IT'S GENETIC: Carson's cerebral palsy diagnosis had to be thrown out after his brother, Chase, began to show similar symptoms.

A BABY IS BORN.
HE SHOWS WORRISOME SYMPTOMS.
AND NO ONE CAN EXPLAIN WHY.

THE Odysseys

BY DENI ELLIS BÉCHARD

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

Danny Miller was spending every free minute searching the internet, reading page after page about medical conditions. His son, Carson, was a year old, and Miller believed something was wrong with him. He and his wife, Nikki, had noticed the first signs a few months earlier, during playdates with other children. He couldn't exactly put his finger on the problem. "It was just the quality of movement and the types of movement," Miller recalls. "He didn't like tummy time. The movements were a little bit stiff and not as smooth as the other kids'."

During an appointment with the pediatrician, the Millers were told that children develop at different rates. And yet Carson's hands were curled tightly into fists, and his movements showed signs of spasticity. The Millers set up appointments with neurologists and behavior specialists, all of whom said there was probably nothing to worry about.

"That's when I sort of began to dive into my research career," Miller says. "I was looking at different conditions and would just enter symptoms into Google to figure out what would come up or what would explain why he wasn't crawling, why he wasn't pulling himself up to standing."

The condition that Miller repeatedly circled back to was cerebral palsy. Its symptoms matched Carson's: tremors, muscle weakness and lack of coordination. The cause was often unknown and usually attributed to atypical brain development or damage during pregnancy or childbirth, or shortly afterward. Miller continued taking Carson to see specialists, and Carson finally received a diagnosis of cerebral palsy in 2013, when he was 15 months old.

Shortly afterward, the Millers had their second son, Chase. The pregnancy was easy, and the baby looked healthy. "But fast forward to 6, 7 months of age," Miller says, "[and] we began to see some of the same things. That's when we really began to get worried."

Suddenly, the cerebral palsy diagnosis seemed unlikely. CP occurs in approximately 2 out of 1,000 births and in 1 out of 1,000 that are not premature. The odds of both boys having it were 1 in a million. Miller turned his research toward genetic movement disorders. Testing for the boys was now more extensive: metabolomics (the study of the body's metabolic byproducts, such as lactic acid or nitrogen compounds), karyotyping (the evaluation of the chromosomes for structural abnormalities), gene panels (to test for common mutations) and then sequencing of the entire exome (the genome's coding portions, which are expressed in proteins and linked to traits). The brothers also received several MRIs. Carson's showed lesions in the brain's basal ganglia, an area important for motor activity. But the neurologist couldn't identify the cause. Many disorders—among them many rare diseases—could cause lesions.

As the Millers did test after test for their sons, the boys' physical development plateaued. By the time Carson was 5 and Chase was 3, neither could speak or walk, and their motor control was extremely limited, and yet both boys appeared to be cognitively intact and could understand spoken language. Though Miller continued researching diseases online, none of the symptoms quite fit.

In 2016, Miller read about the Undiagnosed Diseases Network, a research initiative created by the National Institutes of Health in 2014 in conjunction with six clinical sites at academic medical centers, including Stanford. The UDN accepted its first patients—adults as well as children—in September 2015. In its first 20 months, it would evaluate 601 patients, find diagnoses for 35 percent of them and identify 31 previously unknown syndromes. In 2019, it expanded to include a dozen clinical sites, and it has now accepted 1,393 patients, evaluated 1,190 of them and made 330 diagnoses. The network works collaboratively, sharing data and resources and bringing together the best specialists from multiple institutions to take on the most challenging medical cases. It refuses no one on the basis of ability to pay. The only standard is whether the person has, according to the website, a condition that includes at least one objective medical finding—a detectable biological anomaly—and "that remains undiagnosed despite thorough evaluation."

For the Millers, the UDN was a lifeline after a long, repetitive and frustrating search.

"It was sort of the end of the line for undiagnosed families," Miller recalls. He spent the next several months compiling his sons' medical records. In the spring of 2016, he applied on their behalf to the UDN. By December, they were admitted, and since they lived in Corte Madera, Calif., a 30-minute drive north of San Francisco, they were assigned to Stanford's Center for Undiagnosed Diseases.

"It was very scary," Miller says, recalling the stress of four years of searching for answers and coming up empty. "As a parent, you go through a lot of self-doubt, a lot of blame. You wonder, 'What did we do wrong? Did I not take care of my body the right way as a young man and now that's had an impact on our children?' My wife went through a period where she asked, what did she do wrong during her pregnancy? Did she not get proper nutrition? We were both really determined to try to find answers, and we weren't getting them."

The Millers' first visit to Stanford was in early 2017. Again, they went through a series of consultations with specialists. The team then decided to do whole-genome sequencing for the family—the parents as well as Carson and Chase.

A little more than a year later, the Millers had an answer.

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THE HEAD OF PEDIATRICS AT STANFORD'S CENTER FOR UNDIAGNOSED DISEASES is associate professor Jon Bernstein, MD '03, PhD '03, a pediatric medical geneticist who chose his field of study because it combined the kind of challenging problem solving he found satisfying with a lifelong love of working with children.

After he joined Stanford Medicine's faculty in 2008, much of his focus was on helping families find explanations for their children's chronic conditions. When he heard that several colleagues were applying to join the UDN, he wrote to say he wanted to be involved.

Through the UDN, Bernstein has access to far more diagnostic tools—and more freedom to use them—than he has in a standard clinic, where patients are generally limited to services included in their health plans. Whereas research scientists use techniques under development—such as whole-genome sequencing and RNA sequencing—few clinicians have access to those services and few health plans cover them until the techniques become sufficiently mainstream that their costs decrease.

When the Millers brought Chase and Carson, Bernstein and the UDN team compared their symptoms with those of known conditions shared in databases among scientists around the world. Whole-genome sequencing was the next step. Exome sequencing shows only the expressed genes—1.5 percent of the genome—whereas whole-genome sequencing covers the regions that control many other processes, including which genes get expressed.

When the results came back, they showed two mutations that might have an impact—one in the father and one in the mother, both of which the sons had inherited. A paper published in 2016 in the *American Journal of Human Genetics* had described the mother's mutation for the first time, introducing MEPAN syndrome (an acronym for mitochondrial enoyl CoA reductase protein-associated neurodegeneration). The symptoms matched those of the brothers, from the inability to speak and movement difficulties to the lesions in the basal ganglia. The mutation hadn't come up in the boys' previous exome sequencing possibly because it was discovered so recently and was unlikely to be included in all databases, or because it lay at the boundary of an exon and an intron—DNA that is expressed and that is not.

The father's mutation, however, was entirely in the unexpressed (or noncoding) regions of DNA, which explained why it hadn't shown up during exome sequencing. Though his mutation had never been described in the scientific literature, it lay within a region that was predicted to regulate the same gene affected by the mother's mutation: the MECR gene, which is involved in producing mitochondrial fatty acids in humans.

In both Carson and Chase, the MECR gene from their mother didn't function. The Stanford team established that the MECR gene from their father—though intact—wasn't expressed. Since each parent carried one functioning copy of the gene, neither of them had MEPAN. There was a 50 percent chance that each parent would pass on his or her single mutation, and a 25 percent chance

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that a child would receive the mutations from both parents. Carson and Chase, despite the odds, had each received the two mutations. The result was that mitochondria—the parts of cells that produce energy—functioned poorly.

For the Millers, the boys' symptoms suddenly made sense. The brain, though it constitutes only 2 percent of the body's weight, uses approximately 20 percent of its energy. And the basal ganglia—because it controls motor functions—is one of its most energy-intensive regions. Since Carson and Chase had a genetic mitochondrial disease, this area was most affected, resulting in severe impairment of movement.

Through the UDN, the Millers were put in contact with other families with MEPAN.

"With rare diseases," Miller says, "building community is really important—connecting with the other families."

He acknowledges how scary it was to find out that their sons have a rare genetic condition with no proven treatments, but he was relieved to know what they faced. "It allowed us to turn the page and write the next chapter: connect with other MEPAN families, figure out who the researchers are that can help discover treatments."

Though only seven patients had been identified worldwide, the families were able to compare notes on potential treatments and how the disease might progress. The oldest known patient, Mike Cohn, lived in Minnesota. He had gone decades without a diagnosis and was an exemplar of how a person could embrace life with a disability. He was 50, had a master's in education and ran not only a nonprofit to create awareness around disabilities but also his own dance company.

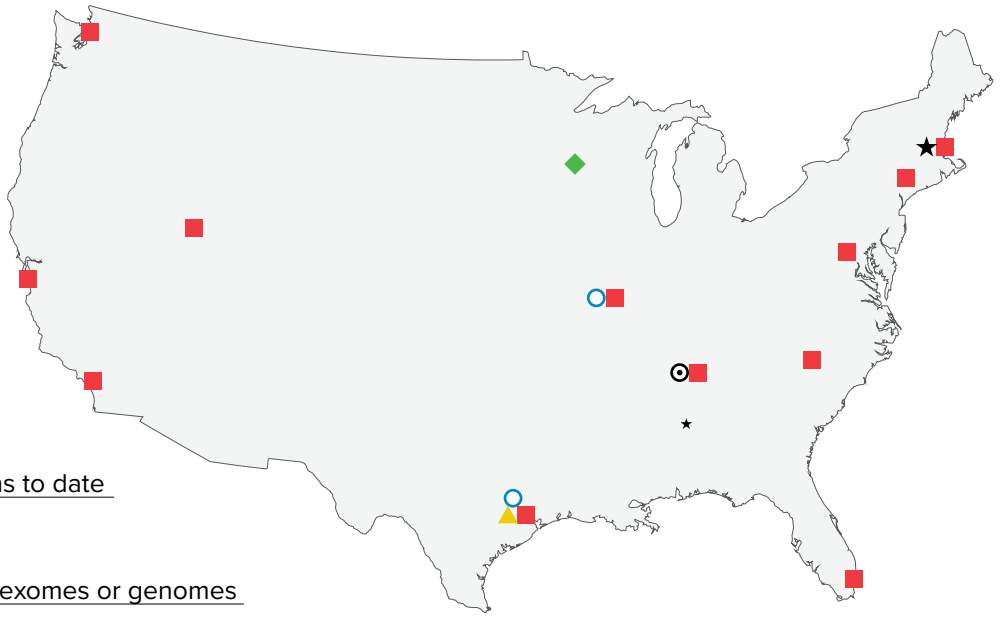
Carson is almost 9 and Chase is 6, and both lead active lives. "Even though they can't talk, they're very vocal in the morning," Miller says. "They just make noises and let us know that they're up."

Neither of them can crawl, but Chase can climb out of bed and roll down the hallway to the kitchen, whereas Carson can roll only a little. Their parents bathe them, feed them and take them to school, where each has a one-on-one aide who serves as their hands and voice. Miller remarks that the boys are often joking and almost always smiling, though once, a few months ago, with a speech therapist, Carson wrote, "I hate my wheelchair."

To communicate, the boys use assistive technology: an iPad for Chase and a speech-generating device with an eye tracker for Carson, whose motor skills were further limited after a brain infection. They have tried VR headsets and like watching YouTube videos of people playing *Minecraft* or *Grand Theft Auto*. Chase enjoys exploring the outdoors with his father and roughhousing, whereas Carson would often prefer to be inside reading or watching TV. Carson has also become fascinated by the science of how the body works and watches videos about everything from digestion to reproduction. And he loves Harry Potter.

"At the very end of the night, as he's falling asleep," Miller says, "I read him Harry Potter. We're reading *Harry Potter and the Order of the Phoenix* right now, and we're on like page 690. It's supposed to be when he's winding

THE UNDIAGNOSED DISEASES NETWORK



- **Clinical Sites** 1,190 evaluations to date
- ★ **Coordinating Center**
- ▲ **DNA Sequencing Core** 1,155 exomes or genomes
- ⊙ **Central Biorepository** 703 samples
- ○ **Model Organisms Screening Center** 225 gene variants
- ◆ **Metabolomics Core** 148 analyses

COMMUNITY: About 50 children, most of them girls, have the same mutation as Lauren. Her family can now turn to others for advice.

down, and as you're reading the part where Harry is about to do battle with Voldemort, he gets very excited and animated."

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EUAN ASHLEY IS ONE OF THE FOUR PRINCIPAL INVESTIGATORS AT STANFORD'S CENTER FOR UNDIAGNOSED DISEASES and served as the first national co-chair of the UDN. Originally from Scotland, Ashley studied physiology and medicine at the University of Glasgow before earning a PhD in genetics from Oxford. He came to Stanford in 2002 as a cardiology fellow, joined the faculty in 2006, and is now a professor of medicine, of genetics and of biomedical data science. As he increasingly focused on precision medicine—which typically involves treating patients according to the genetics of their disease—he heard about the UDN. The National Institutes of Health had started the first center in Bethesda, Md., and, after its initial success, was partnering with academic medical centers. Ashley liked the idea of treating everyone regardless of their ability to pay, and he saw the central role of genetics in diagnostics. He applied alongside the Stanford scientists who would become the other principal investigators at the Center for Undiagnosed Diseases: Bernstein; Paul Fisher, '84, a professor and pediatric neurologist; and Matthew Wheeler, an assistant professor and fellow cardiologist.

A 2018 study conducted by UDN-affiliated researchers and published in the *New England Journal of Medicine* confirmed the power of the UDN model to shorten a patient's diagnostic odyssey. Prior to being accepted by the UDN, in a small group of patients for whom data was available, the cumulative cost of health care was, on average, $305,428. A UDN evaluation leading to diagnosis averaged $18,903.

Ashley attributes the UDN's efficiency in part to its frequent practice of performing immediate exome or whole-genome sequencing, which can identify a syndrome and obviate visits to a merry-go-round of specialists, who may repeat expensive tests or MRIs. "These patients often go and get the same tests in a new place," Ashley says. "One of the reasons I think the network is so successful is because it's much more integrated than our normal health-care system. The key part of the approach for the UDN is that we integrate all the opinions and then find the right person who has seen something like this before."

The story of Lauren Wong illustrates how long the quest for an answer can be and how quickly it can be resolved. She and her fraternal twin, Nathanial, were born prematurely in 2015. Whereas Nathanial spent a day in the newborn intensive care unit, Lauren, who was much smaller, remained for more than two weeks. Afterward, as the twins grew up, their parents, Mary and Craig Wong, noticed that Lauren wasn't developing as quickly. A neurologist diagnosed cerebral palsy, but as the months passed, more and more problems presented themselves. Lauren had little appetite. She developed infantile spasms, resulting in numerous, barely perceptible seizures each day. By the time she was 4, she was cognitively at the level of a 5-month-old and physically at the level of an 8-month-old. Eventually, the family's neurologist ruled out CP and other known conditions. He requested exome sequencing several times,

but the Wongs' health insurance refused the cost.

"When you don't know," Mary Wong says of the family's search for a diagnosis as she tries not to cry, "you feel alone in the world. And you're just uncertain of what to do next."

Every two hours, Lauren is fed via a tube in her stomach, since she doesn't eat on her own. She receives physical and occupational therapy, as well as vision and speech services. During the day, Lauren attends a special class with a one-to-one aide to support her.

"She's a really good kid," Mary says. "She's always smiling. She's never unhappy, which is crazy. Any little thing will make her smile, whether it be a toy or something that lights up or her brother walking by."

In 2017, Lauren was accepted at the UDN. Craig, Mary, Nathanial and Lauren all had their exomes sequenced. Within a month, the team at the Stanford center found that, unlike the other members of her family, Lauren had a defective copy of a gene called ALG13. This type of mutation was known as de novo—newly created in the embryo from an error during gene replication. The Stanford team informed them that roughly 20 other girls were known to have Lauren's mutation and symptoms.

"We were like, 'Excuse me? Did you just say about 20?'" Mary recalls.

In fact, the Wongs have learned, 40 to 50 children have the mutation, most of them girls. (Boys with a defective ALG13 are thought to often die before birth.) The oldest girl with the condition was 16. In many of them, the condition was expressed differently. Some were like Lauren. Others were more active. One was able to walk and run.

"You just don't know what to do for your child," Mary says. "When that unknown is there, it's hard to figure out which way to go. Even with the diagnosis, we're still not sure where this is going to take us. But at least we have a group of people that have the same diagnosis, and we can go to them for advice."

Shortly after birth, blood tests showed very low pH from high levels of lactic acid and ammonia. 'That's the adult human equivalent of having run a marathon,' says Wheeler. 'It could lead to risk of arrhythmia, injury to the brain or death.'

EUAN ASHLEY

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ONE OF STANFORD'S FIRST UDN PATIENTS, Anahi Villanueva, had a condition that was unknown to science. Shortly after Anahi's birth in August 2008, her mother, Maria, saw that her daughter was just sleeping—"She didn't even cry." The doctors soon realized that Anahi had gone into a coma. She was transferred first to a hospital in Oakland and then, as her condition worsened, to Lucile Packard Children's Hospital Stanford. Blood tests showed very low pH from high levels of lactic acid and ammonia.

"That's the adult human equivalent of having run a marathon," says Wheeler, the medical director for adults at the Stanford Center for Undiagnosed Diseases. "You get that sort of burning soreness that's from lactic acid. It could lead to risk of arrhythmia, injury to the brain or death."

For days, Anahi received IV fluids until the acidemia subsided and she recovered. In the years that followed, she had similar crises, brought on by overexertion, not eating enough or—most commonly—a virus like the flu. Each time, her blood levels suggested that her body was exerting itself far beyond the norm. "A couple of times when she got really sick," her mother recalls, "we thought she wouldn't make it."

Though the episodes were caught early and addressed with emergency room visits and IV fluids, the doctors could offer no diagnosis, and yet the symptoms clearly suggested a mitochondrial disorder.

One of the hallmarks of mitochondrial disorders is lactic acid buildup. When people can't generate enough energy from the mitochondria, they produce lactic acid through fermentation—a more rapid but less efficient metabolic process. Anahi's acidemia suggested that she was relying largely on this backup mechanism. Unlike Carson and Chase's mitochondrial condition, hers allowed her to walk and speak so long as she avoided taxing activities and getting sick.

When the UDN began accepting patients in 2015, Anahi was 6 years old. She had an MRI, exome sequencing and sequencing of the mitochondrial genome (mitochondria, being descended from bacteria that were incorporated into larger bacteria between 1.7 billion and 2 billion years ago, have their own set of genes).

The Stanford UDN team identified a mutation in a gene involved in the creation of ATP synthase, the mitochondrial subunit that makes adenosine triphosphate—or ATP—the molecule responsible for all energy in

RARE: Scientists had never before seen Anahi's condition, a mitochondrial disorder that affects energy production.

the human body (people generate their body weight in ATP every day). But the mutation was entirely new, existing nowhere in the scientific literature.

"It looked like it was in both copies from her mom and her dad," Bernstein recalls.

The researchers searched through databases for another patient with a similar mutation, but nothing turned up. Fortuitously, when Wheeler presented Anahi's case at a meeting of the American Society of Human Genetics, British scientist Robert Taylor—a specialist in mitochondrial diseases—said he had been studying a patient with similar symptoms and a similar but not identical mutation in the same gene.

The next step involved creating a model organism—in this case, the fruit fly—to study the impact of the genes. First studied by the geneticist Thomas Hunt Morgan in the early 1900s, fruit flies are among the organisms that—thanks to their rapid breeding time and the facility with which they can be handled—have most furthered our current understanding of genetics.

When a team of UDN researchers at Baylor knocked down the gene—reducing its expression—in fruit flies, no viable flies were born. A partial knockdown of the gene followed, with the researchers reducing expression only in the head. "When you do that," Wheeler explains, "you get a shrunken-head fly, with a tiny head that's very slow to develop." The team then introduced Anahi's mutation into a fly's head, which developed with slight problems, confirming that Anahi's version of the gene was impaired but still functional.

Anahi was 9 when the scientists at the UDN made the diagnosis of the new mitochondrial disorder. Though she is not as tall as expected for her age and has to manage her effort carefully, she can otherwise live a relatively normal life.

"She has missed so many days when she's sick through the years," Villanueva says of Anahi's schooling, "so she's behind a little bit. Sometimes she says she doesn't like herself. Sometimes she will say, 'I wish I was dead instead.' And then at school sometimes kids pick on her because she's short."

When discussing Anahi's future, Bernstein weighs the factors that may influence the girl's life. As people get older, their energy reserves—both fat and starch—increase, allowing them to go longer without food. "In mitochondrial diseases, though, there's a competing thing, which is that the wear and tear on your body's cells apparently over time causes the conditions to actually get worse, even if the shorter-term reserve may be bigger."

Though Anahi has a diagnosis now, she is one of only two people with her condition, and their symptoms and mutations aren't exactly the same. Unlike for other patients who have found a community and learned how their disease will progress, her future remains unclear.

THOUGH THE UDN LARGELY FOCUSES ON DIAGNOSING DISEASE, one of its scientists, Matthew Might, heads up an effort to match rare diseases with potential treatments. Might, who directs the University of Alabama at Birmingham's Hugh Kaul Precision Medicine Institute, earned his PhD in 2007 in computer science and began his academic career researching cybersecurity. But when he and his wife, Cristina Casanova, had their first son, Bertrand, they discovered that he had a rare unknown disease. In 2014, the *New Yorker* article "One of a Kind" described their journey to diagnose it. A struggle they faced was that competing scientists, intent on taking credit for discoveries, weren't sharing data on rare diseases—an obstacle the UDN has tried to solve.

In the process of educating himself on how to treat his son, Might embarked on his own odyssey, as he calls it. "If you read enough Wikipedia, you can do almost anything these days," he says. He taught himself so much about pharmaceutical chemistry that he received a second faculty appointment in the subject at the University of Utah. He then joined Harvard's department of biomedical informatics while working as a strategist at the White House for President Obama's precision medicine initiative.

Might was asked to be the UDN's director of precision medicine so he could scale up what he had done for his son: use algorithms to classify known medicines and determine whether they might be used to treat rare diseases. (In the United States, a rare disease is one that affects fewer than 200,000 Americans, which works out to about the same proportion used in the European Union's definition: one in 2,000 people.) While the number of already identified rare diseases has surpassed 6,000—affecting approximately 25 million Americans and vastly more people worldwide—few treatments exist for the conditions. To address this, Might's team has built an artificial intelligence agent.

"It's really a logical reasoning engine," Might says, "and the first data set it digested to be reasoning over was about 30 million published medical abstracts—so essentially every paper ever published in medicine."

To harness the power of this engine, those attempting to treat a rare disease first examine how the disease affects the body on the cellular level. As in a factory, if any part of the machinery isn't working correctly, material will either stop moving, accumulate or be absent. If scientists can determine where blockages or improper levels of substances occur, they can then use the software to search for a compound that might create balance in the system.

"You can ask it very low-level questions, like 'What's an inhibitor for this gene?'" Might says. "Or you can ask it very high-level questions, like 'What is the potential treatment for this condition?'"

He often finds himself working with parents who, through their own online research, have become experts just as he has. Danny Miller, the father of Carson and Chase, recently reached out to Might to propose a way that an enzyme missing in MEPAN might be circumvented.

"We checked it out," Might says, "and sure enough, it looks like he's right."

The lesson in Might's work is that previous scientific discoveries can be built on; they aren't investments for a single individual or disease. This addresses the skepticism of those who see research, diagnosis and treatment of rare diseases as too costly.

"There is essentially no rare disease," Euan Ashley says, "that doesn't have a correlate in common disease. You can have variants in that gene that are common and have a small effect on the function of the gene, or you can have variants that are extremely rare and have a massive effect."

He gives the example of how studying hypercholesterolemia—a genetic condition that causes unusually high cholesterol—led to treatment of commonplace cholesterol problems.

"That gene," he says, "is now the target of the newest and best drug for cholesterol."

And whereas Ashley acknowledges the satisfaction in the "Sherlock Holmes element" of the work, he finds the human element most compelling.

"Each story is literally an odyssey for a family. What makes it so meaningful is that there's always a face, there's a person, a family suffering. If you can solve this case, if you were staying up late at night wading through data, the chances are that if you solve it, you help that person and another 10 families with the same condition."

'What makes it so meaningful is that there's always a face, there's a person, a family suffering,' Ashley says. 'If you can solve this case, if you were staying up late at night wading through data, you help that person and another 10 families with the same condition.'

IN LIMBO: Doctors suspect Miguel has multiple syndromes.

FOR MANY FAMILIES, THE ODYSSEY THAT THE UDN'S DOCTORS SPEAK OF IS ONGOING AND MAY LAST FOR YEARS. Genetic and patient databases are constantly updated, allowing scientists to find new matches, but the wait can be torturous, as it has been for Miguel Bejar and Georgina Guerrero.

Born in 1977, in the small town of Tizapan, in Jalisco, Mexico, Miguel Bejar moved to Redwood City, Calif., when he was 17. After getting his high school diploma, he took a job as housekeeping assistant at Stanford Hospital. Over more than 20 years, he was promoted first to housekeeping lead, then to housekeeping supervisor, and then transferred to the main operating room, where he is now a lead assistant.

After he married Guerrero, a dentist's assistant from Michoacán, they waited more than four years, preparing their home and finances, before starting a family. Their son, Miguel, was born in April 2015. The pregnancy was healthy, though a doctor detected a heart murmur shortly after birth. "He told me that's pretty normal in babies when they are newborns, and usually it will go away in two or three days," Bejar recalls.

But an echocardiogram showed a deformation of the aortic valve and a narrowing of the aorta, which limited blood flow. Doctors successfully performed heart surgery, but three months later, crystals appeared in Miguel's urine, gathering in his diapers. Further medical tests showed that his red blood cells were slightly smaller than normal, and a genetic test immediately revealed that he had 8p23.1 duplication syndrome—a rare chromosomal anomaly in which the short arm of chromosome 8 is partially duplicated.

Bejar recalls the doctors explaining the syndrome. "They told me that there were 17 known cases and the syndrome in those situations behaved differently. But they all have cardiac issues."

The syndrome, however, didn't explain all of the symptoms Miguel would soon have. He began growing too quickly—his head even more rapidly than his body. In January 2018, his head's circumference was 21.8 inches. By October, it was 22. By May 2019, it was 22.4. An MRI showed that his brain was underdeveloped and had large white ventricles. He was soon diagnosed with autism, and his muscles were weak. He walked poorly, fell easily and hadn't learned to speak. He had kidney stones and would soon need more heart surgery. At the age of 4, he is the size of a 7-year-old, and his head has now surpassed 22.6 inches—almost as big as his father's.

"I was a little blessed by having the job at Stanford and having access to doctors," Bejar recalls. "Without this place, I can't imagine how other families . . . I mean, for me it has been a little hard. For other families, I believe it's harder."

In early 2018, he applied to the UDN, and Miguel was accepted within weeks. The team assigned to Miguel is sequencing the DNA from both his blood and his skin to compare them to determine whether he has mosaicism—a condition in which genetic mutations occur early during development and present only in certain tissues. The team is looking for multiple syndromes, which Bernstein says can be especially challenging: "One condition can mask or confuse you about what's going on with the other one."

As for the next step, that will depend on what current tests reveal—if anything—and what the team decides once it has reviewed the data. After all, more often than not, the UDN does not come up with diagnoses or must wait to connect patients on file to new findings in the scientific literature. Its success rate to date hovers around 28 percent, which means hundreds of people continue to live in limbo.

While Bejar awaits the results, he tries to reconcile the pain of uncertainty with the tenderness he feels for his son.

"If I had the opportunity to be a father and this happens again," he says, "I will take it because it's one of the best experiences, taking care of a child with necessities. It brings the best out of your human side. You go beyond a lot of your limits on the way you love life, and the way you appreciate life and people." ■

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