

A DNA Tragedy

Genetic tests to prevent adverse drug reactions may save tens of thousands of lives a year, but for a troubled boy named Michael they came too late.

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By David Stipp

The death of nine-year-old Michael Adams-Conroy didn't seem at first like a signal event in medicine. It seemed like homicide.

Michael's short life was an uphill struggle from the start. Malnourished as an infant, he was taken from an abusive mother and placed in a temporary foster home before his first birthday. By the time he was 6, his medical record bulged with bad news: Michael was cognitively blunted and violently moody, and appeared to be afflicted with the brain damage of fetal alcohol syndrome, as well as with obsessive-compulsive disorder, tic-inducing Tourette's syndrome, and attention-deficit hyperactivity disorder.

Over the next few years he achieved a semblance of normalcy, thanks to the steadying hands of the resolutely affectionate couple who adopted him at age 3 and to daily doses of drugs to check his tics and obsessions. Small for his age, he took pride at finally being able to fling his coat up onto the grownups' pegs at his home in Martins Creek, Pa., a one-stoplight town two hours north of Philadelphia. He was learning to bowl in a league for handicapped kids and help his dad tend the garden.

Then in 1995 tragedy struck: While recuperating from what seemed to be flu, Michael went into a prolonged grand mal seizure and died. His grieving parents, Jayne and Neil, soon got another shock: An autopsy showed a massive overdose of Prozac in Michael's blood and tissues, raising the specter of a murder charge against them and prompting juvenile authorities to take away their two other adopted children pending the outcome of a homicide investigation.

Thus began the Adams-Conroys' painful pilgrimage to a medical frontier known as pharmacogenetics, the study of how genetic idiosyncrasies influence responses to drugs. In their quest for exonerating answers, they would learn that one of their son's problems was truly insidious: He harbored an unsuspected enzyme deficiency that hindered his ability to me-

tabolize a broad array of drugs, from cough medicines to antidepressants. As it happened, he was taking large doses of one of those drugs, Prozac, to help control his emotional outbursts. The enzyme deficiency, stemming from a quirk in his DNA, apparently caused the drug to build up in his body to a level exceeding any previously reported in cases of Prozac overdose.

At first glance, Michael's case, the details of which were first disclosed last spring in a medical journal, seems a singular tragedy--the ill-starred concurrence of an unusual need for medication, extraordinary dosing, and rare metabolic vulnerability. In one respect it is: Prozac overdoses are rarely fatal.

But hazardous metabolic deficiencies like Michael's are far more common than most patients--and many doctors--realize. In fact, the most unusual thing about his case was that his hidden genetic glitch was precisely pinned down, thanks to a novel, fast-evolving technology. As such, his heart-rending story has the makings of a galvanizing wake-up call about the emergence of a powerful new tool to help doctors abide by their discipline's most fundamental tenet: First, do no harm.

The next time your eyes glaze over when perusing the side effects on a drug label ("Heck, my doctor vetted this stuff") and you take pill in hand ("It wouldn't be on the market if it were really all that risky"), consider this: Adverse drug reactions, or ADRs, kill about 100,000 hospitalized patients in the U.S. annually, not counting accidental overdoses. Another 2.2 million experience serious nonfatal adverse reactions.

Not all medical experts buy these alarming estimates, from a study published in 1998 in the *Journal of the American Medical Association*. But even skeptics concede that ADRs may well wipe out the equivalent of a small town, perhaps 30,000 to 40,000 Americans, each year.

This quiet carnage doesn't imply that the drug industry is unscrupulous, that the Food and Drug Administration is lax, or that doctors are reckless. Many--perhaps most--adverse drug reactions are due to the fact that drugs are developed and prescribed in a one-size-fits-all way, metabolically speaking, as if our bodies were not as wildly different on the inside as they are on the outside.

Until recently there was no alternative. But now that the human genome is an open book, personalized medicines--drugs tailored to our genetic idiosyncrasies--will soon be possible. In a decade or so, pills geared to particular "genotypes" are expected to begin arriving in pharmacies along with tests to show who should get them. Eventually we'll look back in wonder at how we used to play guinea pig in the primitive therapeutic experiments our doctors carried out each time they wrote new prescriptions for us, just as we now shake our heads about the poor chumps who got

blood transfusions before it was possible to match donors' and recipients' blood types. (The adverse reactions included kidney failure and fatal clots.)

Signs of this transformation are already appearing (see box). In a move with revolutionary implications, PPGx, a startup in Morrisville, N.C., is preparing this fall to launch the first direct-to-consumer genotyping service. To be offered via a Website called Spotlight Health (www.spotlighthealth.com), the service's initial test will focus on the so-called 2D6 gene, says CEO Josh Baker. The gene is the blueprint for a "cytochrome P450" enzyme, one of a large family of chemically similar enzymes that break down drugs and toxins in the liver. The one made by the 2D6 gene is particularly important: It helps metabolize about a fourth of all drugs, including about half of the 100 bestselling medicines.

Reams of data exist on such enzymes, showing how fast different variants metabolize various drugs. But until recently, checking patients' enzyme types has been impractical except in special cases--it has usually required administering a dose of a drug known to be metabolized by an enzyme and then monitoring concentrations of the medicine's breakdown products in the urine over many hours. That's now changing because of the same high-speed gene-sequencing technology used to parse the genome--some enzymes, such as 2D6, can now be readily typed by analyzing the DNA from a tiny sample of cells.

Baker says PPGx plans initially to offer its 2D6 test free to at least 5,000 people in a pilot program. If the pilot goes well, the company expects to charge less than \$50 a test. It also plans to market a more sophisticated version for use by doctors. If you request the test, PPGx will send you a cheek-swab kit, which you'll use to scrape a few cells from the inside of your cheek. After you mail this tissue sample back to the company, PPGx technicians will extract the DNA from your cells and examine the pattern of "nucleotides," or chemical building blocks, in your 2D6 gene. If your pattern matches one of the four or five most common 2D6 variants known to cause slow metabolism of drugs, you'll be advised to alert your doctor to the results.

Some 6% to 10% of Caucasians carry the sluggish 2D6 variants, increasing the risk of adverse drug reactions. This unlucky group is also immune to the painkilling effect of codeine--slow metabolizers' 2D6 enzyme can't efficiently process codeine into morphine, the chemical that does most of the painkilling when codeine is taken. People with deficient 2D6 enzymes are also thought to have abnormally low pain tolerance, for their bodies' natural painkillers, such as the morphinelike endorphins associated with "runner's high," aren't produced at a normal rate.

As it happened, Michael Adams-Conroy had one of these hazardous types of 2D6, and Prozac is one of the drugs metabolized by the 2D6 enzyme.

Several other bellwether genomics companies--Orchid BioSciences and Millennium Pharmaceuticals' MPMx diagnostics unit, to name two--are mulling Web-based ventures similar to PPGx's. One motive is that their researchers need DNA samples from lots of people for studies aimed at correlating genetic quirks with susceptibility to diseases and responses to drugs. Such studies promise everything from early-warning tests for old-age diseases to outright cures for age-old scourges. People who tune into pharmacogenetics on the Web should make good candidates for such research, the thinking goes--they might even be motivated enough to hang in for the long-term studies needed to establish how genetic tendencies play out over time.

One startup, DNA Sciences in Mountain View, Calif., is already testing this logic. In a closely watched move, it recently launched a Website explicitly aimed at aggregating volunteers for gene studies. The company declines to disclose how many people have volunteered for its "gene trust" so far--a process that involves filling out an online medical-history questionnaire and agreeing to let a phlebotomist hired by the company drop by to take a blood sample. But chief business officer Steven B. Lehrer boasts, "The response has been phenomenal. Our typical volunteer is someone who's watched a sister go through a lot of terrible treatments for breast cancer and wants to do something to help save others from having to go through the same thing."

Two basic kinds of genotyping will spring from studies at companies like DNA Sciences. One, called predisposition testing, will predict risks for major diseases. Such tests have gotten lots of press because of the gnarly issues they raise, including possible discrimination by health insurers against people with "bad genes." Since predisposition testing is so controversial, it isn't likely to take off for years.

The other kind of testing is designed for use after disease symptoms appear to help pin down a diagnosis, monitor disease progression, or, like PPGx's 2D6 test, help select the best drug. This kind of genotyping will be far less controversial and technically simpler than predisposition tests--which explains why tests like PPGx's represent the leading edge of the personalized-medicine revolution.

Don't expect the one-size-fits-all paradigm to fade quickly, though. A massive tug of war is shaping up over personalized medicine, and how it plays out will have profound effects on health care for the rest of our lives.

The initial lineup on the pro side includes savvy patients anxious to reduce the risk of adverse drug reactions, genomics visionaries out to change the world, and a sparse troop of avant-garde physicians. Waiting eagerly in the wings are personal-injury lawyers, who will doubtless pile on shortly with malpractice suits in cases of adverse drug reactions that might have been avoided with genotyping.

On the other side are HMOs and insurers reluctant to pay for costly new tests and medicines, conservative pharmaceuticals executives loath to forgo one-size-fits-all blockbusters, and, most important, doctors resistant to changing ingrained practice patterns.

"Genotyping patients before prescribing drugs is going to be a tough sell with most doctors," opines Dr. Paul Billings, co-founder of GeneSage, a San Francisco startup that uses the Web to school consumers and health professionals on genetic testing. "Traditionally, we give a patient a standard medication, starting at a low dose; then, if he comes back complaining of side effects, we just switch to another drug. This works quite well in 80% of cases." In the other 20%, it's sometimes hard to tell whether a patient got worse because of side effects or illness.

Further, with the trial-and-error method, says Billings, "physicians get more office visits, so unless they work for HMOs, they get paid more doing things that way." For their part, HMO doctors are likely to be discouraged by their bean-counting bosses from using tests to predict drug responses until studies prove the costs are offset by savings from avoided adverse drug reactions. That could take many years.

Another barrier is that "most doctors don't understand how much impact pharmacogenetics can have in routine practice," says Peter J. Wedlund, a University of Kentucky expert on the metabolism of psychiatric drugs. A few years ago he genotyped a patient's 2D6 gene and found she was a slow metabolizer. "I ran over to the psychiatry department where she was being treated for depression and told them about all these drugs she wouldn't be able to handle. About a year later she called me and said that she'd had this awful reaction" to one of the 2D6-metabolized drugs he'd cautioned her doctors against. "It turned out they had just tossed out the information I'd given them." Even doctors knowledgeable about pharmacogenetics rarely think to apply it, adds University of Cincinnati psychiatrist Floyd R. Sallee.

Last spring, Sallee, an expert on pharmacogenetics, co-authored a case report in *The Journal of Child and Adolescent Psychopharmacology* that can be read as an urgent plea for the medical world to pay more attention to the genetic land mines that cause many adverse drug reactions. Its terse, detached style--standard issue for such reports--does little to deflect the emotional wallop of its subject: the events surrounding the death of Michael Adams-Conroy.

Michael's parents, who agreed to be interviewed in the hope that their story will help avert similar tragedies, knew little about their son's frailties when they adopted him and his year-older biological sister, Tamra, in 1989. "We were told they had some delays, maybe learning disabilities or emotional problems," says Jayne.

Gradually, though, their hopes that the two siblings' problems were temporary faded. And "Michael just wasn't developing in nursery school," says Jayne. "He had a real explosive temper and a lot of sleep disruption." And though diminutive, he showed amazing stamina when upset--his tantrums often lasted for hours, during which offers of comfort would be repulsed.

The couple found themselves in continual child-proofing mode. They removed most of their doors so their hyperactive youngsters couldn't shut each other's fingers in them. They tacked Plexiglas over the inside of Michael's bedroom windows--more volatile than his sister, he sometimes hurled toys at the glass during his rages. They raised their kitchen cabinets so Michael couldn't get to dangerous objects--he was terrified of heights.

To Jayne, a former preschool teacher with an air of practiced composure, and Neil, a quiet but affable high-school special education teacher, Michael's hyperactivity and impulsiveness looked familiar--they are hallmarks of attention deficit-hyperactivity disorder, or ADHD, thought to affect perhaps one in 20 children.

But ADHD clearly wasn't his only problem. Michael repetitively picked at his face and clothes. Sometimes he chewed his tongue as if it were a wad of gum. These were signs of Tourette's syndrome, a neurological disorder that causes involuntary movements and vocalizations. Once seen as affecting no more than one in 10,000, Tourette's is now thought to afflict as many as one in 250 people.

Yet other quirks led to a diagnosis of obsessive-compulsive disorder, which often accompanies Tourette's. "Michael did a lot of patterning behaviors," says Jayne. "He had an obsessive thing about tying all his shoes together in knots and would get very angry when you untied them. He'd insist on doing things in threes, like brushing his teeth three times." Normal childhood fears became obsessions. "He'd see a cobweb somewhere in the house and stay awake until two in the morning thinking there might be a spider in his room. Sometimes I could help him get to sleep by taking a plant mister and spraying the walls--I'd tell him that spiders hate plant water."

On the worst days, Michael's maladies seemed to gang up: "Something would set him off and it would spiral into the attitude of the day," says Jayne. "If you told him he couldn't have his sister's cookies in the morning, he'd wake up at night hanging on to his anger about that and throw his trucks at his window."

For all his inner devils, though, Michael could be as endearing as any little kid, sometimes even when he was fussing. Jayne recalls that "he would get hold of notes his teachers sent home about his behavioral problems and try to scribble out what they'd written. He'd tell me, 'I know that's about what

I did today. It's a lie.' Then when I looked at the note, he'd say, 'I still love you, Mom, but you're a bad Mom for reading that.' "

When Michael was about 5, his erratic ways grew more alarming. One morning his parents found him groaning with a bellyache--in the night he'd quietly brought all the food in the refrigerator to his room and obsessively gulped down as much as he could. They weren't amused--they had seen how he could impulsively gobble things and choke, and Jayne had recently had to perform the Heimlich maneuver on him. The episode was a turning point. Worried about further misadventures, the couple sought help from a Philadelphia neurologist, Douglas Wilkerson. He prescribed clonidine, a drug often used to curb Tourette's and obsessive-compulsive symptoms.

A year later another crisis led to a fateful decision. One night when the parents and their three children were having spaghetti, recalls Jayne, "Michael decided his veggie 'meatballs' were smaller than everyone else's. He was so outraged that he screamed and stuck his hands into his spaghetti and threw it all up into the air. It hit the fan and flew everywhere. Suddenly the other kids were screaming and pushing their plates away, 'This is gross! His spaghetti landed on my plate!' Nobody could eat, and everyone was upset. That night Michael screamed nonstop for five or six hours.

"I called the doctor that evening. He could hear Michael screaming in the background and said, 'Why don't we go ahead and try Prozac.' We'd already talked about trying it, and I thought, 'I hate to put this little guy on more medication. But now this is affecting all of us.' "

As is sometimes the case, the drug helped but then gradually lost effect, prompting higher doses. Over the next nine months, Michael's daily Prozac dose was raised from five to 30 milligrams. Soon after it reached 30, he came down with flu. But it wasn't an ordinary case--dehydrated by prolonged vomiting, he became delirious and had to be hospitalized for three days. In hindsight, the severity of his symptoms seems portentous: Nausea was the most frequently reported adverse reaction to Prozac by patients who took it for depression in clinical trials, according to the drug's package insert.

A few months later Michael's Prozac dose was raised to 40 milligrams a day. More bouts of nausea followed over the next year, one leading to another brief hospital stay for dehydration. By the time Michael was 9, his Prozac dose had been ratcheted up to 80, then to 100 milligrams a day. It was a high dose. Adult doses for depression typically range between 20 and 60 milligrams a day, and the maximum recommended daily dose is 80 milligrams. Still, even very high doses of Prozac generally pose little risk. The drug is notably benign compared with older antidepressants, and suicidal patients have been known to gulp down many hundreds of milligrams without dire effects.

Meanwhile, Michael's inner storminess was abating some. Ritalin, a standard treatment for ADHD, was added to his daily medications, helping stem his impulsive outbursts. He was finding ways to channel his obsessiveness--in the Adams-Conroy family room hangs a framed picture he drew at 8 depicting a deer with painstakingly symmetrical antlers. He had found a star to hitch his wagon to: He wanted to grow up to be just like major-league outfielder Jim Eisenreich, who had struggled with Tourette's syndrome and gone on to play in the World Series.

But one day in August 1994, Michael suddenly went down hard while chasing after a ball in the backyard. Says Neil: "I ran over, and he looked up and said, 'Dad, I'm all dizzy and can't get up.' That's when we knew something was wrong."

Similar exercise-induced bouts of dizziness, often accompanied by nausea, occurred over the next few months. "I started carrying plastic bags in my purse in case he vomited on the way to or from school," says Jayne. The couple's anxious calls to Dr. Wilkerson about the episodes led to a somewhat reassuring diagnosis: Michael appeared to be having migraine symptoms. Given their son's obsessive tendencies, adds Jayne, "we didn't want to make a big deal about migraines, so we tried to stay really calm about it."

In late February 1995, Michael came down with what looked like flu. After a day of nausea, he seemed on the mend, recalls Jayne, and by bedtime was keeping down fluids. Soon after, however, the couple heard something banging on the wall of his room.

Running in, they found Michael in a seizure--while convulsing, his elbow was hitting the wall. The scary symptoms quickly passed, and when they phoned Wilkerson a few minutes later, he advised closely monitoring the boy at home rather than taking him to the hospital ten miles away. It had started snowing heavily, and driving was becoming more hazardous by the minute.

Lying on a pallet next to her son's bed, Jayne put a hand on his covers and lulled him with talk about how the whole family had worn red sweatshirts that day. About 3:30 A.M. she was jerked awake when he started convulsing again. This time his seizure didn't stop. His panicky parents called an ambulance, but by the time it arrived, he had stopped breathing. Scooping up her son, Jayne burst out into the snow and thrust him into a paramedic's arms. Riding in the ambulance on the way to the hospital, she says, "Every pore in my body prayed for him to breathe. When we got to the emergency room, there was a wall of white coats between me and Michael. Then they said, 'We're sorry.' "

The grieving couple got through the next few weeks on automatic pilot. Finally, Neil braced up one evening and took his daughter swimming at

the community center. While they were gone, officials from the county children, youth, and families division arrived at the couple's home with a squad of state police. "At first I thought they were salespeople at the door," says Jayne. "Then they shoved a warrant in my face to take the kids."

When Neil arrived home an hour later, he says, "I got out of the car and suddenly all these guys surrounded me. My head was spinning. That's when we found out the coroner had said Michael died of a Prozac overdose and put the word homicide on his death certificate. And it was pointing at us. The assumption was that someone in our house had thrown drugs at him."

Fighting back tears, Jayne managed to pack school lunches to send along for the next day and to make sure Tamra's hair was dry before the kids were taken away. The following morning the couple began a wrenching fight to get them back. They wrested a minor victory during their first session in juvenile court: The children were placed in the custody of Jayne's brother and sister-in-law, who lived nearby. They also won the right to visit their kids. But it would be ten weeks before the children were allowed to return home.

Meanwhile, "we thought the police might charge us with murder any day," says Neil. Grasping at straws, the couple asked Philadelphia psychiatrist Peter J. Meyer, a Tourette's specialist they'd known for some time, for advice. When Meyer saw the coroner's report on Michael, he was immediately struck by something that didn't add up: Both fluoxetine, the active compound in Prozac, and norfluoxetine, a similar compound produced when the drug is processed in the liver, were found at the same high level in the boy's blood at the time of death. "You wouldn't expect to see that in a case of acute overdose," says Meyer.

In acute overdoses, he explains, fluoxetine is usually present in the blood at a much higher level than norfluoxetine. That's because Prozac is metabolized very slowly--patients on the drug don't reach "steady state," in which blood levels of fluoxetine and norfluoxetine are roughly the same, until weeks after they begin taking the medicine. The one-to-one ratio of the two compounds strongly suggested that Michael had died of a chronic accumulation, says Meyer, not a sudden overdose.

The extraordinarily high level of fluoxetine in Michael's blood--way above the highest level previously reported in Prozac overdoses--also argued against the idea that foul play or parental negligence had caused his death. "To get that level as an acute overdose, you'd have to assume he'd been force-fed a huge number of pills. But the autopsy showed there were no pills in his stomach or any signs of trauma," says Ralph Bellafatto, an attorney representing the Adams-Conroys.

Putting the pieces together, Meyer concluded that Michael must have been a slow metabolizer of Prozac, causing the drug and its metabolite to gradually build up to toxic levels. With Meyer's help, the Adams-Conroys contacted Sallee, the Cincinnati pharmacogenetics expert, who initiated the complicated process of getting samples of Michael's tissues from the autopsy in order to check for a 2D6 deficiency. When the county coroner finally handed over the requested samples last year, the test results came back just as expected: Michael was indeed a 2D6 slow metabolizer.

By that time the Adams-Conroys' children had long since been allowed to go home--Meyer's testimony in juvenile court about Michael's probable enzyme deficiency had proved decisive. Following Sallee's finding, the homicide investigation was closed. The Pennsylvania State Police now classify Michael's death as an accident.

After their children were returned, the couple filed a malpractice lawsuit against Dr. Wilkerson, charging that he had been negligent by prescribing high doses of Prozac and then failing to heed symptoms that, in their view, indicated the drug was toxic to Michael. Wilkerson maintains the boy died from a seizure disorder stemming from fetal alcohol syndrome. He also argues that Prozac shouldn't build up to toxic levels in people with 2D6 deficiencies, since test-tube studies indicate that 2D6 isn't the only enzyme able to metabolize the drug.

But several studies reported after Michael's death suggest that 2D6 deficiencies can cause Prozac to build up. In one, published in 1996 in *Clinical Pharmacology & Therapeutics*, a Canadian team gave Prozac to volunteers with and without 2D6 deficiencies, then tracked their blood levels of fluoxetine and norfluoxetine over eight days. The results were clear: "Poor metabolizers appear to be at increased risk for accumulation of fluoxetine and the possible development of fluoxetine-associated toxicity," the team concluded.

In any case, Wilkerson won the suit's first round in a two-day "summary jury trial," a proceeding allowed under Pennsylvania law involving abbreviated presentation of evidence. The two sides settled out of court last year.

Though their legal battles are over, the Adams-Conroys have no sense of closure about their son's death, and probably never will. Only someone who has lost a child, they say, can fully grasp how impossibly painful it is and how tormenting are the regrets about what might have been. "After Michael died, we found out that there were tests" to spot enzyme deficiencies that can cause adverse drug reactions, says Jayne. "I felt devastated when I heard that. It should be the norm that the tests are used whenever there are concerns about possible side effects." Adds Neil: "If it had been the norm, we wouldn't have lost Michael."

As cruel as fate has been to Jayne and Neil, it hasn't tinged all their memories of Michael with anguish. For the past several years Neil has found pumpkins springing up in odd places around the yard. At first he couldn't understand it. Then he remembered: Michael loved to hide pumpkin seeds all over for the squirrels. As Neil walks out with me to my car, we run across one of the ripening, greeny-orange mementos. He looks down at it and, for a fleeting moment, just smiles.

FEEDBACK: dstipp@fortunemail.com