairs were worthy of study via cellular testing. The Tribune contacted firms that developed the drugs or are current sales leaders. They emphasized their commitment to safety; several said their own research had shown no evidence that their drugs caused such interactions.

Drug pairs *Treatments*		MEN Change in QT interval *	Patients with at least one QT value above 500 milliseconds *One drug*	 *Both drugs***	WOMEN Change in QT interval*	Patients with at least one QT value above 500 ms *One drug*	 *Both drugs***
Metoprolol *Blood pressure, chest pain*	**Fosphenytoin** *Seizures*	**+18ms**	**13%**	**22%**	*n/a*	*n/a*	*n/a*
Cefazolin *Bacterial infections*	**Meperidine** *Pain*	**+12ms**	**14%**	**20%**	**+14ms**	**13%**	**25%**
Ceftriaxone *Bacterial infections*	**Lansoprazole** *Stomach ulcers, reflux, heartburn*	**+12ms**	**14%**	**19%**	*n/a*	*n/a*	*n/a*
Meperidine *Pain*	**Vancomycin** *Bacterial infections*	*n/a*	*n/a*	*n/a*	**+7ms**	**20%**	**28%**

* Difference in average highest QTc value in 36-day period for patients prescribed both drugs vs. one drug. QTc is QT interval duration corrected for heart rate.

Tatonetti leaned in. Bit by bit, the line fell as more of the drugs were added — suggesting the drug combination was indeed blocking the cell's electrical current.

But the test wasn't over. "It might not be stable," Sampson said. Minutes later, he announced: "Ah! It's holding up."

"Holding up!" Tatonetti said triumphantly.

The test had supported the hypothesis. The drug combination blocked the current — by up to 58 percent, later analysis found.

Tatonetti, who cautioned that the results were preliminary, said testing is planned in coming months for other suspected drug pairs. He said he will also apply for a grant to find and test dozens more.

"The most exciting thing about this project," Woosley said, "is that it's right on the cutting edge of science. It's using all of the science out there in novel ways."

Drug companies for the two medications that were injected into the cells said they had no prior evidence that the combination was potentially risky.

Swiss drugmaker Roche, which discovered ceftriaxone, said the firm would not comment further until the study was published. Japanese drugmaker Takeda, which helped develop lansoprazole, said it would analyze the results but no evidence has emerged since the drug hit the market to indicate it would adversely affect the heart.

Among the other drug combinations flagged in the data mining effort that Tatonetti now wants to test in the cell lab: the blood pressure medication metoprolol, which had nearly $1 billion in sales in 2014, and the anticonvulsant fosphenytoin.

AstraZeneca, the 2014 sales leader for metoprolol, said its own research found no sign of QT prolongation attributed to taking metoprolol and fosphenytoin together. Pfizer, the sales leader for fosphenytoin, said it was unaware of any data for the drug that signals concerns regarding the heart condition.

To meet growing demands for data science, Columbia moved the biomedical informatics department into the renovated top floor in an adjacent building. There are two terraces with skyline views. Tatonetti's office has a sliding glass door and a large window overlooking the Hudson River.

It's an exciting time for data scientists, he said. He predicted that he and others will discover hundreds of dangerous drug interactions, one after another, and by doing so will create new knowledge in many fields — molecular biology, pharmacology, genetics.

"That's the dream," Tatonetti said. "I think we will."

From big data to cell testing

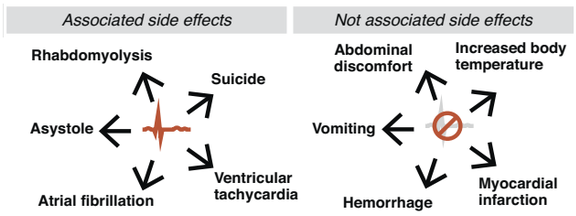
To search for hidden drug interactions, the Tribune collaborated with data scientist **Nick Tatonetti** of Columbia University Medical Center, who had pioneered a new method of data mining called latent signal detection. The team also included a top pharmacology expert and cellular researchers.

The team went looking for drug pairs that could raise the risk of a cardiac condition called QT prolongation, an abnormality of the electrical activity in the heart that can lead to a potentially fatal arrhythmia. If the team succeeded, the project would demonstrate the potential of a method that ultimately could help protect patients and save lives.

The research had three steps:

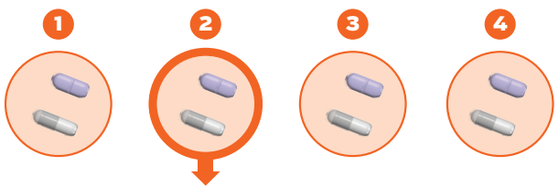
Step 1: Data mining

Some medications are known to cause QT prolongation. The team compiled all the side effects associated with these drugs, plus a list of side effects that were definitely not associated. Tatonetti then searched through a federal health database, looking for drug pairs that seemed to fit this specific profile.



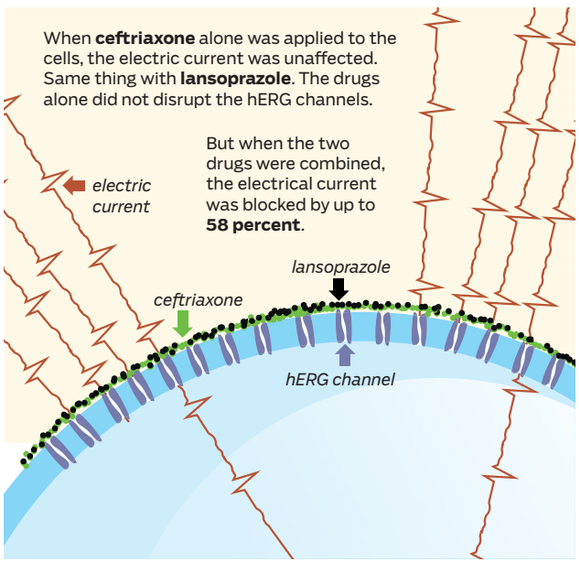
Step 2: Patient records

The data mining yielded a long list of suspected drug pairs. The next step was to check the pairs against patient records at Columbia University Medical Center to see if the association with QT prolongation could be confirmed. For eight pairs, a significant number of patients prescribed those drugs had longer QT intervals. The team chose four combinations as the best candidates for cellular testing.



Step 3: Cellular tests

The membranes of cells have thousands of hERG channels that are conduits for electricity and help coordinate the beating of a heart. If a drug pair blocked these channels, it would provide a biological explanation for why this combination might increase QT intervals. The first pair tested was ceftriaxone, an antibiotic, and lansoprazole, a heartburn medication.



SOURCES: Columbia University Medical Center; Centers for Disease Control and Prevention; FDA; Dr. Ray Woosley; Tribune reporting

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