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The X File

Can researchers solve Xander's case before it's too late?

AULD,XANDER
AULD
X

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Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as cancer, diseases of aging, lupus and cardiovascular disease.

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Hope in the Fight Against Sickle Cell

FOR MARY LONG, THE ANSWER TO HER PAIN MAY, LITERALLY, BE RIGHT AROUND THE CORNER.

Her grandmother would hum as she rubbed Mary Long's limbs with liniment. "You're just a puny child," she would say, shaking her head. The rubdowns soothed the youngster, but they didn't erase the aches that seemed ever present in her arms and legs.

In 1950s rural Oklahoma, doctor's visits were reserved for emergencies. So, Long, who played softball and was the point guard on her high school basketball team, lived quietly with her bouts of pain.

When she became pregnant with her first child in 1970, her feet felt as if they were being stuck with needles. Her hands throbbed. Eventually, the pain forced her to stop working. When Long visited her doctor, blood tests revealed her pain stemmed from a form of sickle cell disease.

In SCD, red blood cells change from their customary round or oval shapes to the form of a crescent or "sickle." Unlike normal cells, which are pliable and slide easily through the blood vessels, sickled cells become hard and sticky. They stack up inside vessels, which eventually results in inflammation and excruciating pain. In some cases, long-term lack of oxygen can lead to organ damage, stroke or even death.

The disease can affect people of all races, but it's most prevalent in those with African-American heritage, like Long. Health authorities estimate that 100,000 people in the U.S. suffer from SCD, which has no known cure.

When Long received her diagnosis, her doctor offered no real solutions. "I figured I would just have to live with the pain," she says. And she did.

Despite chronic aches and discomfort, Long returned to the workforce. In the 1980s, she came to work at OMRF. Since then, she's been a member of the staff that cleans the foundation's offices and labs, ensuring that researchers at OMRF can focus their time and attention on developing a deeper understanding of human biology. One of those researchers is Dr. Rodger McEver, who started his lab at OMRF a few years after Long came aboard.

McEver trained as a hematologist, a physician who specializes in blood disorders, and focused his research on white blood cells. Specifically, he studied P-selectin, a protein that mobilizes white blood cells to hunt down and stop invaders like bacteria in the body. McEver and his colleagues created an antibody that blocks P-selectin's functions. Research indicated that, in laboratory mice, P-selectin exacerbated sickle cell disease symptoms.

To explore clinical applications in humans, McEver helped create a biotechnology company, Selexys. The company fine-tuned the antibody, making an experimental drug that bound to human P-selectin and blocked its function.

An initial round of clinical testing found the drug to be safe and well tolerated by patients. Then, in a larger, multi-center trial in the U.S., Jamaica and Brazil, the medication showed a marked reduction in pain crises suffered by SCD patients.

Based on those results, the pharmaceutical company Novartis purchased Selexys and its experimental drug in late 2016. McEver hopes the medication, now known as SEG101, will soon be approved for treatment of sickle cell disease.

"As a physician, I've seen these patients," McEver says. "Their suffering is extreme." SEG101 is "still not the ultimate cure," he says. "But I hope it will help a lot of people until we can do more."

For Long, relief can't come soon enough. Last year, she experienced what she describes as the worst sickle cell flare of her life. "Even my face hurt," she says. The pain left her bedridden for days.

She can't take pain-relieving medications like ibuprofen or acetaminophen because of stomach issues. Bedrest and a heating pad can dull her symptoms, but they're far from an adequate remedy. And while she realizes that sickle cell may be inflicting long-term damage on her body, she is more concerned with the children she's known with the disease. "It just hurts me to know what they go through with this," she says.

Long hopes McEver's drug will be a success and that it might also encourage some who've lived with SCD to seek assistance. "If you don't talk about it, you might never know who could help you," she says. "Dr. McEver has used his knowledge, and it might make life better for many who suffer with sickle cell disease. I really hope it happens."

A FRIEND IN NEED
Dr. Rodger McEver helped create a drug that could ease the symptoms of patients like Mary Long.

OMRF Named Oklahoma's Top Workplace

Scientific excellence requires a host of ingredients: dedication, attention to detail, resilience, innovation. Each of these, in turn, relies on having a staff that's both talented and committed to solving difficult problems.

In other words, says OMRF President Dr. Steve Prescott, "The key is people. They have to believe in the scientific mission of the institution. And they have to be excited about their jobs and being here every day."

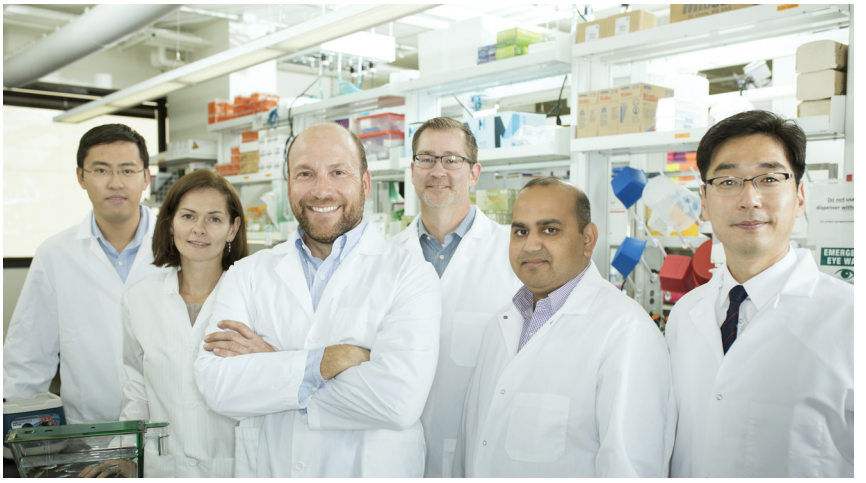
Judging from the results of *The Oklahoman* newspaper's 2017 Top Workplaces competition, OMRF's staff is. Based on employee responses to a confidential online questionnaire, OMRF took the top spot in the category of large organizations (350-plus workers).

An independent polling firm conducts the survey, which includes as many as 800 workplaces each year. It asks workers to rate their employers on a variety of factors that include job satisfaction, management quality, pay and benefits, and opportunities for growth. The firm then uses the responses to rank employers from across Oklahoma.

In each of the previous four years of the survey, OMRF finished in the top 10. But, says OMRF Vice President of Human Resources Courtney Stevens Greenwood, this year's top ranking is particularly special. "It's quite an honor to be named number one by your own employees."

One of the factors that makes OMRF special, she says, is the diversity of the workforce. "We have employees here from almost 30 different countries," she says. "They bring fresh ideas and different approaches, and that really supercharges our organization."

To encourage co-workers to get to know one another, OMRF holds monthly "First Thirstday" gatherings. They're foundation-wide events with free food and beverages, and some months they feature a trivia contest or a musical performance by an employee. "The idea is to create opportunities for staff from different parts of OMRF to bump into one another in a fun, low-pressure setting," says Greenwood.



AFTER FOUR STRAIGHT TOP 10 FINISHES, THE FOUNDATION IS NUMBER ONE IN 2017.

Another hub is OMRF's employee fitness center, which offers boot camps, yoga and fitness classes like Zumba and kick-boxing. By participating in fitness challenges, they can earn "LifeLab" points, which can translate into year-end financial rewards.

For OMRF scientist Dr. Chris Sansam, who came to OMRF from the Massachusetts Institute of Technology in 2010, even small things can help take some of the stress out of work. "I've had jobs in the past where I had to walk 15-20 minutes from my car to my office," he says. "It really makes a difference in your day when you can park just steps away from the entrance to your building."

Accounting clerk Nancy Flesher says OMRF's generous vacation and sick leave policies make a major difference in her life. "I'm a caregiver for my elderly mother, and OMRF has given me the flexibility to take the time I need to spend with her and still do my job. That's important to me."

While perks are nice, says Sansam, ultimately, they're secondary. "When I came to OMRF, I noticed right away that the people who work here—at all levels—really care about doing a good job. When you see that attitude around you day after day, it makes you want to do a better job yourself."

Coming Clean

With OMRF's new germ-free facility, researchers can study the role of microbes in human health

We are outnumbered. For every human cell in our bodies, 10 others belonging to microorganisms reside in our mouths, on our skin and in our digestive tracts.

To study the role these hordes of tiny hitchhikers—which we commonly think of as "germs"—play in our health, OMRF has opened a new research facility. Ironically enough, the new center is designed to ensure that it's free from all of these germs.

The idea, says facility director Dr. Sai Tummala, is to start with a pristine setting in which laboratory mice are free of the trillions of microorganisms that ordinarily populate their bodies.

All mice that enter the facility are bred in a germ-free fashion. Once inside, they make their homes in flexible plastic bubbles called isolators that are ventilated with twice-filtered air. Food, water and bedding, plus any equipment or supplies, must go through a two-day sterilization process in a high-temperature autoclave. Likewise, personnel must don sterilized clothing and undergo an air shower before entering the facility.

"Then scientists can introduce a single microbe or group of microorganisms and see how they affect the mice," says Tummala, who serves as OMRF's associate vice president of comparative medicine. "By knowing precisely which microbes enter the environment, we can learn their specific role in disease."

Already, research has shown that microorganisms may play a role in predisposing us to obesity and a range of chronic diseases. It has likewise suggested they may be responsible for a rise in allergies to nuts and other compounds. Evidence is also mounting that intestinal microbes exacerbate or perhaps even cause some of the symptoms of autism.

"We are entering a new frontier in research, and OMRF is in an excellent position to make contributions to the field," says Tummala.

With funding from the Presbyterian Health Foundation, OMRF opened the center in the fall. Known officially as the Gnotobiotic Mouse Core Facility, it's the only one of its kind in Oklahoma, and it's available to researchers across the state.

Initially, OMRF researchers will use the facility to study the role that microorganisms play in the autoimmune disease Sjögren's syndrome, where the body mistakenly uses its immune system to destroy moisture-producing glands in the mouth and eyes. Another is planning a project to examine whether gut microbes can affect the development of certain intestinal conditions. Meanwhile, researchers at the University of Oklahoma Health Sciences Center have also lined up projects at the center.

"It's truly an exciting time for us," says Tummala.

MOUSE HOUSE Protective barriers ensure that technicians don't introduce germs even when handling the rodents.

Peanuts and Shellfish and Eggs, Oh My!

Dear Dr. Prescott,

How close are we to solving food allergies?

Russell Edwards
Norman

Unfortunately, not as close as we'd like.

For many years, health experts didn't focus on the cause of food allergies. Instead, they devoted their efforts to helping those with allergies—and those at risk to develop them—avoid offending foods. These efforts translated into more stringent requirements for labeling (so that folks could know if even a small amount of, say, peanuts were in a product) and the advent of things like peanut-free classrooms.

Meanwhile, the prevalence of peanut allergies kept increasing. So, researchers decided to take a closer look. What they've found is quite intriguing.

Scientists recruited hundreds of infants who were deemed at high risk of developing a peanut allergy because they had eczema or an allergy to eggs. They then randomly assigned some of the babies to be regularly fed peanut products, while denying the others all foods containing peanuts. By the age of 5, 1.9 percent of those children fed peanuts developed an allergy, compared to 13.7 of those who'd avoided peanuts. A second, smaller study involving children who already showed peanut sensitivities at the beginning of the study yielded similar results.

These results shook up the food allergy world. In 2017, the National Institute of Allergy and Infectious Diseases issued new guidelines that recommended giving babies puréed or finger food containing peanut powder or extract before the age of six months—and even earlier if the child is prone to allergies (so long as the child's doctor says it's safe).

Of course, not all food allergies come about in childhood. Recent data suggest that roughly half of all adults with food allergies report developing them after the age of 18. Anecdotal reports point to certain "triggering" events, such as pregnancy or exposure to certain viruses, but much research remains to be done in this arena. Scientists are also looking into the role that the overuse of antibiotics and other environmental factors may play.

As you can see, we still have more questions than answers.

Fortunately, many allergic reactions to food can be treated with an over-the-counter antihistamine and don't require an Epi-Pen or a visit to the ER. And even if you have a reaction once, it doesn't necessarily mean you must remove a food from your diet forever. Still, if you have concerns, your best bet is to see an allergist for testing.

THE HATEFUL EIGHT

According to the U.S. Food and Drug Administration, 90 percent of food allergies stem from these foods.

- Milk
- Eggs
- Fish
- Shellfish
- Tree nuts
- Peanuts
- Wheat
- Soybeans

Dr. Lorin Olson
OMRF SCIENTIST

"I had a really fantastic eighth-grade biology teacher, Mr. Whitaker. He taught us the coolest things about science, like slime molds and other organisms and how viruses infect bacteria. His descriptions really spoke to me. I was the kid who'd do the regular classwork plus more for extra credit. It was easy to do all the extra things because I just loved his class."

Dr. Olson came to OMRF from the Mt. Sinai School of Medicine in New York in 2010. His research focuses on fibrosis, the creation of scar tissue in disease, which is a cause of organ failure in the heart, kidneys and liver.


TuneSquad

A head-scratching set of symptoms

A boy who may be in grave danger

Can researchers solve this medical mystery before it's too late?

What's Wrong With Xander?

By Adam Cohen

Photos by Brett Deering

XANDER AULD was not a fussy baby. He slept well, at least for an infant. He didn't get sick often. And on those few occasions when he did, he didn't carry on much.

Not long after his first birthday, Xander ran a fever for a couple of days. As usual, he seemed pretty even-keeled. But it was a Friday, and his mother, Felicia Gamble, thought she'd better take him to see the doctor before the weekend.

When the pediatrician examined Xander, she noticed red, dry patches of skin dotting his legs. Felicia hadn't thought much of the blotches, which he'd had since he was an infant. Another doctor had diagnosed them as eczema and prescribed a topical cream, which Felicia had been dutifully applying ever since.

Still, the pediatrician was concerned. She ordered a blood test. When the results came back, the doctor told Felicia that her son had a condition called polycythemia. "I was terrified," remembers Felicia. "I had no idea what that meant."

Xander's blood, the doctor explained, contained an abnormally high level of red blood cells. These are the cells in the blood that carry oxygen from the lungs to the rest of the body. But in excess, they can cause the blood to grow overly thick, increasing the chance of cardiac events. So the pediatrician referred Xander to a physician specializing in blood disorders at the Children's Hospital at OU Medical Center in Oklahoma City.

At the hospital, the intake exam revealed a new concern: high blood pressure. In conjunction with his red-blood-cell levels, Xander's hypertension put him at risk for stroke. The doctor immediately admitted him to begin treatment.

After a restless night in the hospital—Felicia eventually climbed into Xander's oversized crib to help him sleep—the blood pressure medication seemed to be working. Still, doctors had no idea what was behind Xander's condition. And a CT scan soon revealed another symptom that only served to deepen the mystery: small growths, or "micro-cysts," on Xander's kidneys, pancreas and stomach.

The rush of developments was dizzying for Felicia and Xander's father, Matt Auld. In the blink of an eye, it seemed, their son had gone from a healthy toddler to a patient facing grave health challenges. "It felt so unfair," Felicia recalls. But, she says, they quickly dried their tears. "We knew we had to tackle this, to do whatever's best for Xander."

What was best, it turns out, would be far from clear. But the search for answers would lead them on an odyssey they never could have imagined.

THE X FACTOR At the age of 1, Xander Auld developed unexplained hypertension and excess hemoglobin levels.

THE NATIONAL INSTITUTES OF HEALTH define a rare disease as one that affects fewer than 200,000 Americans. In statistical terms, that comes out to .06 percent of the population, or one in every 1,600 or so people. Yet with physicians and scientists now having identified more than 6,000 such conditions, the total number of people in the U.S. suffering from rare diseases is estimated to be 25 million.

A federal law known as the Orphan Drug Act created incentives for pharmaceutical companies to develop drugs for rare diseases. That, along with advances in DNA sequencing technologies that have enabled scientists to identify genetic abnormalities more easily, has spurred increased interest in conditions that once would have gone unnamed and untreated. Plus, the Internet and a growing number of disease societies focused on rare conditions have enabled people and families who once felt isolated to find communities of people grappling with the same issues.

Still, for Felicia and Matt, the quest to understand their son's condition proved lonely and frustrating.

After Xander was released from the hospital, he underwent a host of follow-up assessments. Doctors searched his tiny body for more lesions. They tested him for a rare genetic disorder known as Von Hippel Lindau syndrome, which is associated with tumors in multiple organs. They outfitted him with a hospital-grade monitor to track his blood pressure. None of it, though, brought Xander's medical team any closer to a diagnosis.

At the time, Felicia and Matt were both in their early 20s. They and their two sons (Xander was the second of three boys they would have together) were living with Matt's father in Shawnee and driving regularly to Oklahoma City to see a string of different physicians. Eventually, the parade of doctors' visits, tests and medical expenses threatened to overwhelm them. "We were worried about Xander. And we were worried about whether we could afford to pay for it all," says Felicia. "It was so stressful."

Because a one-year-old wouldn't stay still for the sensitive machinery physicians used to probe his condition, each medical test—and there were many—required doctors to put Xander to sleep. The anesthetics, recalls Felicia, caused "adverse reactions. He would flail. It was terrible."

And then there were the phlebotomies.

Even with medication controlling his blood pressure, due to his elevated hemoglobin levels, Xander remained at high risk for cardiac events, especially stroke. With no answer to why the toddler's body was producing excess red cells, his physicians could only treat the symptoms. That meant regularly extracting several vials of blood from his small body.

Felicia still shudders when recalling the sessions, which took place every one to three weeks. "Phlebotomizing a one-year-old," she says, "is no fun."

With one of his parents attempting to hold him still, a nurse would insert a needle into a vein in Xander's arm. As he squirmed and wailed, the nurse would pull back on the syringe's plunger to extract the blood. "It required so much physical pressure to get the blood out that the nurse's arm would be shaking." And getting Xander's red cells down to acceptable levels required extracting multiple syringes worth of blood. "Sometimes, they would poke him five or six times to get everything they needed."

Scar tissue eventually dotted Xander's forearms. As he grew older, "It became a struggle every time we had to get him to the phlebotomist," remembers Matt. "He would scream and yell and hide in a corner."

"He's crying. I'm crying. It was awful."

Things only got worse when they arrived at the appointment. "It took a few nurses to hold him down," says Felicia. "He's crying. I'm crying. It was awful."

Meanwhile, Xander's physicians struggled in vain to figure out what, exactly, was driving his elevated blood pressure, red-cell levels and cyst-like growths on his organs. Although an ongoing battery of tests and scans failed to point to the root of Xander's condition, over time, they did seem to indicate that not much was changing. His blood pressure remained controlled. The cysts didn't appear to be growing larger or spreading. And while he dealt with asthma, allergies and repeated cases of strep throat that led to the removal of his tonsils and adenoids, he otherwise seemed to be a healthy, happy child.

Years passed. Xander began elementary school. He started playing tee ball and, soon after, basketball. The doctor's visits grew less frequent. Around the time Xander turned six, Felicia and Matt stopped the blood draws. They waited to see if anything changed.

It didn't.

They breathed a deep sigh of relief. Maybe, they thought, we can just forget this whole chapter of Xander's life. And for a while, they pretty much did.

Bring me some puzzling cases, the OMRF researcher told the OU geneticist.

DR. PATRICK GAFFNEY began his medical career as a hematologist, diagnosing and treating patients with blood diseases. But his career took a turn when a research fellowship led him to the study of autoimmune diseases, conditions in which the body mistakenly turns the weapons of its immune system against itself. In particular, he focused his research on the genetic roots of conditions like lupus.

"Most diseases are caused by a combination of the genes we inherit from our parents and environmental factors like substances we're exposed to, the food we eat and our exercise habits," says Gaffney, who holds the J.G. Puterbaugh Chair in Medical Research at OMRF. "My research centers on the role of the genes."

At OMRF, Gaffney established a "next-generation" DNA sequencing facility in 2009. Using an array of sophisticated analytical equipment, he and his research team could perform scans of people's genes at speeds and costs that, only a few years before, had been unimaginable. "We saw the power inherent in this technology," says Gaffney. "And almost immediately, we got interested in studying conditions outside the realm of autoimmunity."

Specifically, he wanted to use his sequencers to decode previously unexplored genetic questions. So, Gaffney reached out to the OU College of Medicine. "I knew that would be the gateway for patients coming in with undiagnosed rare diseases."

There, a genetic counselor introduced him to Dr. Klaas Wierenga, who holds the McLaughlin Family Chair in Genetics. A recent transplant from the University of Miami, Wierenga specializes in diagnosing and treating young patients affected by rare conditions caused by mutations in their DNA.

The vast majority of serious childhood illnesses occur in three ways. Infectious agents (chiefly viruses) cause conditions like mumps, measles and whooping cough. Meanwhile, diseases like childhood leukemia and juvenile diabetes are brought about by factors that scientists don't yet fully understand but, most likely, consist of some mix of genetics and environment. Finally, researchers have identified another group of conditions—perhaps the best known are cystic fibrosis and sickle cell disease—where an alteration in a gene is responsible for the disease.

When primary care physicians can't fit a child's particular collection of symptoms into one of those three boxes, they'll refer the patient to a pediatric geneticist like Wierenga. The suspicion is that the child may be suffering from some rare or unknown genetic disease. But, says Wierenga, "Not every patient who walks into my office has a genetic disorder."

His role is like that of a medical detective. Or, as he puts it, "What I do is a more cerebral version of testing someone with a sore throat."

Using tools like medical records, tests of the patient and family members, and interviews about family history, Wierenga attempts either to establish or rule out that a child is suffering from symptoms caused by a genetic mutation. For years, he relied largely on what he calls "pattern recognition," trying to tease out details from different sources to help form a coherent diagnostic picture. Still, even when he felt relatively certain that he'd pinpointed a DNA mutation responsible for a child's condition, he hesitated. "Even if I was convinced a patient had a genetic disorder, I'd make a diagnosis only 30 percent of the time." That, however, began to change with the advent of sophisticated genetic sequencing facilities like the one Gaffney established at OMRF.

The human genome consists of 3 billion nucleotides or "letters" of DNA. But only a fraction—less than two percent—of those letters are actually translated into proteins, the functional players in the body. Using a technique known as exome sequencing, Gaffney could isolate and analyze that part of the genome that tells cells how to build all the proteins in the body. It's in this precious real estate that errors leading to genetic diseases typically occur.

"Up until exome sequencing, you'd have to do other, less specific tests," says Gaffney. Even when results pointed to a genetic culprit, physicians often could not be sure. "But with the advent of exome sequencing, you could conclusively identify mutations."

Nevertheless, with a hefty price tag and limited utility for the lion's share of cases, insurers were reluctant to pay for exome sequencing. This left the test beyond the reach of physicians like Wierenga. "While geneticists realized how important it was, it was not a clinical test that was routinely available for patient care," he says.

So, when Gaffney asked him if he'd like to collaborate, Wierenga jumped at the chance. Bring me some head-scratching cases, said the OMRF researcher, and I'll test them. Gaffney also volunteered to use funds from his own research account to pay for the testing.

In essence, says Wierenga, "Pat was sitting on a gold mine." And he'd just handed the physician a pickaxe and a license to chip away.

DNA DETECTIVES Drs. Klaas Wierenga (left) and Patrick Gaffney decided to team up to help patients suffering from difficult-to-diagnose genetic disorders.

WIERENGA SOON FOUND his first case for Gaffney: a 10-year-old girl who'd suffered from a bleeding disorder since birth. "When she was just a baby, she would bleed spontaneously from the mouth," says the girl's grandmother. "She didn't act sick, but she would bruise so easily."

The girl also had weakness in the muscles close to the midline of her body, and her eyes lacked the ability to control the pupils. Wierenga recognized this trio of seemingly unrelated symptoms as Stormorken syndrome, a condition named for the Norwegian scientist who'd first identified it. With only a handful of cases, the illness was seldom seen. But when it had been previously found, the patient was not alone in the illness; a parent had also been affected. Here, though, neither of the girl's parents exhibited symptoms.

Due to previous cases, scientists were already confident that Stormorken came about because of an alteration in a specific gene. In those instances, a parent had passed that defective gene on to a child. Now, it seemed, Wierenga had found a situation in which the gene had spontaneously mutated at conception, causing the condition. "That's when a geneticist's heart starts beating faster, because we think this might be something we can more easily solve," he says.

The reason for Wierenga's excitement was that the spontaneous genetic change might enable him to place his finger on the exact letters of the DNA responsible for the condition. That's because, unlike in previous cases, this portion of the child's genome would differ from the comparable strands of her mother's and father's DNA. And with Gaffney's help, he could now put the evidence under the proverbial microscope.

Using exome sequencing, Gaffney and OMRF's Dr. Graham Wiley compared genetic samples donated by the girl with those of her unaffected family members. With this technique, they narrowed their analysis to the 180,000 or so protein-producing letters of DNA. There, they found three promising "hits," areas in which the patient's sample differed from those of her relatives. After comparing the girl's DNA with that of a Stormorken patient from Switzerland, they eliminated two of those candidates—and established that the third gene showed a common mutation.

The research, published in the journal *Proceedings of the National Academy of Sciences*, broke new scientific ground. It definitively identified the gene responsible for this rare condition. The study also included follow-up research by Wierenga's colleagues at OU that helped explain the cellular mechanisms by which the altered DNA caused the particular symptoms of Stormorken syndrome. Still, the findings didn't allay any of the medical problems experienced by those with the condition. It didn't change anything about how Wierenga or other physicians treated their patients moving forward.

The OMRF researcher and the OU physician continued their partnership. For some patients, they identified the genes responsible for the rare diseases that affected them. For others, they delivered something that had, up until that point, been elusive: an authoritative diagnosis.

With conditions that cannot be easily categorized or identified, says Wierenga, "just having a diagnosis can be a success." That definitive diagnosis, which often comes after a years-long medical odyssey, "can really help the family." It changes the focus from "What's wrong with my child?" to "Let's explore the available treatment options."

Gaffney also found satisfaction in solving unanswered questions and bringing certainty to patients and their families. "I originally went into medicine to take care of patients," he says. "So I enjoy helping them work through disease."

But, perhaps, he imagined, his work with Wierenga could still go a step further. One day, they might find something that could change a patient's life.

XANDER AULD'S LIFE, meanwhile, seemed just fine the way it was. A rambunctious kid with big brown eyes, he liked to crack jokes and goof around with his friends. He loved sports and spent lots of time on the baseball diamond, football field and basketball court. In his group of friends at Surrey Hills Elementary in Yukon, where he'd attended since pre-kindergarten, he seemed like a natural leader.

The doctors' visits had grown less frequent, to the point they almost seemed invisible. Yes, the annual check-ups with specialists continued, but nothing much seemed to change. And the phlebotomy sessions were but a distant memory.

But around the time Xander began middle school, one of his physicians, Dr. Alecia Hanes, expressed concerns about his red-cell levels. When Xander saw his hematologist at OU, Dr. William Meyer, "He said we really needed to get them down," says Felicia. That meant a return to regular blood draws.

Xander was less than enthused. "It was a rough start getting him to phlebotomize again," says Matt. He and Felicia had divorced, so they took turns bringing Xander to his phlebotomy sessions, which, once again, came at one- to three-week intervals. However, by then a preteen, Xander quickly adjusted.

"It just became a part of life," says Felicia. Where once he'd screamed and wriggled, he'd, instead, stoically extend his arm for the nurse. "All he'd say was, 'Just count to three before you stick me,'" says Felicia. As they'd sit in the doctor's office, mother and son would see other patients, often children suffering from cancer. Many were visibly struggling with illness—some gaunt, others bare-scalped from chemotherapy. "I'd say to Xander, 'I know this stinks,'" recalls Felicia. " 'But you're lucky.' "

Meyer, though, was not content to leave Xander's future to chance. A hematologist, he'd been the primary care provider for the 10-year-old Stormorken patient. He'd referred her case to Wierenga, his colleague at OU, who'd worked with

He seemed healthy, but Xander's symptoms remained puzzling.

OMRF's Gaffney to find the roots of her illness. Perhaps the geneticist could also piece together Xander's puzzling case.

With Xander's persistently elevated red-cell levels, Wierenga suspected a hereditary condition. There were four known genes associated with the syndrome, which was called familial erythrocytosis. At that time, 2013, the only laboratory that could test for the condition was in Germany. Because its work wouldn't be covered by insurance, that turned out to be a nonstarter.

Instead, Wierenga ran a series of other tests. Once again, though, they failed to offer any real answers.

Xander continued his phlebotomies and kept seeing Meyer. Then, in 2016, the test for the hereditary blood condition became available in the U.S. Now 13, Xander came in and gave a blood sample, but the results came back negative. Wierenga got the same outcome when he re-tested the teen for another rare genetic disorder.

"We had an erythrocytosis disorder"—one associated with the excess production of red blood cells—"and all the genes ordinarily associated with the disorder are negative," says Wierenga. Plus, the small growths on Xander's kidneys remained, as did his high blood pressure. Wierenga was worried. And stumped. But then he had an idea.

"I thought, 'It's time to talk to Pat.'"

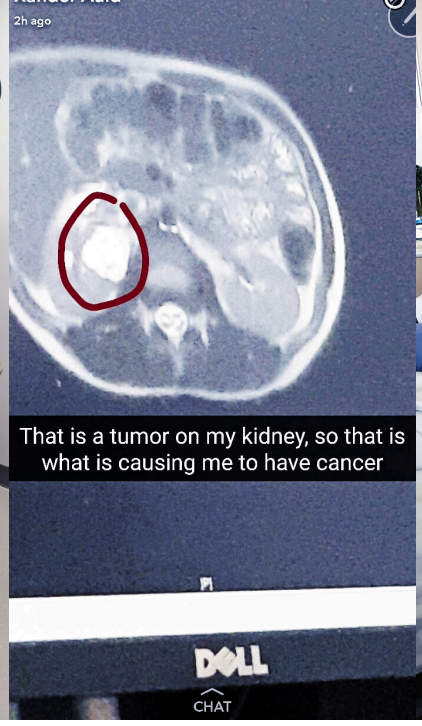
GAFFNEY AGREED TO lend his expertise. The best hope, he and Wierenga thought, was to perform an exome sequence on Xander and all of his direct family members. That way, they could do a deep dive into any potential genetic differences between him and his mother, father and two brothers, none of whom appeared to share any of Xander's symptoms.

For Xander, one more test was no big deal. Not so for his younger brother, Landon. When the 10-year-old went to Wierenga's office—along with Matt, Felicia, Xander and his oldest brother, Isaiah—"he was scared," says Felicia. Still, knowing it could help his brother, he bravely allowed Wierenga to extract blood from his arm.

Working with Graham Wiley at OMRF, Gaffney processed the blood samples. Then he shared the results with Wierenga, and the two of them began sifting through the data.

Studying the results of an exome sequence can be like trying to examine individual flakes in a snowdrift. While the test narrows the analysis to two percent of the human genome, that still leaves almost 30 million letters of DNA to analyze. And here, Gaffney and Wierenga were not only comparing each of Xander's letters to its counterpart in a typical "reference" human genome; they were also cross-referencing it against the four other data points generated by each of his family members. In total, that left the pair to study and compare more than a million data points. Not surprisingly, it proved slow going. "We looked at exome data for a long time and made very little progress," says Wierenga.

Fortunately, Gaffney's software allowed users to sort the test results into different bins. One Saturday night, with the case still haunting him, Wierenga decided to sift through the bin—shown on his computer as a column of



figures in a spreadsheet—that contained every "pathogenic" gene variant in Xander's results. These are regions of the DNA where Xander had a different letter than the typical genome, and that particular variation was known to be damaging to the gene.

Wierenga found his eye drawn to a gene that coded for an enzyme called fumarate hydratase. "I knew this gene. It's associated with renal-cell carcinoma," a malignant cancer of the kidney. Xander's copy of this gene differed from the reference genome. Wierenga sent a text to Gaffney.

"So I have lung cancer?"

"No, baby, it's your kidney."

From his training as a hematologist, Gaffney was also familiar with fumarate hydratase. He knew the enzyme played a key role in metabolizing food products and extracting energy from them. "But if this enzyme is not working, it triggers a chain of events that leads to an increase in oxygen-carrying red blood cells." Xander's mutation in this particular gene, Wierenga and Gaffney both thought, could lead his cells to believe mistakenly that they lacked oxygen. As a result, his body might respond by producing more oxygen-carrying red blood cells—even though he didn't actually need them.

Then, there was the link between the mutated gene and kidney cancer. Xander's kidneys had for many years exhibited tiny, cyst-like growths. Perhaps, thought Wierenga, "there was something cooking in the kidney" that was driving the red-cell production.

With the mutation in the fumarate hydratase gene came a heightened risk of kidney cancer. At 15 percent over a patient's lifetime, the increase was relatively small. And in those patients who ultimately developed the cancer, it typically didn't occur until they were in their 50s or 60s. So, Xander seemed at relatively low risk. Still, says Wierenga, "The typical recommendation with this mutation is to get the kidneys checked regularly."

Xander had undergone regular ultrasounds of his kidneys, which had shown no changes for many years. But Wierenga and Gaffney were concerned this wasn't enough. After confirming the results with a second, independent lab, the pair presented their findings to Xander's two primary physicians at OU, Meyer and Dr. Martin Turman, a nephrologist. "We wanted to make a case to have his kidneys imaged more aggressively and with different modalities," says Wierenga.

Specifically, they pressed for an MRI, "which brings better resolution and more detail," says Gaffney. By the end of the presentation, Meyer and Turman agreed. They would bring Xander in as soon as they could.

"We were excited but also concerned," says Wierenga.

One particular worry gnawed at Gaffney. "I was afraid he'd have a malignancy."




XANDER HAD THE MRI. When Turman received the results, he asked Matt and Felicia to come in. They brought Xander with them.

"Dr. Turman said the MRI had found fatty tissue," Felicia recalls. That seemed innocuous enough. "We weren't even worried about it," she says. But, Turman explained, the MRI had revealed a tumor in Xander's kidney. It was cancer.

Felicia began to sob. With Xander beside her, she did her best to regain her composure.

Turman explained that Xander would need surgery immediately. Then the physician asked Xander if he had any questions.

"So, I have lung cancer?" the teen asked.

"No, baby," said his mother, "it's in your kidney."

Xander began to cry. Eleven days later, OU urologists Dominic Frimberger and Mohammad Ramadan removed his right kidney.

Before the surgery, additional scanning had shown a cancer that was about four centimeters in diameter, roughly the size of a golf ball. The tumor was malignant and fast-growing, but it had been contained in his right kidney and had not yet spread to other parts of his body.

The surgery took several hours. The waiting room at Children's Hospital was filled—Matt, Felicia, both their families, Felicia's husband's family—with people wearing "Team Xander" tees. The surgeons eventually emerged to tell Felicia and Matt that the procedure had gone well.

When Xander awakened, he was groggy from the anesthesia and in a good deal of pain. Still, the first words he said to his parents were, "Will you please tell the doctors thank you?"

Xander had imagined that recovery would be seamless. "He thought he was going to eat Buffalo Wild Wings right after surgery," laughs Matt. "That didn't happen." Still, he was able to leave the hospital after two days. Three weeks later, he was back at school.

He underwent a single phlebotomy after surgery. When doctors did follow-up testing, his red-blood-cell count had decreased to a normal level. And it's remained there ever since—without a single phlebotomy.

Similarly, after a few months, Xander's blood pressure dropped. It fell so much that his doctors took him off all blood pressure medications.

Since that time, Xander has grown several inches and put on 20 pounds or so. With the phlebotomy sessions behind him, he no longer misses class regularly. He continues to take medicines for his allergies and asthma, but that's it.

This past fall, he began his freshman year at Yukon High School. Like his older brother, Isaiah, he's joined the swimming team. His coach tells him that his breast stroke is really coming along.

ON A SUNNY DAY in November, Felicia, Matt and Xander are gathered around a table in a conference room at OMRF. It's their first visit to the foundation.

"We never knew this existed," says Felicia. Even when Gaffney had sequenced all of their exomes, "All we knew is that Dr. Wierenga had found somebody who'd do this for research, so it wouldn't cost us anything."

Xander sits quietly as his parents talk about his medical odyssey. Now 14, he wears shorts, which reveal long, spindly legs. His light brown hair peeks out from a gray hoodie he's pulled over his head. It's mid-morning, but his eyelids still seem to hang at half-mast. It's hard to tell if he's sleepy, wary, or a little bit of both.

FAMILY GUY Xander, now 14, with his parents, Felicia Gamble and Matt Auld, on December 3, 2017

For him, the process leading up to the surgery had been something of a blur. "It happened really fast." When Turman told him about the tumor in his kidney, he says, "I didn't really care." But then, "I saw Mom crying. And that's when I started to cry."

Still, he claims, the prospect of having his kidney removed didn't frighten him. "I didn't think about it. I knew I was going to get it out." When he awoke, he remembers being pushed on a gurney through a network of tunnels in the OU Medical Center "and going over all those freaking bumps."

As soon as he returned to school, he says, "I felt normal."

And how about now—does he feel in any way different from other kids?

He shakes his head.

Felicia looks at her son and rolls her eyes. "I think you think it's cool to act like you don't care." She pats his knee.

But the reality, she says, is that he is different. He had a genetic mutation that fueled the growth of cancer in his right kidney. "We stay on top of the scans," she says. That means MRIs of his remaining kidney every four months.

"The doctor told us early last week there was a small change," adds Matt. "Some growth."

"I have been really worried about it," says Felicia.

Right about then, Gaffney enters the room. It's the first time the OMRF researcher has met Xander and his family.

Gaffney explains a little bit about his work and about Xander's case. Matt, it turns out, has the same gene variant as his son, but he's never shown any symptoms. Why? "We just don't know."

It's this kind of ongoing unknowability that keeps Felicia awake at night. "I don't know how this gene mutation works." With each new MRI, she says, "I get super nervous about the results."

Still, the discovery of the mutation and the ensuing surgery have been "life-changing," she tells Gaffney. "I am so thankful for your research."

"It could have been really bad if you didn't catch it when you did."

A FEW DAYS LATER, Gaffney and Wierenga meet. It's a Friday afternoon, a time when the pair customarily gets together to go over their projects. As usual, it's in Gaffney's office, where he stands (not sits) at his desk, in front of photos of his wife and three children and a row of champagne bottles, each of which commemorates a successful grant application. But the main décor is a whiteboard, covered in magic marker drawings of cells.

No more phlebotomies. No more cancer. "He can just be a normal kid."

They discuss cases until, eventually, Gaffney turns the conversation to his meeting with Xander and his family. "I was a little nervous," he admits. "I didn't want to say anything and have them say, 'Well, none of the doctors told us that.'"

But, he says, the session soon felt a bit like riding a bicycle. "This is what I used to do when I was practicing, to help patients work through diseases. So, it was rewarding for me to put faces on the genetics."

Playing genetic detective, says Wierenga, isn't always satisfying. "Only rarely do you get a diagnosis where you can change the course of care. In many cases, the options to make life better after a diagnosis are limited. You give an etiologic answer"—a name for the condition that afflicts a patient—"and a community of families to share."

But Xander's case, he says, "was quite overwhelming, in a way that's very unanticipated and very gratifying. Neither of us realized the urgency of what we were accomplishing. All of sudden, it wasn't a research project anymore."

Gaffney nods. "We really made a tangible impact on the clinical care of a patient. We triggered a chain of events that ended up helping this family."

No more phlebotomies. No more hypertension. No more cancer. "He can just be a normal kid," says Wierenga.

Continued vigilance for his other kidney, they agree, is a must. But even if a cancer grows there one day, Wierenga says, "We have solutions for that, too."

"Yes," chimes in Gaffney. "People live very productive lives with renal transplants."

As a physician and researcher, he knows a kidney transplant carries a much brighter prognosis than metastatic cancer. Still, for Matt and Felicia, "We've sort of replaced one set of worries with another."

Now it's Wierenga's turn to nod. "Yes, there's still something missing, a piece of the puzzle that escapes us so far."

The conversation meanders for a few minutes. They discuss potential next steps. Maybe they should analyze a genetic sample from the tumor itself. But, soon enough, Gaffney's thoughts return to the family.

Not the case. Not their genes. Just the people.

"Xander's a typical 14-year-old kid. And his mom and dad were genuinely appreciative about what happened." He waits a beat, maybe two. "But this is not over for them."

Paying it Forward

Mentors helped shape Dr. Courtney Griffin's scientific career. Now she's doing the same for the next generation of aspiring researchers.

As a teenager, Courtney Griffin kept busy during the summers. Sometimes, she babysat her siblings. Others, she'd lend a hand at her father's law office in Athens, Georgia, where she grew up. But it was the summer following her senior year in high school that would end up mapping the course of her professional life.

And it might never have happened if not for music.

When she was 17, Griffin was at her piano teacher's house, awaiting a lesson. She struck up a conversation with Lois Miller, the mother of another piano student. It turned out that when Miller wasn't taxiing her daughter to music lessons, she was a high-powered biologist who ran a lab at the University of Georgia. When she learned that Griffin was interested in science—Griffin had particularly enjoyed an Advanced Placement chemistry class where she'd determined the chemical makeup of a bobby pin she'd found on campus—and was headed to Harvard University in the fall, Miller offered the teen a summer job in her lab.

"That was the turning point for me," says Griffin. "After two weeks in Lois' lab, I was completely hooked on research. There was no going back."

In addition to the hands-on exposure to biology, Griffin relished the times when Miller took her aside to talk about science and her career aspirations. "I was amazed that she identified somebody with no experience, but with real interest, and reached out to me and spent time with me," Griffin says. "That was powerful and meant so much at that time in my life. I didn't know it then, but she was teaching me how to mentor others."

Griffin continued working in Miller's lab for several summers during college. After graduating with a biology degree from Harvard, she went on to earn her Ph.D. at the University of California, San Francisco. Having decided to pursue a career as a cardiovascular biologist, she accepted a postdoctoral fellowship at the University of North Carolina at Chapel Hill. It was there that she reconnected with Dr. JoAnn Trejo, whom she'd met in California and who would become another mentor to the young scientist.

"Finding JoAnn was instrumental in my progress as a postdoc," says Griffin. "I was able to watch her make her way as a faculty member and see firsthand the steps it took to get there. She helped relieve my fears, because she made it all seem attainable."

Following the completion of her fellowship, Griffin joined OMRF, where she runs her own lab and has enjoyed considerable success as a cardiovascular biologist. That means spending the lion's share of her days studying how blood vessels develop.

Still, she knows the part that mentoring played in her professional development, so she's taken on that mantle for a number of junior scientists in her lab at OMRF. Recently, she's also assumed broader responsibilities for guiding young researchers at OMRF, serving as the chair of OMRF's postdoctoral training committee. That means helping to shepherd the careers of 40 or so trainees at OMRF who are at a pivotal point in their lives.

"Courtney always makes herself available to us when we need answers to questions or advice about developing our career choices," says Dr. Erola Ainsua Enrich, a postdoctoral fellow who also leads OMRF's postdoc association. "She encourages and guides us to become better scientists."

For Griffin, that encouragement extends beyond students who've earned their graduate degrees. She and her husband, Tim, who's also a researcher at OMRF, helped organize annual science nights at Oklahoma City's Wilson Elementary School, introducing children to biology and chemistry through a series of fun, hands-on activities. This past fall, she also co-hosted an event with the American Heart Association designed to attract teenage girls to careers in science, technology, engineering and mathematics (STEM) fields.

"I might not have considered becoming a scientist if I hadn't met an influential female scientific role model when I was a teenager," Griffin says. "I just hope I can inspire other young people to consider science as a rewarding and creative career option."

LEADING BY EXAMPLE
"The best mentors help you see what you want to become and show you the steps to get there," says Dr. Courtney Griffin, pictured here with Siqi Gao, Melinda Wu and Sarah Colijn.


TORQUE

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Oklahoma City, OK 73104

Peace Be With You

In 1957, volunteers donated their time, labor and construction materials to build a 24-seat chapel in OMRF's research hospital. From then until the research hospital closed in 1976, the interdenominational chapel served as a place of respite. Its organ even piped music throughout the hospital, providing a soothing atmosphere for patients and their families.