SPECIAL ISSUE

Translational Genomics Research Institute

# TGen Today



## TGen's Medical Miracle

Shelby's Success Inspires TGen to Establish the Center for Rare Childhood Disorders

TGen
A Non-Profit Medical Research Institute

# A Look Inside...

Dear friends, families, and colleagues,

This special issue of *TGen Today* commemorates your commitment and support, which led to the formal launch of TGen's Center for Rare Childhood Disorders (C4RCD). We thank you for joining us in our efforts to fundamentally change and improve the evaluation and management of children with rare disorders.

Since our founding in 2002, TGen faculty have eagerly joined with clinicians, geneticists and bioinformaticians in their effort to better understand rare and undiagnosed childhood disorders. Only recently, however, have technological advances enabled our efforts to align more precisely with the needs of a patient community in search of answers. The coming together of technology and the right mix of talent, combined with the tremendous needs of our patients, led to the establishment of the C4RCD.

This issue highlights stories from several families we have had the privilege to work with, and highlights the diversity of challenges these and similar families cope with in their search for answers.

The four major building blocks of the C4RCD are clinical evaluation, diagnosis, treatment, and outreach. As we lead the C4RCD into the future, our task is to continually "push the envelope" for patient care. In the coming months, we expect to open the C4RCD clinical office, which will lead the evaluation and treatment charge through our frontline work with patients and their families.

To facilitate diagnosis and inform treatment in a timely manner, TGen successfully established a federally certified clinical services laboratory. Known as CLIA certification, this designation provides clinicians the ability to treat immediately based upon TGen's genetic findings, a process that otherwise would require outsourcing and could take several weeks or longer, time many patients simply can't afford. We highlight the CLIA laboratory in this issue.

Our ability to swiftly treat based on laboratory findings is enhanced by our collaboration with leading technology partners, which allows the C4RCD to be among the first in the nation capable of performing rapid whole-genome sequencing. Over the past year, we have enrolled more than 30 families into our research studies. We expect that in 2013, as we transition much of our work into the CLIA lab, a number of physician-partners from around the country will refer their patients to the C4RCD.

Our ultimate goal is to develop new treatment approaches that will allow us to halt or reverse the disease process, and improve the lives of our patients. In terms of progress toward this goal, Shelby's story, updated in this issue, continues to inspire all who know her. Shelby serves to remind us, however, that a genetic diagnosis is just the beginning of a new chapter for our patients, and that our work is far from over.

The final block of the C4RCD is community outreach – this begins with the families that reach out to our center, and extends through their networks. By facilitating the development of this community, and fostering constant interaction among our families, clinicians, and scientists, we will all learn and progress.

Please join us in thanking the families who have shared their stories in this issue. They are our inspiration and remind us to keep our research focus sharp on the final goal – understanding disease and developing new treatments.

**David Craig, Ph.D.**
Co-Director, C4RCD

**Matt Huentelman, Ph.D.**
Co-Director, C4RCD

**Vinodh Narayanan, M.D.**
Medical Director, C4RCD

Translational Genomics Research Institute

# TGen Today











**About TGen |**

The Translational Genomics Research Institute (TGen) is a non-profit organization dedicated to conducting groundbreaking research with life changing results. Research at TGen is focused on helping patients with diseases such as cancer, neurological disorders and diabetes. TGen is on the cutting edge of translational research where investigators are able to unravel the genetic components of common and complex diseases. Working with collaborators in the scientific and medical communities, TGen believes it can make a substantial contribution to the efficiency and effectiveness of the translational process. For more information, visit: www.tgen.org

# TGen Launches the C4RCD

## Bringing Hope to Children with Rare Disorders

TGen recently announced the creation of a new center that could have life-changing effects on the lives of potentially thousands of children and their families.

The TGen Center for Rare Childhood Disorders (C4RCD) harnesses the latest technologic leaps in genome sequencing to pinpoint the causes of rare childhood disorders that largely remain a mystery to modern medicine.

> "Through the C4RCD, TGen has a unique opportunity to significantly improve the lives of these children and their families."

"We envision a Center that leverages today's genomic technology toward diagnosing children with a baffling array of seriously debilitating, and often lethal, symptoms for which there is no known cause or treatment, let alone a cure. In many cases, it's merely a collection of symptoms," said Dr. Jeffrey Trent, President and Scientific Director of TGen. "Through the C4RCD, TGen has a unique opportunity to significantly improve the lives of these children and their families."

Often, there are just a few children, or even a single child, with a particular set of symptoms. Collectively, according to the National Institutes of Health, there are close to 7,000 rare diseases and about 25 million people in the U.S. have one.

"Too often, the parents of these children are left with nowhere to turn. They often are simply prescribed medications for their child, such as anti-seizure drugs, that only address the symptoms," said Dr. David Craig, TGen's Deputy Director of Bioinformatics and Co-Director of the C4RCD.

"At TGen, we now have the tools to sequence the entire genome of these children, in a relatively short time and at ever-lower costs. Through this examination of the billions of chemical letters that spell out each human being's unique genome, and analyzing all the potential genetic changes, or mutations, we now have the ability to potentially identify the root cause of each child's condition," said Dr. Craig.

Understanding what is causing the disease or condition enables TGen to consider treatment options that could best help each child.

If the sequencing reveals a genetic target, C4RCD scientists search the catalog of existing FDA-approved drugs in hopes of repurposing one to treat the rare disorder.

TGen's C4RCD has four major components: clinical evaluation and genomic diagnosis; optimizing conventional therapy; novel therapy development; and community outreach.

Each child will be clinically evaluated and have their genome tested, including the use of whole genome sequencing, which spells out the entire 3 billion letters of each individual's DNA genetic code.

"We want to use this genetic information to understand more about the particular disorder, and develop novel approaches to treatment. That is what is going to differentiate us from other services — complete integration of the clinical center and the genomic research lab," said Dr. Vinodh Narayanan, Medical Director of the C4RCD.

Dr. Trent said that there is a critical unmet need in the medical community, which only now can begin to be addressed through the advent of new genomic technologies.

"We continue to be amazed at the way families of children with debilitating conditions are able to find each other, share stories of their victories and of what is wrong, and try to come up with answers," said Dr. Trent. "We hope to become an active partner and leader in these communities as we learn from the families and patients, and then try to come up with new and better answers for these children — today."

Bennett and Jacquie Dorrance with Dr. John Carpten officially open the CLIA laboratory at a ribbon cutting ceremony

Grandchild's rare disorder inspires Dorrance family philanthropy

# $1 Million Gift Creates TGen CLIA Lab

Bennett and Jacquie Dorrance, supporters of TGen since its inception, know what it's like to go without answers. Their grandson, Anton Baiker, was born with a rare childhood disorder that went undiagnosed until age 4, when he was enrolled in a groundbreaking study at TGen.

His first year of life, he required a feeding tube and was frequently in hospitals as his mother, Ashley Kaplan, searched in frustration for explanations about what caused his abnormal fevers, cold sweats, and his unusual response to pain. It was unknown if his condition would worsen.

"Every day was a guessing game," Ashley said. "I had no idea why he was the way he was."

Aided by expert assessment of his condition, TGen scientists sequenced and analyzed his genome. Doctors diagnosed him clinically with Crisponi syndrome, an extremely rare condition generally characterized by excessive muscle contractions, fevers, seizures, hyperthermia and respiratory problems.

Now, at age 6, Anton is doing well, even excelling at soccer. Ashley said that with a diagnosis, she and Anton are better equipped to deal with his condition and anticipate the future.

"We would never have been sure about what he had without TGen's intervention," said Jacquie Dorrance, who empathizes with other families of children with rare childhood disorders. "There are so many families going through this agony and nightmare of not knowing. This is made especially difficult after having taken their children to hospitals all over the country and still coming up with no solutions or leads."

TGen's whole genome sequencing spells out the 3 billion letters of each patient's DNA, enabling researchers to identify potential problems in their genetic code.

"That makes all the difference," Jacquie said. "Just knowing what it is. Just having some idea of what your child has. It's just huge. Putting a name on it. Not feeling like you're totally in the dark. That's why we're so involved in the C4RCD."

One of the key ingredients to quickly sequencing and analyzing a patient's genome is access to a laboratory certified under CLIA, Clinical Laboratory Improvement Amendments, passed by Congress in 1988 to ensure quality laboratory testing.

Thanks to a $1 million donation from the Dorrance Family Foundation, TGen now has its own CLIA lab, recently christened the Dorrance Clinical Laboratory. This new lab will enable the C4RCD to quickly find answers for more families like the Dorrance's.

"We are extremely grateful for the tremendous support we have received over the years from the Dorrance's," said Dr. John Carpten, TGen's Deputy Director for Basic Science. "This new lab represents a quantum leap for the capacity of TGen to conduct our science and make new strides to benefit patients as quickly as possible."

Having its own CLIA lab means TGen doesn't have to wait weeks or months working with an outside CLIA facility to complete the analysis of a patient's genome. Instead, it can be completed in-house in as little as a three or four days.

"That's the amount of time you need to do things, not three or four months," said Bennett, noting that a quick turn-around makes the sequencing data beneficial for the treating physician.

Bennett is amazed at the progress TGen has made over the past 10 years since its establishment in 2002, and he believes the progress and commitment to rapid translational medicine will continue under the leadership of TGen President and Scientific Director Dr. Jeffrey Trent.

"The advances in the last 10 years have been stunning. Jeff has accomplished so much more than I ever thought was possible," Bennett said. "TGen does things differently. They will continue to do it with Jeff at the helm. They'll continue to partner. They'll continue to think out of the box. The status quo just isn't cutting it. TGen is always going to be pushing the envelope."

Dr. Lisa Baumbach-Reardon (left) and Dr. Janine LoBello (right) are CLIA Lab Co-Directors

Patients benefit from timely analysis of DNA sequencing

# TGen Launches

As more TGen studies use whole genome sequencing — decoding DNA to determine a patient's molecular make-up — TGen has a growing potential to share clinically relevant test results with patients and their oncologists.

Sharing that information is a cornerstone of TGen's ongoing initiative to help provide patients and their physicians with personalized therapeutics.

But to share that information, TGen's studies must be performed, or confirmed, in laboratories certified under Clinical Laboratory Improvement Amendments (CLIA), passed by Congress to ensure quality laboratory testing.

Until now, TGen has contracted with outside CLIA-certified laboratories. This has meant an oftentimes cumbersome, costly and time-consuming back-and-forth exchange of data among the parties involved in our studies, sometimes adding as much as four weeks to generate a report for the patient.

Thanks to a $1 million grant from the Dorrance Family Foundation, TGen has created an in-house CLIA Laboratory on the 4th Floor of the Phoenix TGen headquarters, the Dorrance Clinical Laboratory. Government approvals are anticipated before the end of 2012.

Once CLIA certification is established at TGen, all applicable testing results, including genomic sequencing assays, can be directly reported to a patient's medical record.


# CLIA Lab

## Drs. Baumbach-Reardon and LoBello are CLIA Lab Co-Directors

TGen CLIA Lab's Co-Directors are Dr. Lisa Baumbach-Reardon, Associate Professor of TGen's Integrated Cancer Genomics Division, and Dr. Janine LoBello, D.O. and TGen's Research Pathologist.

Dr. Baumbach-Reardon also is Director of the DNA Diagnostic Laboratory in Cancer Genomics, which involves clinical molecular diagnostics, the sequencing branch of the CLIA Lab.

"Having developed and maintained CLIA labs elsewhere, I am excited to help create this state-of-the-art facility at TGen, and I look forward to helping enable our scientific staff make substantial new discoveries that will benefit humanity," Dr. Baumbach-Reardon said.

Dr. LoBello also is Director of TGen's CLIA Histopathology Lab, which examines biopsy samples. She also continues as Director of TGen's Macromolecular Analysis and Processing Center (MAPC), which now includes TGen's Tissue Microarray Service Center, for non-clinical research. The Histopathology Lab and MAPC are housed within the CLIA Lab.

"The successful establishment of a CLIA-certified laboratory aligns superbly with our existing commitment to full-spectrum research support," said Dr. LoBello. "We will now have the ability to provide results for clinical, prospective studies with direct individual patient impact, while maintaining our support for non-clinical research endeavors."

TGen's CLIA program will fall under the auspices of Dr. John Carpten, TGen's Deputy Director of Basic Science.

"The advent of a CLIA-certified lab here at TGen will be of incalculable benefit for our researchers, our collaborators and the doctors and patients who look to TGen for new therapies and hope," said Dr. Carpten, who also is a Professor and Director of TGen's Integrated Cancer Genomics Division.

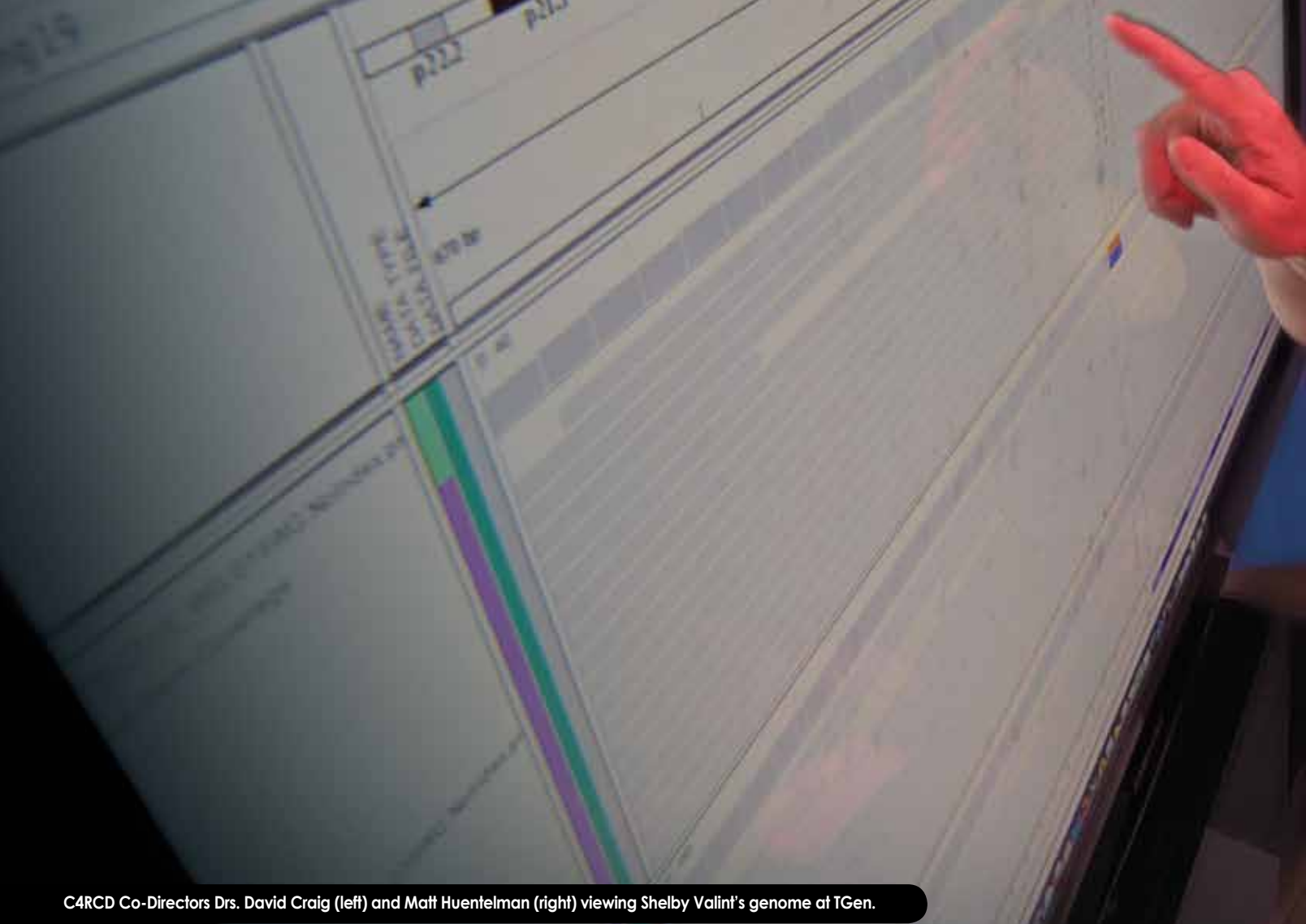
## How TGen's CLIA Lab will work

Biospecimen samples will ship directly to TGen from clinical collection sites for immediate nucleic acid extraction under CLIA certified quality control conditions, and lead to a report summarizing the results of sequencing analysis without need for further validation.

The new CLIA Lab will enable TGen's identification of genetic mutations and molecular targets to be more easily shared with oncologists so they can be used to guide patient treatment.

This will save money. But it also will save time, a precious commodity for patients. Getting critical information to physicians and patients should accelerate treatments, and could even save lives.

TGen's CLIA Lab provides a critical step in accelerating patient care and treatment. With a CLIA-certified lab, TGen can validate and apply research knowledge immediately to help those patients sitting in front of us today.



C4RCD Co-Directors Drs. David Craig (left) and Matt Huentelman (right) viewing Shelby Valint's genome at TGen.

# TGen's Medical Miracle

Shelby Valint's birth in August 2000 — the second of eventually four girls — went off without a hitch. Her mother carried to term with no complications and within 24 hours both mother and daughter were safely and happily on their way home.

"I thought everything was fine," said her mother, Renee Valint.

But when the Phoenix girl was just a few months old, Renee noticed that Shelby wasn't progressing. Shelby had difficulty holding her head up and her body was generally limp. As time passed, Shelby had difficulty walking, talking and swallowing food.

"We were waiting to see if this was something she would outgrow," Renee said.

But while Shelby's brain developed, her physical condition worsened to point of needing a wheelchair. What was wrong? The family had no answers.

Shelby and her family began what would become a decade-long search for a diagnosis. Shelby visited countless doctors and underwent numerous examinations and tests at medical facilities across the nation.

Anesthetized nearly a dozen times, her tests included multiple brain scans, nerve conduction studies and muscle biopsies, all of which came back negative.

"The doctors could not discover what was wrong. They just put their hands in the air," Renee said.

Eventually, Shelby wound up in the State of Arizona's Children's Rehabilitative Services (CRS) program, where she saw Dr. Vinodh Narayanan.

"We met Dr. Narayanan, and I knew it was going to be different," Renee said. "He was very interested in her case, and I knew he wasn't going to be just like one of the other doctors. He was going to stick with her to the end."

Shelby's case puzzled even Dr. Narayanan for several years. "We suspected some things, but we did not have an exact diagnosis," he said.

Shelby continued to deteriorate to the point that her mother feared the worst. "We were so worried that we were never going to find an answer. The hardest part was not knowing what was wrong," said Renee.

Meantime, technologic advances in whole genome sequencing were making it easier to apply the techniques to patient care. Sequencing that once took over a decade and nearly $3 billion could now be completed in a matter of weeks, and for a few thousand dollars.

Dr. Narayanan felt Shelby was a good candidate for WGS. TGen scientists sequenced her genome, and the analysis revealed a problem in a gene known as

DDC, which codes, or provides genetic information for, an enzyme critical for the production of dopamine, a brain chemical responsible for movement, muscle control and balance.

In December 2010, Shelby began taking bromocriptine and selegiline, drugs often prescribed for Parkinson's disease, a disorder of the nervous system associated with diminished dopamine.

Within a few weeks, Renee noticed that Shelby was getting stronger. She could hold her head up. Her speech was clearer. She started doing more things on her own. She didn't use her wheelchair as much.

"It happened so quickly. It was amazing," Renee said. "She got stronger and stronger, and we just watched her flourish."

One day, Shelby took her mother's hand, walked out the front door and walked down the street. "That's when I thought, this is a miracle," Renee said.

Shelby said, "I was able to go to restaurants. Go to the store. Walking. It was amazing."

Soon, Shelby was walking to school.

"I remember the first day she walked in to school. The students and staff were crying. They had seen Shelby through the years in a wheelchair, and here she was on her own two feet," her mother said.

Now 12 years old, Shelby is a 7th Grade honor-roll student.

"She's my biggest joy. I just thank God for every day she's with us. She's so happy now. She's not bound to a wheelchair any more. She's free," said Renee, a tear in her eye. "For us to be able to find TGen has been a miracle."

In recent weeks, Dr. Narayanan said Shelby has shown even more improvement after substituting pramipexole, another Parkinson's drug, for the bromocriptine.

"She was starting to get a little weak again. She was getting fatigued during the middle of the day," Dr. Narayanan said. With the new drug, pramipexole, he said, "She's really done quite well; a fairly dramatic improvement in her functions."

Shelby's case inspired TGen officials to establish the Center for Rare Childhood Disorders (C4RCD).

"Shelby, to us, demonstrated that this can be done," said Dr. Matthew Huentelman, Co-Director of TGen's C4RCD. "What I hope we can do is to provide answers for these families. We strongly believe that, for a lot of these rare childhood disorders, the root cause is going to be found in their genome."

Shelby's continued monitoring by TGen also could lead to more discoveries about her condition.

"We're not trying to stop there, at the genetic diagnosis. We're trying to provide even more information back to the physician, back to families, about how we might now attack this disease," Dr. Huentelman said. "It gets us to a new foothold. It's a new answer for these families, where in a lot of cases they've had none."

Three of four Belnap children are diagnosed with Mitochondrial Disease; from left are: Seth, Newell, Sydney, Sierra, Becky and Spencer Belnap

# Belnap family puts faith in TGen

Seth Belnap is an energetic 6-year-old from Show Low, Arizona, ready to engage in a conversation with anyone, and a constant source of joy in his family.

For now, Seth is doing well, ever since his parents, Newell and Becky Belnap, found Dr. Vinodh Narayanan, Medical Director of TGen's Center for Rare Childhood Disorders (C4RCD). The Belnap's said they feel Dr. Narayanan saved Seth's life.

When Seth was 2 ½, his parents worried that something was very wrong. Seth still hadn't started speaking. And worse, he kept falling; sometimes hurting himself so badly that his parents had him start wearing a bicycle helmet and his father Newell, a physician's assistant, had to stitch him up.

An electrocardiogram indicated some abnormalities in his heart, and an MRI revealed some benign cysts in his brain. But when Seth was taken for a thorough check-up at a hospital, he seemed so happy that, his parents said, no one took any of his problems seriously.

"Seth has always been the happiest kid ever. It doesn't matter what goes on, he's happy," said Newell. "He just radiates love."

Discharged from the hospital, the Belnap's believed their son must be fine. "We didn't do anything about it," Newell said, and Seth remained untreated for nearly a year.

Still, Seth continued to fall, and failed to speak.

Not satisfied, Seth's parents eventually took his test results to other doctors. One suggested he might have Leigh's Disease, a form of Mitochondrial Disease, which includes broad range of conditions that are tied to the parts of cells (except red blood cells) that generate energy. (In the Star Wars movies, mitochondria are the source of The Force.)

**History of genomic sequencing**

## A DECADE OF PROGRESS

**TGen Milestones**

**2001**
- First draft of human genome completed ($2.7 billion)

**2002**
- **TGen is founded**

**2003**
- Array-based technology allowing the assay of 10,000 genomic positions for $1,000 in a person
- Human Genome project finished
- First neurogenomics employees begin research
- Identification of a gene for Sudden Infant Death in Old Order Amish

A new MRI showed Seth's cysts had grown in size and number. They were connected, and doctors began referring to them as lesions.

One doctor suggested Seth be seen by Dr. Narayanan and his pediatric neurogenetic team in Phoenix. But the initial news in February 2010 was devastating for the Belnap's, who were told by Dr. Narayanan that he had never before seen a case like Seth's.

Still, Newell said he was impressed by Dr. Narayanan because of his intelligence and humility; his willingness to say that he didn't know what was wrong, to consult specialist with greater expertise, and the confidence he expressed by saying he would do everything possible to find the source of Seth's problems.

"We had been bounced around from doctor to doctor to doctor," Newell said. "We were devastated that Seth's condition continued to deteriorate and that nobody knew what it was. But we left feeling confident that we finally had someone who was going to help us."

After more testing, Dr. Narayanan was highly suspicious of Mitochondrial Disease and recommended a specialist in Atlanta, who confirmed the diagnosis of Leigh's Disease. Seth was put on a collection of vitamins, antioxidants and supplements known as a "mito cocktail," as well as folinic acid to counter a folic acid deficiency detected in Seth's brain.

He also recommended that TGen sequence Seth's genome, spelling out his DNA code to see if he had a genetic defect.

At first the Belnap's thought TGen's research was being done to further medicine for others in the future. Now, they understand that sequencing the genomes of all the Belnap's might lead to better medical treatments for their entire family.

Not long after Seth's diagnosis, tests showed that his 18-year-old sister, Sydney — who has similar facial features, cognitive problems and a small stature like Seth — also has Leigh's Disease. Sydney also was put on a mito cocktail.

Then, in March 2012, the Belnap's older son, 15-year-old Spencer — who had excelled in school and sports — was suddenly stricken with a paralysis on his right side that left him temporarily numb and unable to properly speak. Tests showed Spencer also has a form of Mitochondrial Disease, though not as severe as the Leigh's Disease suffered by Seth and Sydney.

"Spencer's diagnosis threw our world upside-down," Newell said.

Spencer also is now on a mito cocktail, as is the Belnap's younger daughter, 10-year-old Sierra. While Sierra has not been diagnosed with Mitochondrial Disease, she is receiving medication as a preventative measure.

Nearly two years after the start of his medications, Seth is talking — to everyone — and he only wears a bike helmet when he's riding his bike.

While the Belnap children appear fine, for now, their parents continue to worry. They don't really know if the mito cocktails are working.

Dr. Narayanan said TGen is studying all members of the Belnap family in an effort to go beyond diagnosis. "We're still trying to figure out what is the genetic basis of their mitochondrial disorders."

Mitochondrial Disease is progressive. It can lead to: a loss of muscle coordination and muscle weakness; visual and hearing problems; learning disabilities; heart, liver and kidney disease; gastrointestinal and respiratory disorders; neurological problems, autonomic dysfunction, and dementia. Many children diagnosed do not live to adulthood.

"It's such a different way to live when you have sick kids. Things that used to be important to us, aren't," said their mother, Becky. "Our lives revolve around taking medications and the next doctor's appointment. We try to live each day in the moment. You're just grateful for every day, and for the joy that they bring to us."

And the Belnap's have renewed hope. They are excited about TGen's creation of the C4RCD.

As with all of the patients in the C4RCD program, Dr. Narayanan said, using genetic sequencing should one day enable better treatments. "Our hope is, if we pinpoint the genetic basis of the disease, we might get some new insight into its mechanism, and that might allow for a new attack; a new therapy."

**2004**

- Travis Dunckley Lab formed

**2005**

- David Craig Lab formed
- Neurogenomics interns Anne Lee and Albert Shieh win prestigious *Siemens Westinghouse Competition in Math, Science and Technology*
- TGen and St. Joseph's launch Pediatric Neurogenetics Clinic
- TGen arrays 7,000 individuals for Autism Genome Project at 10,000 markers

TGen's C4RCD provides closure for family of Ryder Cash Hauer; from left are: Tyler, Ryder, Les, Noah and Denise Hauer

*Photo courtesy of the Hauer family*

# Chasing a diagnosis

The day he was born, Ryder Cash Hauer didn't fuss or even make a peep. His parents, Denise and Les Hauer of Mesa, Arizona, said doctors told them that Ryder was simply a quiet child with nothing to say. The next day, Ryder started making sounds.

"We thought everything was OK," said Denise.

But at Ryder's 5 month routine check-up, the pediatrician noticed that Ryder had nystagmus, an involuntary movement of the eyes. Over the next several months, Ryder began missing developmental milestones. He didn't sit up on his own until he was 10 months old.

At 11 months, an eye exam showed his vision was fine, but a subsequent MRI was abnormal, and the Hauer's were told that Ryder might have an inherited disorder, a form of leukodystrophy, a progressive neurological condition.

But it wasn't a definitive diagnosis, and the Hauer's would spend most of the next two years chasing down what was ailing their youngest son.

"I was overwhelmed, researching on my own, trying to understand," Denise said. "It was very scary."

Through much of that time, with the help of therapy, Ryder slowly developed skills such as walking, running, throwing and kicking balls, climbing stairs, riding his big wheel bike, playing baseball and hanging out with his older brothers, Tyler, 8, and Noah, 7. He often fell and was unbalanced, but the skills he did gain were tremendous accomplishments.

"He was such a delightful, lovable toddler. His personality was really starting to shine," his mother said.

Even though Ryder was making slow developmental gains, his health began to decline. He started having gastro-intestinal problems, and eventually was placed on a feeding tube. His occasional absent gazes led Denise to suspect

**2006**

- Array-based technology allowing the assay of 100,000 genomic positions for $1,000 a person
- Matthew Huentelman Lab formed
- TGen identifies gene in Amish with autistic-like language regression using 10,000 marker array

**2007**

- First Illumina sequencers capable of 500 million bases for $10,000

**2008**

- Array-based technology allowing the assay of 500,000 genomic positions for $1,000 in a person
- Kendall Van Keuren-Jensen Lab formed

that he might be having seizures. She quit her job as a special education teacher to stay home and take care of Ryder.

Through a friend, the Hauer's learned of Dr. Vinodh Narayanan, Medical Director of TGen's C4RCD, who suggested whole genome sequencing, a search of the 3 billion letters in Ryder's DNA code for any possible genetic defects.

Meanwhile, the Hauer's said their insurance company balked at paying for some of Ryder's tests, telling them essentially that they were reluctant to pay because the tests wouldn't change the outcome.

> "He was such a happy, sweet toddler. His personality was really starting to shine."

Through the summer of 2012, Ryder began vomiting uncontrollably and was hospitalized repeatedly. Denise tears up when she recalls the first of several 911 calls on July 25, after waking up to an unresponsive son. Ryder suffered what she describes as a horrific seizure lasting all day long. During the 3 weeks that followed, Ryder began having cluster seizures and at times his breathing stopped. He rapidly declined after these episodes losing the ability to sit up on his own, even roll over, and could not fully open his eyes.

On Aug. 11, while at the hospital, the Hauer's received a definitive diagnosis from TGen: Ryder had a mutation in his POLG gene associated with Alpers syndrome, a progressive form of mitochondrial disease characterized by seizures, developmental delay and progressive dementia.

While there currently is no cure for Alpers syndrome, the Hauer's were grateful to finally end the 2-year search for the mystery diagnosis, along with the natural feelings of frustration and wondering if they should be doing anything differently.

"Even though it was a heart-wrenching diagnosis, it gave us peace of mind and took a big weight off our shoulders," Denise said.

The morning of Aug. 22, Ryder passed away in his parents' arms, two weeks shy of his 3rd birthday.

"I think, from the outside, its hard to realize how important that diagnosis was to us," said Ryder's father, Les Hauer. "It really was the best thing that happened during that whole time."

A flood of 'What ifs' pour from Denise as she considers what might have been possible if only Ryder's whole genome sequencing had been available sooner.

If properly diagnosed two years earlier, she said, Ryder might have had quicker access to long-term health care, home-therapy, received more appropriate tailored medications, and endured fewer painful pokes and invasive tests, avoiding those that require general anesthesia, a procedure that can aggravate Alpers syndrome.

Just as importantly, there might have been fewer medical appointments and the Hauer's might have had more time to enjoy with their child.

"Without a diagnosis, each appointment was just a guessing game and a new test to try. I missed out on so much extra time I could have spent with Ryder, instead of hassling with everyone to get Ryder what he needed," Denise said. "We would have understood the course of this disease better and made more appropriate goals for him. Ryder wasn't given any medication for his seizures until it was too late to control them."

The Hauer's are grateful to Dr. Narayanan for doing all he could to help, and they are heartened by TGen's establishment of the C4RCD. "Dr. Narayanan and TGen are heroes in our eyes. They have been true blessings in our journey and we will be forever grateful," Denise said.

"It means, perhaps, that fewer families might have to endure what we went through," added Les.

For Denise, it means more hope, awareness and meaning. "It's knowing that something positive might come out of what happened to Ryder."

In his memory, and with the hope that others will be helped in the future, the Hauer's have established The Ryder Hauer Fund for Rare Childhood Disorders.

**2009**

- TGen begins first whole-genome sequencing in autism (3 billion positions for $150,000 in a single person)

**2010**

- Begin 5-case pilot for rare-childhood disorders sequencing program

**2011**

- TGen completes 5-case pilot for rare childhood disorders, reports initial successes
- Lisa Baumbach-Reardon joins TGen, initiating research into spinal muscular atrophy

# Embracing the C4RCD

## In memory of 'warrior' son, Laffoon family seeks to help others

Photo courtesy of the Laffoon family

When TGen announced the formation of the C4RCD, Steven and Shannon Laffoon were ready to help.

The Scottsdale couple had spent the past three years caring for their only child, Wylder James Laffoon, pursuing whatever treatments might be possible for his diagnosis of Niemann-Pick Type A, an extremely rare and fatal disease characterized by an inability to metabolize fats.

Following TGen's announcement of the C4RCD in October 2012, the Laffoon's now want to help other families of children with rare disorders.

"The C4RCD is everything we wanted to do. We want to provide options for people who don't have options," said Steven.

While the Laffoon's had a definitive diagnosis, what they didn't have was a captain, a champion, a go-to person willing to steer Wylder's treatment.

"We were alone; frustrated. We were the driving force," said Steven, who with Shannon spent years initiating and building relationships with doctors, scientists, biotech and pharmaceutical companies — even negotiating with the U.S. Food and Drug Administration for approval of an experimental drug trial.

"We're pretty self-sufficient. We can make things happen. But we also got chewed up and spit out by the medical system," Steven said. "If this is complicated for us, it's just got to be so hard for other families."

With Shannon providing intensive day-to-day care for Wylder, and Steven pursing a relentless Internet search for treatments, the Laffoon's navigated their son through 27 blood transfusions and 15 medical procedures, including 5 brain surgeries.

"There are families dealing with the same things we dealt with," Steven said. "They're getting diagnoses, but then getting essentially the same feedback from doctors that we did: 'There is nothing we can do. Go home and enjoy what time you have left with your child.' But we couldn't just sit there and watch his disease progress and be OK with it. For us, it was hard to fathom that we didn't have even one option."

Steeped in the culture of Hawaii, the Laffoon's described Wylder as their "warrior," fighting to survive while teaching his parents, and everyone who came in contact with him, what it means to care, to love, to live in the moment and never give up hope — how each of us are on a journey that teaches appreciation, patience, compassion, kindness and wisdom.

Though he could never speak, Wylder communicated to his parents when it was time to stop. In July 2012, he passed away — his ashes scattered with 6,000 flowers and an Aloha spirit across a shining bay in Maui, a bay now visited by a young humpback whale called Wylder.

Even before their son was gone, the Laffoon's started focusing on how their experience might help others. They are in the process of setting up a foundation, Warrior Nation, and Shannon even wrote a children's book, *Warrior Baby*.

"Since Wylder has passed, the thing that gives us the most peace is doing things for him, in his honor," said Shannon. "And long-term, to help parents have an easier journey, because we know how complex and difficult it is."

You can learn more about Wylder at wylderjames.com.

Genome in a day sequencer released

**2012**

**January**
- TGen begins planning the Center for Rare Childhood Disorders (C4RCD)

**May**
- TGen begins series of projects focused on rare childhood disorders, including Aicardi syndrome project

**August**
- First meeting of National Advisory Panel
- TGen completes 10th genome for the C4RCD

**October**
- TGen completes 30th Genome for the C4RCD
- Media launch of the C4RCD

**October**
- 10-family *Understand Your Genome* event with Illumina

**November**
- Second meeting of National Advisory Panel
- TGen acquires genome-in-a-day HiSeq2500

# Advisory committees help guide the C4RCD program

In an effort to draw on the expertise and resources of the community, TGen's Center for Rare Childhood Disorders (C4RCD) has established a National Advisory Committee and a Parent Advisory Committee.

These panels will help guide the C4RCD, provide a catalyst for the rapid exchange of concepts and ideas, enable families to share their challenges and triumphs, and muster support.



*NAC Co-chairs, Jacquie Dorrance and David Harbour*

## National Advisory Committee

The National Advisory Committee (NAC) of the Center for Rare Childhood Disorders (C4RCD) is a core group of advisors and supporters with a passion for helping children and families affected by rare and neglected pediatric diseases and disorders. Members of the NAC, Chaired by Jacquie Dorrance and David Harbour, provide key volunteer leadership, resources, and vision for the C4RCD. The NAC leverages their diverse professional expertise and relationships to inform strategic planning, promote TGen and the Center among thought leaders, and identify potential community partners and volunteer leaders for the C4RCD.


*PAC Chair Karie Dozer*

## Parent Advisory Committee

From the beginning, TGen's Center for Rare Childhood Disorders (C4RCD) has sought the guidance of our families. The Parent Advisory Committee (PAC) is a vital component of the C4RCD's institution-wide effort to provide family centered care. The PAC, Chaired by Karie Dozer, works closely with TGen staff to ensure parents and caregivers have a voice in policies, programs and practices affecting the delivery of care and services. Members share their experiences, opinions and suggestions in areas including quality of care, marketing, research, strategic planning, and grassroots fundraising efforts.

For more information about the C4RCD advisory panels, please contact:

**Terry McManus**
*TGen Foundation*
*Vice President, Strategic Initiatives*
602-343-8527
*tmcmanus@tgen.org*

**OUR MISSION**
To better diagnose, treat and ultimately cure rare childhood genetic disorders

**OUR DIFFERENCE**
We go beyond diagnosis and use our molecular tools to inform new treatments

**OUR GOAL**
To improve the lives of children and families affected by rare disorders worldwide

# How to get involved

*Genetic Studies of Patients and their Families with Neurological Diseases of Unknown Etiology* is a study conducted by TGen's C4RCD that aims to use molecular technology to identify or explain the genetic causes of neurological disorders that physicians have previously been unable to identify in children and young adults.

The study will look at DNA (structures in our bodies that make up our genes) and RNA (structures in our bodies that show what genes are turned on or off) from people with neurological disorders of unknown causes.

Criteria for participation in this study includes: Children or young adults with a disease or condition whose genetic cause(s) are unknown; and approval, willingness and ability to donate biospecimens — urine, blood, tissue, cells, DNA, RNA — to TGen for the purpose of advancing our research efforts.

## Learn More About Our Studies

If you would like to talk to a clinical research coordinator about participating in one of our studies, please complete our online research registry form at **www.c4rcd.org**.

An expert from the C4RCD will contact you to discuss your case.


# Donate

TGen is a nonprofit institute, and philanthropic support from passionate and visionary donors is critical to the groundbreaking work of the C4RCD.

The opportunities to make a difference in children's lives are innumerable. Our only limitation is the availability of funding. Simply put, your financial support will provide the resources we need to help more families affected by rare disorders.

You can donate online at **www.c4rcd.org**. To donate by check, please make your check payable to TGen Foundation, and send it to:

**TGen Foundation**
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Phoenix, AZ 85004

*To learn more, please contact the TGen Foundation at **602-343-8411** or e-mail **foundation@tgen.org**.*

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