

100 TRILLION REASONS  
TO LOVE ST. JUDE

YOUR BODY, YOUR GENES,  
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St. Jude

# promise



SPECIAL EDITION 2020  
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**CRYSTAL BALL:**  
WHERE DO WE  
GO FROM HERE?

**KNOWLEDGE  
IS POWER**  
THE CANCER  
PREDISPOSITION  
PROGRAM

*featuring*

## Pediatric Cancer Genome Project

A DECADE OF  
DISCOVERY

**WHAT'S  
DNA GOT  
TO DO  
WITH IT?**

CLINICAL  
GENOMICS  
AT WORK

# The twisted ladder of life

In the lobby of the Children's GMP, LLC, a massive DNA sculpture stretches from floor to ceiling. At once delicate and imposing, the artwork pays homage to the galaxy of discoveries made possible at St. Jude Children's Research Hospital.

This issue of *Promise* celebrates the 10th anniversary of the Pediatric Cancer Genome Project, or PCGP.

Thanks to that project, scientists and clinicians worldwide are unraveling the twisted ladder of life to solve the mysteries of childhood cancer.

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Made possible by the Pediatric Cancer Genome Project



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ON THE COVER: Photo by Seth Dixon

The mission of St. Jude Children's Research Hospital is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment.

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# Your Body, Your Genes, Our Future

By Elizabeth Jane Walker

**YOUR BODY** is amazing in its complexity. For starters, it contains more than 30 trillion cells. Every one of those cells has a different job. How does each tiny cell know what to do? It gets its marching orders from a molecule called DNA.

**DNA** contains sets of instructions called genes. The complete set of DNA and genes is called the human genome.

**Genome sequencing** involves figuring out the order of four chemical building blocks – called “bases” – that make up the DNA molecule. The human genome contains about 3 billion base pairs.

**Cancer** is triggered by harmful changes, called mutations, in the DNA of normal cells.

Since 1962, St. Jude Children’s Research Hospital has made steady progress in curing childhood cancer. Even so, cancer remains the top killer by disease of children ages 1–14 in the U.S.

Ten years ago, buoyed by the success of the Human Genome Project, our scientists knew the time was right to unlock the mysteries hidden deep within the DNA of childhood cancer. Inspired by generations of children who passed through the doors of St. Jude, we embarked on a voyage of discovery: The St. Jude–Washington University Pediatric Cancer Genome Project.

St. Jude was perfectly poised to take

on this massive project, the largest such initiative in the world. The speed of DNA sequencing had recently increased, while costs had decreased. For nearly 40 years, the hospital had stored patients’ tissue samples—awaiting the day when technology would evolve so that those samples could give up their secrets. By comparing the complete normal and cancer genomes of hundreds of cancer

patients, scientists could pinpoint the genetic origins of the disease.

Today, scientists worldwide have only begun to explore the vast landscape of data generated by the Pediatric Cancer Genome Project. As researchers make discovery after discovery after discovery, we move inexorably toward a day when—as St. Jude founder Danny Thomas once said—no child dies in the dawn of life. [f](#)

# The Spark That Ignites Innovation

The architect of the Pediatric Cancer Genome Project reflects on the initiative's origins and legacy.

By James R. Downing, MD

## THINK ABOUT THE INVENTION OF THE LIGHTBULB.

The creation of a vaccine. The mass production of the Model T. What is the spark that ignites innovation? It's seldom a single point, but rather the convergence of ingenuity and imagination.

A decade ago, we had the talent, time and technology to launch a project that would transform how we understand and treat childhood cancer.

The Pediatric Cancer Genome Project (PCGP) began with simple sketches on envelopes and napkins. Those scribbles by scientists from St. Jude Children's Research Hospital and Washington University in St. Louis would usher in the next wave of discovery.

In 2010, pediatric cancer survival rates hovered around 80%. Success had been incremental. Progress had plateaued.

Researchers worldwide had not yet uncovered the genetic changes that lead to cancer. As a result, the drivers of cancer remained elusive, especially in children. Genomic sequencing projects that were underway largely ignored childhood cancer. The void underscored the need.

Thanks to recent leaps in technology, the cost of whole-genome sequencing had dropped, and the speed had increased.

"What if" conversations gave way to formal proposals.

Timothy Ley, MD, a Washington University cancer genomics and leukemia researcher, as well as Richard Wilson, PhD, and Elaine Mardis, PhD, then co-directors of the university's McDonnell

Genome Institute, offered their expertise in high-speed, large-scale genomic sequencing. St. Jude would provide research and treatment experience — and access to one of the world's largest collections of childhood cancer tissue.

With those pieces in place, St. Jude committed \$65 million to a three-year collaboration with Washington University to uncover why childhood cancer arises, spreads and resists treatment. We unveiled the PCGP January 25, 2010, at the National Press Club in Washington, D.C.

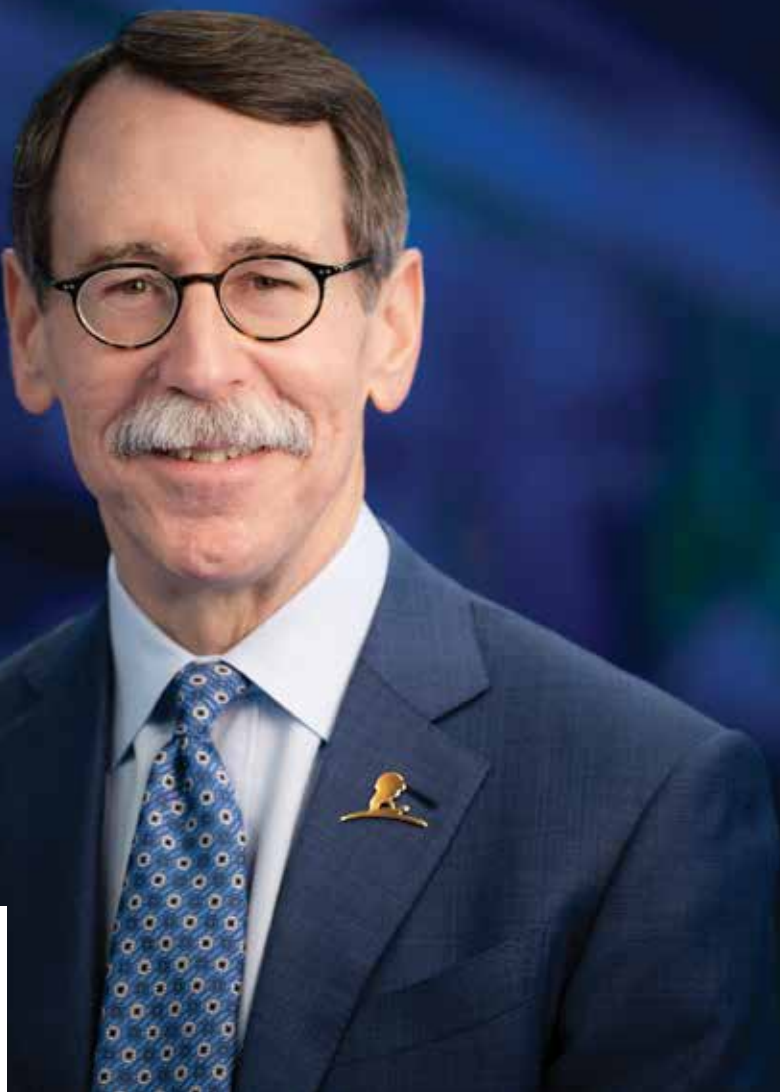
As I traveled back to Memphis after that announcement, the weight of the task ahead set in. Many sleepless nights followed. At the time, scientists had not sequenced even one pediatric cancer genome. No one else had tried to conduct this level of sequencing on such a massive scale.

The collaboration among PCGP scientists made all the difference. The project included more than 150 faculty and staff at St. Jude and more than 200 people at Washington University.

In general, brain tumor doctors don't work with leukemia doctors, and

**“The PCGP came into being because of the need to accelerate progress. It succeeded because we were willing to chase big ideas and make the most of a unique moment in history.”**

**James R. Downing, MD**



SAM HURD

#### **Birth of the PCGP**

James R. Downing, MD, and other leaders officially launch the project in January 2010 at the National Press Club in Washington, D.C.

leukemia doctors don't work with solid tumor doctors. People in computational biology don't often talk with clinicians. But the PCGP brought everyone together. It transformed the culture of St. Jude and brought the power of collaboration to the forefront.

The first year, we sequenced the normal and cancer genomes of 50 patients, with another 250 in the second year. By the end, we had whole genome

sequences from 800 cancer patients with 23 types of cancer.

The project unearthed a treasure trove of discoveries in brain tumors, high-risk leukemias, solid tumors and even a non-cancerous disorder called Lou Gehrig's disease. We also learned that about 10% of children with cancer are born with genetic changes that increase their cancer risk.

The PCGP generated new computational tools. Five of our new software applications helped identify key driver mutations that other methods had missed.


Based on the success of the first phase, St. Jude committed another \$30 million to extend the project in 2014.

The PCGP served as a catalyst for a decade of transformative research. St. Jude Cloud, the world's largest storehouse of childhood cancer genomics; pre-clini-

cal resources such as PROPEL and the Childhood Solid Tumor Network; and the St. Jude Cancer Predisposition Clinic can all be traced back to the project.

Current clinical trials for children with cancer reflect insights gained from the PCGP. Those trials include SJMB12, an international study for young people with the brain tumor medulloblastoma, and TOTAL 17 for children with acute lymphoblastic leukemia.

An old adage tells us that necessity is the mother of invention. In many regards, the PCGP came into being because of the need to accelerate progress. It succeeded because we were willing to chase big ideas and make the most of a unique moment in history.

Scientists worldwide continue to make discoveries based on the project's data. The beneficiaries are the children of today as well as the generations to follow. 

# The 'Library' of the Pediatric Cancer Genome Project

By Keith Crabtree, PhD

The St. Jude Biorepository collects and stores biomedical samples, allowing scientists to explore the origins of pediatric cancer and develop new diagnostic tests and therapies.

**SARAHBETH HOWES WAS DIAGNOSED** with embryonal rhabdomyosarcoma, a soft tissue tumor, when she was 15 years old.

“I was a sophomore in high school; I was on the varsity soccer team; I was in honors classes,” she says. “I had a lot going for me.”

When asked to donate tissue to the St. Jude Children’s Research Hospital Biorepository to be used for research, she quickly agreed.

“If I could help someone else,” says Howes, now a third-year medical student, “I was all for it, and so was my family.”

Recently, Howes hit the 10-year survivorship mark – “a pretty big deal in the survivorship world,” she says. Coincidentally, the Pediatric Cancer Genome Project (PCGP) also marked its 10th anniversary. This project has revolutionized our understanding of the genetic factors that underpin rare pediatric cancers. More than 800 patients donated tissue samples for use in the PCGP; 66% of those samples came from the St. Jude Biorepository.

## THE LIBRARY

The Biorepository, also known as the tissue bank, isn’t a financial institution. You won’t find a drive-through teller or an ATM. You won’t find a bank vault, even though stringent security measures are in place. The Biorepository is more like a library that collects and stores biological samples instead of books. To protect privacy, specimen samples are coded to reveal important clinical data without patient names or other identifiers.

Researchers approved by the hospital’s Tissue Resource Distribution Committee and the Institutional Review Board can “check out” samples to explore basic genomic questions.

Technical Director Matt Lear says the Biorepository’s first sample was collected in 1976. A reorganization of the collection in the early 2000s marked the beginning of the modern era of the tissue bank. In 2015, its name was changed from the Tissues Resources Core Facility to the St. Jude Biorepository.

The Biorepository collects the little bits of material that remain after procedures such as blood draws and surgeries. Staff



members place that tissue in the racks of nearly 30 tall freezers cooled with liquid nitrogen to temperatures as low as -196 degrees Celsius.

The facility stores more than 500,000 samples from children with solid tumors, brain tumors, leukemia and non-malignant blood disorders, such as sickle cell disease and bone marrow failure syndromes. The specimens come from patients in active treatment and, increasingly, long-term survivors taking part in the hospital’s



## St. Jude Biorepository

Contains more than **500,000 tissue samples** donated over the past 44 years by St. Jude patients

About **5,000 specimens** donated each month

Includes nearly **30 freezers** cooled with liquid nitrogen

Cells suspended in temperatures as low as **-196 degrees Celsius**

**One of the first 5 banks nationwide** to be accredited by the College of American Pathologists

Supports about **200 clinical trials** worldwide

About **3,400 samples** from the bank sequenced as part of the Pediatric Cancer Genome Project and its offshoot studies

**“We want to make our inventories as future-proof as we can. We never know what’s coming down the line.”**

**Charles Mullighan, MBBS, MD**



long-term follow-up study, St. Jude LIFE.

PCGP scientists sequenced about 3,400 samples for use in the PCGP and its offshoot studies. The facility also supports about 200 clinical trials worldwide.

Charles Mullighan, MBBS, MD, the Biorepository’s medical director, was a member of the PCGP steering committee.

“I extracted the first 20 samples that were sequenced,” he says. Today, sample extraction, processing, storage, distribution and other day-to-day tasks are handled by a cadre of lab technicians.

### **QUIET ACHIEVERS**

The Biorepository was small — a side room connected to a pathology lab — when the PCGP launched in 2010. Since then, the facility has had a three-fold increase in lab technicians and the addition of three bioinformatics experts, which required moving to a larger, dedicated space.

Mullighan often commends his staff for their hard work and ingenuity, dubbing them “quiet achievers.” For example, when the Biorepository needed new

sample-tracking software, the team tried a disappointing off-the-shelf product.

“Out of frustration with the new software, they said, ‘We can do this so much better,’” Mullighan said. “And within a week, they mocked up their own version and showed that it could work.”

### **VOLUNTARY DONATIONS**

At one point during her treatment, Howes lost her ability to walk.

“For my 16th birthday, I got a walker instead of a car,” Howes recalls. For an athlete who used exercise to cope with stress, it was devastating. But the hardships of her cancer journey didn’t sway her decision to donate tissue to the Biorepository. She says she found meaning in the idea of paying it forward, of contributing toward future research efforts.

More than 95% of St. Jude families agree to donate tissue samples. The conversations about that donation, however, are sometimes delicate. Suzanne Baker, PhD, who directs the Division of Brain Tumor Research, has spent years



researching an incurable brain tumor called diffuse intrinsic pontine glioma (DIPG). Located deep in the brain, these tumors were not typically biopsied, which limited research.

Oncologist and clinical collaborator Alberto Broniscer, MD, formerly of St. Jude, suggested approaching families to discuss planned autopsy donations. At first, Baker was unsure how parents would respond to a request for tumor samples to be taken after a child’s death.

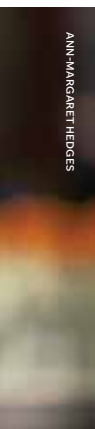
“Overall, families shared that dona-



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tion was important to them, that it gave some meaning to what they had gone through,” says Baker, who, along with Jinghui Zhang, PhD, Computational Biology chair, identified a DIPG mutation that had never been found before.

“This specific mutation in histone H3 is found in 80% of these brain tumors,” Baker says. “It’s potentially a new target for therapy.”

Mulligan and Baker credit the children and their families who have donated

samples to fill the Biorepository.

“We have focused so much effort on these rare pediatric cancers. In many cases, it involved many years of treating patients with these diseases and collecting clinical samples so that there was material available for research,” Baker says.


#### FUTURE PROOF

Biorepository staff try to preserve samples in their native state in the

hope that tissues will be fit for as many potential research uses as possible.

One way to safeguard the specimens is through the Biorepository’s Noah’s Ark program, an insurance policy of sorts. To prepare for an unlikely disaster, a portion of the facility’s samples are stored at an offsite location, an accredited lab in the Northeast. Biorepository staff can monitor and retrieve the samples at any time.

The Biorepository is expanding its physical footprint, with space in the new Shared Resource Center and more space to come when the Advanced Research Center opens in spring of 2021. These facilities will advance the Biorepository’s transition from manual, time-consuming processes to automated, robotic ones. Sample extraction, processing and storage will be more efficient and of higher quality.

“We want to make our inventories as future-proof as we can,” Mullighan says. “We never know what’s coming down the line.” 

*\*Photos for this article were taken pre-COVID-19.*

# What's DNA Got to Do with It?

The Pediatric Cancer Genome Project has changed the landscape of how pediatric cancer patients are diagnosed and treated at St. Jude.

**FROM ALMOST THE MOMENT** she was born, Taryn Peterson has been an astute observer. The 4-year-old Colorado girl reacts to the world with curious glances and precocious responses. When her parents, Angela and Kenan, talk, she is quick to add her thoughts.

Taryn often wakes up and chats with her dolls, Elsa and Anna. These mornings of pretend and joy are a world away from how she spent her time last year.

Before her second birthday, Taryn began to have trouble sleeping. Her breathing was harsh, high-pitched and sometimes interrupted—a condition known as stridor. Her problems persisted after a sleep study and adenoid removal. Finally, partial paralysis on the left side of Taryn's face prompted an MRI scan.

The scan revealed a tumor in her brain stem. Taryn had surgery right away to reduce the pressure on her brain.

"The doctors came in and told us that her tumor presented as DIPG, and that it was inoperable," Angela says. "It was a whirlwind for all of us. We had no idea what we were going to do."

## OUT OF SEQUENCE

DIPG, or diffuse intrinsic pontine glioma, is a tumor that forms in the brain stem. Fewer than 10% of children with the disease survive more than two years. Treatment consists of radiation therapy,

often with chemotherapy. Given the growth pattern and critical location, surgery is not possible.

Scientists at St. Jude Children's Research Hospital have studied DIPG for many years. In the last decade, findings from the St. Jude - Washington University Pediatric Cancer Genome Project (PCGP) helped us better understand the disease and its causes.

As part of the PCGP, scientists sequenced the genomes of normal and cancer cells in about 800 patients. Researchers then looked for differences in the DNA that lead to cancer.

The scientists learned that in DIPG and other gliomas in midline structures of the brain, specific mutations occur frequently in histone H3 proteins. Suzanne Baker, PhD, director of the Brain Tumor Research Division, along with Jinghui Zhang, PhD, St. Jude Computational Biology chair, and their colleagues led research that identified this mutation as histone H3 K27M.

"When the Pediatric Genome Cancer Project began, it wasn't clear how different DIPG and other gliomas in children were compared to gliomas with similar features in adults," Baker says. "These unexpected findings from sequencing showed not only

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## Possibilities and PCGP

Physicians were able to provide a correct diagnosis for Taryn Peterson (shown with her parents, Angela and Kenan) based on the genetic characteristics of her tumor. Taryn's diagnosis and treatment were made possible because of discoveries emerging from the Pediatric Cancer Genome Project.

*\*Photos for this article were taken pre-COVID-19.*

By **Mike O'Kelly**



**“The Pediatric Cancer Genome Project gave us the next big breakthrough into the biology of some of these tumors that we could never have achieved if we hadn’t had that insight.”**

**Amar Gajjar, MD**

that different mutations had been found in childhood gliomas than had been discovered in adults, but that some of these mutations had never been seen before in human cancer.”

The discoveries changed the way patients are diagnosed and selected for clinical trials. The findings also altered how clinicians evaluate treatment responses.

### REVEALING SCANS

After looking at Taryn’s MRI, Christopher Tinkle, MD, PhD, of St. Jude Radiation Oncology, called the Petersons. He assured Angela that St. Jude was the place for Taryn.

“He was so hopeful, so calm and explained everything really well. So, we said, ‘This is what we need to do,’” Angela says.

When the family arrived at St. Jude, they met with Tinkle; Amar Gajjar, MD, director of the Neuro-Oncology Division; and Paul Klimo, MD, of Neurosurgery. Although biopsy of DIPG tumors is rare, the physicians thought it was the best option for Taryn.

The surgery yielded surprising results.

Taryn’s tumor was not DIPG. It was an angiocentric glioma with a MYB-QKI fusion—a tumor with a much better prognosis. This allowed Taryn to be treated

with proton therapy, which reduced exposure to more of her healthy brain cells.

“Sequencing assisted with the tumor diagnosis, as this type of fusion is found in most cases of angiocentric glioma,” Tinkle says. “Other more harmful mutations were not found in the tumor, including the histone H3 K27M mutation. When coupled with the histologic grade of the tumor, this allowed us to confirm that it was not DIPG.”

After the surgery, Taryn had six weeks of radiation to shrink the remaining tumor. She continues to have quarterly MRIs and is thriving a year after coming to St. Jude.

### INTO THE CLINIC

The PCGP continues to affect the diagnosis and treatment of patients at St. Jude. The project’s success laid the groundwork for the hospital’s clinical genomics program.

Genomic testing is now an option for all eligible St. Jude cancer patients. That led to the creation of the hospital’s Cancer Predisposition Program (*see related story, page 14*) and several clinical trials.

“The Pediatric Cancer Genome Project gave us the next big breakthrough into the biology of some of these tumors that we could never have achieved if we hadn’t had that insight,” says Gajjar, who

SETH DIXON



### Data comes to life

Suzanne Baker, PhD, director of the Brain Tumor Research Division, and Amar Gajjar, MD, director of the Neuro-Oncology Division, discuss findings gleaned from the PCGP. Discoveries from that project have transformed cancer diagnosis and changed how clinicians evaluate treatment responses.

co-leads the SJMB12 study for children with brain tumors. “Over the past decade, those insights have rapidly been translated into clinical protocols, which hopefully will improve the cure rate for some of these tumors.”

Researchers used PCGP data to reveal that the most common malignant pediatric brain tumor—medulloblastoma—is not a single molecular entity, but a complex tumor with four major subgroups. That discovery was a surprise, because the tumors look similar under the microscope. Clinicians also had a hard time predicting outcomes for patients with medulloblastoma. Now we know that survival rates vary widely by subtype.

Today, specific therapies can be developed for each subgroup. The findings help direct the treatment of more than 500 patients enrolled in the SJMB12 study.

Two additional clinical trials with origins in the PCGP are Genomes for Kids, also called G4K, and SJFAMILY.

Through sequencing, G4K will allow



researchers to learn more about how leukemia, lymphoma and solid tumors are formed and how they respond to treatment. All St. Jude cancer patients are eligible. The study also assesses patient and family opinions about genetic testing.

SJFAMILY explores why some cancers run in families and why certain people get more than one cancer. Scientists look for changes in sequenced genes to help answer these questions.

### A TOTAL APPROACH

Genomics also plays an important role in the hospital's TOTAL 17 clinical trial for children with acute lymphoblastic leukemia or lymphoma.

Every child in the study has genomic testing of both normal tissue and leukemia cells to help guide treatment. Using genomic data from cancerous cells, researchers can identify mutations and target them with new chemotherapy agents. This practice of precision medicine uses genetics to tailor therapy.

With a goal to treat 1,000 patients, the study is the largest clinical trial ever run by the hospital and requires collaboration with other institutions. This study design helps researchers gather more data faster and share their findings.

"Genomics plays an important role in guiding therapy in this study," says Hiroto Inaba, MD, PhD, of St. Jude

### Total Therapy

Hiroto Inaba, MD, PhD, chats with Dakota Cunningham, who took part in the TOTAL 17 clinical trial (see *Dakota's story*, page 28). "Genomics plays an important role in guiding therapy in this study," Inaba says.

Oncology, who leads the study. "We have the available technology. If we identify a patient as high-risk, we're going to do whatever it takes to improve their outcome."

Researchers worldwide have also incorporated findings from the PCGP into clinical trials. The results have led to National Cancer Institute initiatives to create therapies designed for children with cancer and to guide precision medicine. [2](#)



By **Jane Langille**

As a result of the Pediatric Cancer Genome Project, families facing an increased risk of inherited cancers can now turn to the **St. Jude Cancer Predisposition Program**.

# Knowledge is Power

**IN DECEMBER 2017**, at the tender age of 6 weeks old, Braxton Avery had surgery to remove most of a rare brain tumor called choroid plexus carcinoma. His parents, Nadine Moats and Tim Avery, learned that his condition was likely caused by a gene mutation that puts him at risk of developing other cancers in the future.

As they worried about their baby, they wondered if one of them carried the mutation. If so, what would that mean for their family?

“Everybody we spoke to said we should go to St. Jude,” Nadine says. “It was a big decision to leave our home, travel to another state and trust a new team with a different plan.”



Braxton Avery and his parents, Tim and Nadine

In Memphis, Braxton received chemotherapy and brain surgery to remove the rest of the tumor. His family also received genetic testing and counseling through the St. Jude Cancer Predisposition Program. Nadine and Tim learned more about the gene mutation that caused Braxton's cancer, how to best manage his risks, and how their family may be affected in the future.

*\*Photos for this article were taken pre-COVID-19.*

### **PINPOINTING FUTURE CANCER RISK**

As an outgrowth of the Pediatric Cancer Genome Project (PCGP), St. Jude cancer patients are now offered clinical genomic testing of their tumor and healthy tissue (usually a blood or skin sample). Test results may reveal mutations that drive the growth of cancer cells, allowing doctors to select targeted therapies linked to better outcomes. The results may also uncover changes

in genes that are inherited and lead to a higher risk of causing diseases such as cancer. These are called cancer predisposition genes.

“Patients who carry changes in cancer predisposition genes may develop additional cancers later in life or experience complications following certain cancer treatments, like radiation therapy,” says Kim Nichols, MD, St. Jude Cancer Predisposition Division director. “Unfortunately, we cannot prevent these cancers from happening. Our goal is to empower patients and parents to be aware of the signs and symptoms. In addition, through frequent screenings, we aim to catch new cancers early, when they are easier to treat and more likely to be cured.”

Test results showed Braxton had a rare genetic condition called Li-Fraumeni syndrome. This disorder is caused by a mutation in the *TP53* gene. People with the condition are more likely to develop cancers in their brain, breasts, bones, blood, adrenal gland, muscles or connective tissue.

### **ROOTED IN RESEARCH**

Launched in 2010, the PCGP was the world's most ambitious effort to discover the origins of childhood cancers and seek new cures. Researchers sequenced the genomes within blood samples of about 800 children with cancer.

Analyzing the treasure trove of data, scientists searched carefully for changes



### Care and conversation

Stacy Hines-Dowell, a nurse practitioner in the Cancer Predisposition Program, counsels 11-year-old Zoey Austin and her mom, Pam Nobles. Zoey and Pam have DICER1 syndrome, a rare disorder that increases their risk of developing certain types of tumors.

in 60 genes known to be linked to cancer predisposition. The most common hereditary disorders in the children in this study were hereditary retinoblastoma; neurofibromatosis type 1; familial adenomatous polyposis; and Li-Fraumeni syndrome, the genetic condition Braxton has.

St. Jude scientists add new genes to the list every year. For example, Nichols and Jun J. Yang, PhD, of Pharmaceutical Sciences and Oncology, found a new predisposition gene called *ETV6* that is linked with a common form of childhood leukemia. Nichols, Yang and Charles Mullighan, MBBS, MD, deputy director of the Comprehensive Cancer Center, also identified *IKZF1*, another leukemia predisposition gene, in children with B-cell acute lymphoblastic leukemia.

### EARLY-CATCH BENEFITS

Nichols joined St. Jude in the fall of 2014 to start the Cancer Predisposition Division and help translate the PCGP's findings to the clinic. The program has grown substantially since then. Last year, Nichols and her team saw more than 1,100 patients, up from 400 patients in their first year.

In all, the team has evaluated more than 5,670 children with cancer and found underlying cancer predispositions in almost 540 of them.

"About 10% of the patients with cancer predisposition who we monitor using radiology tests and blood work have de-



### Education and evaluation

Rose McGee (center), a certified genetic counselor in the St. Jude Cancer Predisposition Division, consults with Nadine Moats, mom of Braxton Avery, who is undergoing treatment for a rare brain tumor. Because 3-year-old Braxton has Li-Fraumeni syndrome, he is at risk for developing other cancers, as well.

veloped new cancers," Nichols says. "The vast majority of these cancers are picked up at a very early stage and have been successfully treated."

St. Jude patients are followed for 10 years after they complete treatment, or until they turn 18, whichever is later. After Braxton's initial therapy, he returned to

Memphis every three months for comprehensive screening, which included ultrasound and full-body magnetic resonance imaging. After about 18 months, a scan showed that his brain tumor had returned. He had another surgery in November 2019. In January 2020, he began six more months of chemotherapy.

Each step of the way, a team of surgeons, oncologists and geneticists collaborated on his therapy in consultation with Nadine and Tim.

"We have to look carefully at the side effects of different treatment options," Nadine says. "Radiation is not recommended due to his gene mutation. The doctors always hear our concerns about different chemotherapy alternatives and have already checked with the genetics team."

# St. Jude Cancer Predisposition: By the numbers

Since 2014, the St. Jude Cancer Predisposition Program has helped thousands of children and families manage their risk for developing inherited forms of cancer.

- **5,671** total visits
- **2,936** new-patient visits
- **2,735** follow-up visits
- **539** individuals from **466** unique families identified with underlying cancer predisposition syndromes
- **211** children undergoing tumor surveillance or actively undergoing screening
- **17** children identified with one or more cancers as a result of screening

## The St. Jude Cancer Predisposition Program team includes:

- 1 doctor (a pediatric hematologist-oncologist)
- 1 genetics nurse practitioner
- 2 registered nurses
- 5 genetic counselors
- 2 staff scientists
- 8 other clinical and research professionals

## WHOLE-FAMILY BENEFITS

Genetic counselors with the Cancer Predisposition Clinic focus on the whole family. They study the patient's disease and medical information in the family tree to find out if any family members, including future children, might have a higher risk of developing cancer.

"St. Jude is unique compared with other centers because we offer genetic testing and counseling to parents and



## Help for the whole family

"St. Jude is unique compared with other centers because we offer genetic testing and counseling to parents and siblings," says Kim Nichols, MD (right), St. Jude Cancer Predisposition Division director. "Any siblings who have a mutation become our patients, and we monitor them closely. If they develop new cancers, we refer them to the appropriate treatment service team."

siblings," Nichols says. "Any siblings who have a mutation become our patients, and we monitor them closely. If they develop new cancers, we refer them to the appropriate treatment service team."

Nadine and Tim decided to have their genomes tested to find out if they were also at risk. Fortunately, they learned that neither of them has the same mutation as their son.

"It was a huge relief to find out that my husband and I were negative," Nadine says. "We want the opportunity to have another child without worrying about passing on a mutation."


## TOWARD BRIGHTER FUTURES

St. Jude patients can opt into an ongoing study called Genomes for Kids. This project combines information on 150 cancer predisposition genes with clinical data to learn more about how the mutations influence cancer development and future outcomes. Nichols plans for this initiative to include results from several thousand children in the upcoming years.

"About 98% of DNA lies between our genes. It's unclear what role that DNA plays," Nichols says. "St. Jude researchers are working hard to see if changes in those poorly understood regions of the genome are associated with cancer development and hereditary predispositions to cancer. I am sure that they will be; we just don't know enough about those areas yet."

Now 3 years old, Braxton has a head full of strawberry blond curls. He is a bundle of energy and wants to understand how everything works. His favorite toy is a stuffed R2-D2, the droid robot from the movie *Star Wars*.

Besides the neuro-oncology experts who are part of his primary cancer treatment team, others at St. Jude are assisting Braxton. An occupational therapist helps him work on fine and gross motor skills to address left-side weakness. A speech-language pathologist helps him catch up on speech skills. And Braxton's physical therapist gently reminds him that even though it's fun to run down the hall and high-five everyone, it's not a good idea while attached to an intravenous pole.

"Just like every toddler, Braxton is full of energy and can have tantrums about small things," Nadine says. "But he sure loves all of the attention he gets at St. Jude. We're glad they're looking after him every step of the way." 



# Era of Discovery

**In 2010, St. Jude embarked on the world's most ambitious effort to discover the origins of childhood cancer and seek new cures. Here's how that historic project has unfolded.**

## 2003

An international team of scientists completes the Human Genome Project, the world's first effort to sequence our genome's 3 billion base pairs.

## 2008

Scientists report that they have sequenced the first whole cancer genome. The patient is an adult with leukemia.

## 2010

St. Jude and Washington University launch the Pediatric Cancer Genome Project (PCGP). Scientists will ultimately compare the complete genomes of both cancerous and normal cells of about 800 children with some of the toughest and least understood pediatric cancers. Most of the tissue samples come from the St. Jude Biorepository (*see related story, page 6*), which was created in the 1970s to store biological samples for research.

## 2011

The amount of data generated by the PCGP is staggering: For every patient, scientists sequence the 3 billion base pairs of the child's normal genome and the 3 billion base pairs of the child's cancer genome. St. Jude researchers push to create data mining tools to maximize discoveries, including a computer tool called CREST. This new system outperforms prior tools so well that it is adopted by scientists worldwide.

## 2012

PCGP leaders announce the largest-ever release of comprehensive human cancer genome data for free access by the global scientific community. The amount of information released more than doubles the volume of high-coverage, whole-genome data available from all human genome sources combined.

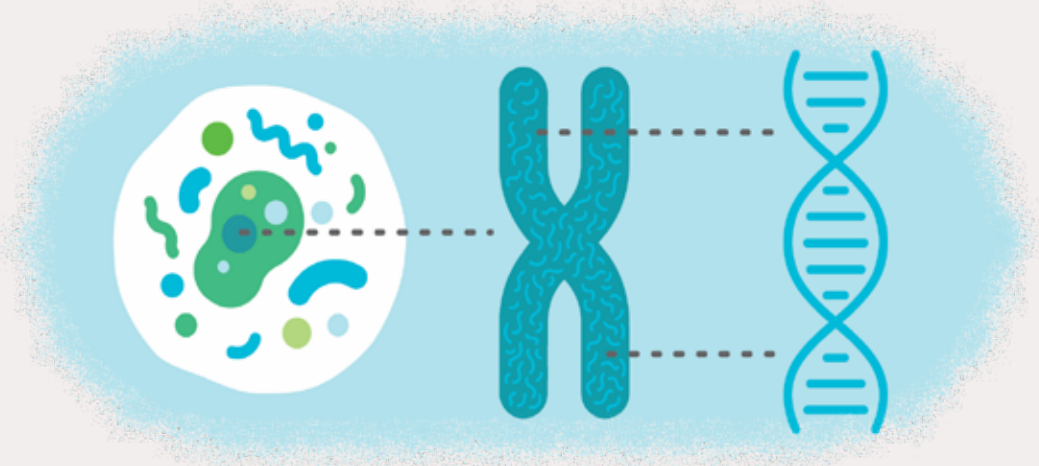


*TIME* magazine names the PCGP to its list of top 10 medical breakthroughs.

Researchers begin to publish discoveries gleaned from the PCGP. The project will yield groundbreaking findings regarding brain tumors, leukemia, solid tumors and a neurodegenerative disorder known as Lou Gehrig's disease. The findings will pinpoint mutations never before linked to cancer, identify subtype-specific mutations, define novel cancer subtypes, highlight how cancer develops and reveal changes that affect how cells "read" genes.

## 2013

St. Jude and the Howard Hughes Medical Institute collaborate to create the Childhood Solid Tumor Network. This service was launched to fuel research by providing preclinical resources to scientists worldwide. That network and PROPEL, offered in 2018 as one of the world's largest collections of leukemia samples, will accelerate global progress toward understanding and treating pediatric cancer.



## 2014

The hospital embarks on the second phase of the PCGP, which takes genomic medicine to the next level. Phase II includes digging deeper into the genomic makeup of pediatric cancers. This phase also signals a new era of clinical genomics as St. Jude moves toward comprehensive genomic testing for all eligible patients.

Success of the PCGP sparks creation of the St. Jude Cancer Predisposition Program for children and families who may have inherited genetic mutations that leave them at higher-than-normal risk of cancer.



## 2015

The PCGP reports that a surprisingly high percentage — nearly 1 in 10 — of childhood cancer patients carry germline (inherited) mutations in known cancer predisposition genes.

St. Jude announces development of ProteinPaint and CONSERTING, the first of more than a half dozen data analysis and visualization tools. These free tools allow researchers worldwide to access and evaluate PCGP data.

## 2017

The hospital opens the TOTAL 17 clinical trial for children with leukemia and lymphoma. This is one of several studies that reflect insights gained from the PCGP. The PCGP findings are also incorporated into other clinical trials at St. Jude and internationally that aim to improve cure rates for children with medulloblastoma, diffuse intrinsic pontine glioma and other cancers.

## 2018

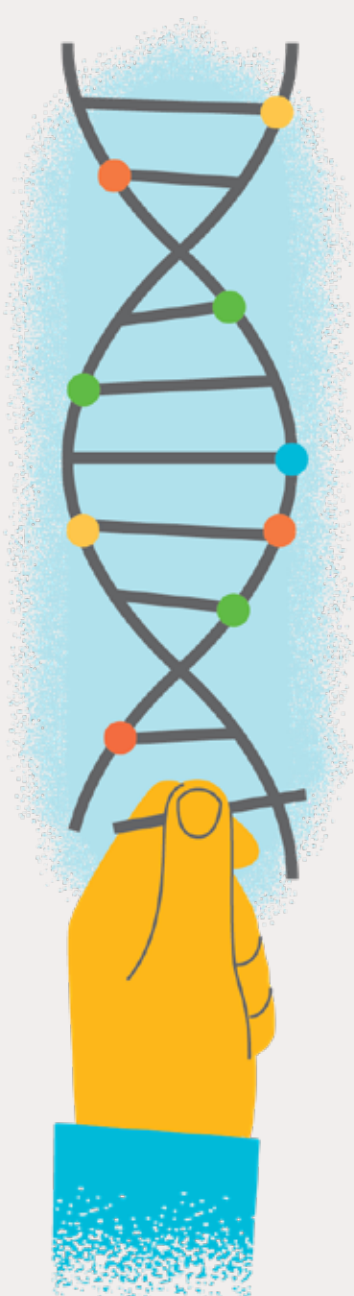
St. Jude launches St. Jude Cloud, an online data-sharing and collaboration platform that provides researchers access to the world's largest public repository of pediatric cancer genomics data. The project is a partnership among St. Jude, DNAnexus and Microsoft.

## 2020

In the largest comprehensive genomic analysis yet of neuroblastoma, scientists dramatically increase our knowledge about how many mutations drive the cancer's growth and spread. Researchers also show how a common mutation may fuel this cancer. The findings highlight possible strategies for precision medicine.

St. Jude scientists create orthotopic patient-derived xenograft models representing a variety of pediatric brain tumor types. These molecularly characterized models are available through a cloud-based data portal.

St. Jude scientists have published more than 35 articles in peer-reviewed journals outlining discoveries that originated with the PCGP. Publications continue to appear and have included the *New England Journal of Medicine*, *Nature* and other prestigious journals.



What will be the legacy of the Pediatric Cancer Genome Project? Several scientists offer predictions.

# Crystal Ball



## The Pediatric Cancer Genome Project provided transformational insights into how to approach research and treatment for childhood cancer.

### For instance:

- The project has yielded discoveries across **23 types of childhood cancers** and even the non-cancerous degenerative disorder ALS, also known as **Lou Gehrig's disease**.
- Researchers found that about **10%** of patients studied were **born with genetic changes or mutations** that increased their cancer risk.
- The findings led to major **National Cancer Institute initiatives** to develop specific pediatric cancer therapies.
- The project's data and its analytic and data-visualization tools are freely shared worldwide through **St. Jude Cloud**, one of the largest online repositories of pediatric genomics data.

**Based on these and other PCGP accomplishments, what's next? Where do we go from here?**

*\*Photos for this article were taken pre-COVID-19.*



"We've gained new insights into every tumor subtype we've sequenced, but there are still many discoveries to be made from PCGP data. There are still genetic alterations that affect or drive cancer that we haven't found.

"The legacy of the PCGP is that it has stimulated new research questions. What we continue to learn from this project will influence not only pediatric cancer, but adult cancer and many other diseases."

**James R. Downing, MD, St. Jude president and CEO**  
**Pediatric Cancer Genome Project architect**

"From the Pediatric Cancer Genome Project, we learned that medulloblastoma, the most common malignant brain tumor, is not a single entity. It has four major subgroups driven by specific mutations. We used to treat all these tumors the same, because they looked similar under the microscope. Now we know that molecularly they're very different, so we're developing specific therapies for each of the molecular subgroups.

"The PCGP has opened up a completely different concept of how to approach treatment now and in the coming years."

**Amar Gajjar, MD**  
**Pediatric Medicine chair**

"We thought sharing data from the Pediatric Cancer Genome Project was the best way to accelerate progress in curing childhood cancers. We thought that if we put that information in the hands of scientists and doctors around the world, it would advance their research and that would do the greatest good for the entire pediatric cancer research community. So, we announced at the start of the PCGP that we would share the data as soon as it passed our quality control—well before we actually used it for our own publications—and there are many examples of where this accelerated the research of other scientists.

"We think that's really a legacy of this project—the impact it has had and continues to have on research globally, not just here at St. Jude."

**William Evans, PharmD, Pharmaceutical Sciences**  
**Former St. Jude president and CEO**



"The Pediatric Cancer Genome Project has already revolutionized how we study cancer and find cures for previously incurable patients. This project has set the stage for true precision medicine."

**Ching-Hon Pui, MD**  
Oncology chair



"The Pediatric Cancer Genome Project has provided insights that will have a lasting impact for how we classify, diagnose and treat pediatric cancer. We're now able to more precisely define cancer subtypes based on molecular genetics."

"The PCGP also changed the way testing is done, with less reliance on conventional pathology and more on molecular and sequencing approaches. We've developed tools and portals that allow anyone to mine the work of the PCGP—facilitating research worldwide. As we continue to mine the genome, our understanding of the genetic basis of cancer susceptibility will continue to grow—which will have a profound effect on diagnosis and management."

**Charles Mullighan, MBBS, MD**  
Comprehensive Cancer Center deputy director

"As part of this project, our validation laboratory confirmed hundreds of thousands of mutations. How many of those mutations directly drive cancer? As technology evolves, we're asking those kinds of questions in a more detailed way."

"We're already using PCGP data and applying it in ways we weren't thinking about at the beginning of the project. In the coming years, we will continue to go back to this raw data to decipher perplexing samples from PCGP by employing more sophisticated analysis in combination with new technologies."

**John Easton, PhD**

"For me, one of the most surprising findings of the PCGP is that at least 1 in 10 children with cancer develops the disease due to an underlying disposition. These children may be at an increased risk to develop complications from the cancer treatment and to develop other cancers later in life. Some of these children may also pass the genetic condition to their future offspring."

"I predict that we will use the PCGP as a stepping stone to further explore the rest of the genome, to better understand why cancers form, and to use this information to improve upon the treatment of children with cancer."

**Kim Nichols, MD**  
Cancer Predisposition Division director





“The thing that’s most amazing to me about the Pediatric Cancer Genome Project is the way it has exponentially expanded our research. For each of the discoveries from this project, there’s now a massive explosion in research into the basic mechanisms of cancer biology. Those discoveries will lead to new therapies that will improve the survival and quality of life for children with cancer.

“At St. Jude, children’s cancer genomes are now routinely sequenced. In some cases, that information is used to select a therapy for that particular child. So, the PCGP will continue to have an impact both in the laboratory and in the clinic.”

**Michael Dyer, PhD**

**Developmental Neurobiology chair**

“The Pediatric Cancer Genome Project opened exciting new avenues of research. We identified mutations, or mistakes in the DNA, in pediatric cancers that advanced understanding about how pediatric cancer forms and how we may develop more effective therapies.

“Our efforts mostly focused on the parts of the DNA that contain the code for making proteins in the cell. This is only a small proportion of all of the DNA in the genome. The data generated by the PCGP will be mined by scientists from St. Jude and around the world for many years to come as a rich resource to discover important disease-causing changes in parts of the pediatric cancer genome that we have not yet extensively explored.

“Importantly, we learned that epigenetic regulation, which does not change the sequence of our DNA, but changes the way that the code is packaged and read, is very important in pediatric cancer. This has resulted in an explosion of new research focused on rare pediatric cancers like childhood gliomas that were previously understudied.”

**Suzanne Baker, PhD**

**Brain Tumor Research Division director**



“PCGP has ushered in big-data science to pediatric cancer research. Discoveries made on the 23 cancer subtypes have helped set the direction for basic and translational research on pediatric cancer.

“The genomic data and the underlying analysis infrastructure provide a rich resource. That resource enables the design of pediatric-cancer precision medicine and continued data exploration.

“More than 400 research groups around the world have accessed the genomic data. So, PCGP serves as a role model for data sharing with the global research community. The goal is to engage everyone in finding cures for pediatric cancer.”

**Jinghui Zhang, PhD**

**Computational Biology chair**



# 100 Trillion Reasons to Love St. Jude

AS PART OF THE PEDIATRIC CANCER GENOME PROJECT, scientists sequenced the complete normal and cancer genomes of more than 800 children and adolescents with 23 different childhood cancers. Each of those genomes contains about 3 billion base pairs.

The project has produced more than 100 trillion pieces of data.

In 2012, St. Jude began to release the data to scientists worldwide. The information more than doubled the volume of whole-genome data available from all human genome sources combined.

St. Jude collaborated with DNAnexus and Microsoft to create St. Jude Cloud. This resource for the global research community offers:



Data with more than  
14,470 samples  
200 diagnoses



80,940 total files



Powerful tools that allow  
scientists to quickly and  
privately gain novel insights



Visualizations to  
explore the data

PCGP generated one of the world's largest collections of childhood cancer genomics. This resource will serve both cancer and non-cancer researchers for years to come.

The cost for  
scientists  
worldwide  
to access  
and use this  
data: \$0

# Research Highlights

## Making the invisible visible

### NUCLEAR MAGNETIC RESONANCE (NMR)

spectroscopy is a leading-edge scientific tool. The device helps researchers visualize protein structures in great detail. Scientists at St. Jude used the most powerful NMR device in the U.S. to study a protein called the ABL kinase. This kinase drives some leukemias. The first widely used targeted therapy for cancer disrupts the ABL kinase.

Cancer cells can become resistant to targeted therapies, and the drugs stop working. The scientists discovered two ABL kinase structures that occur only briefly but are important for understanding drug resistance.

“This is the first time such fleeting shapes have been captured for any protein kinase,” said Charalampos Babis Kalodimos, PhD, St. Jude Structural Biology chair. “The ABL kinase has been studied for 20 years, but we now have a new place to start for improving targeted therapy.” Science published an article on this work. [t](#)

Charalampos Babis Kalodimos, PhD

## Research Highlights



Mario Halic, PhD

# Building bridges: PARP enzymes bring broken DNA together

**ST. JUDE SCIENTISTS** have identified the structure of double-strand DNA break repair by PARP enzymes. The findings show that PARP2 can bridge the gap, bringing two broken DNA ends together.

DNA is constantly damaged and repaired. This can occur naturally or due to exposure to DNA-damaging agents like some chemotherapies used to treat cancer. PARP is a family of enzymes involved in several key cellular processes including DNA repair. However, exactly how PARP inhibitors

interact with DNA and chromatin to accomplish this process was unknown.

"Quite unexpectedly, we found that the PARP enzyme itself is bringing two broken DNA ends together," said Mario Halic, PhD, of St. Jude Structural Biology.

Insights scientists gleaned from this study may help researchers understand resistance to cancer drugs that inhibit PARP.

A report on this work appeared in *Nature*. [1](#)



St. Jude Children's  
Research Hospital  
Graduate School of  
Biomedical Sciences

## Graduate School adds Master of Science in Clinical Investigations

**AS THE ST. JUDE GRADUATE SCHOOL** of Biomedical Sciences welcomes its fourth cohort of PhD-seeking students, the school is also unveiling a Master of Science in Clinical Investigations degree program.

"The impetus for originally developing the Graduate School at St. Jude was to academically leverage three major strengths of the hospital: basic research, global medicine and clinical research," said Stephen White, DPhil, president and dean of the graduate school. "Having developed the PhD and Global Master's programs, we complete our triad with the newly approved Clinical Investigations Master's Program." [1](#)

# Shining a light on hidden mutations

### JUST AS A HEAD LAMP HELPS

reveal hidden risks, St. Jude researchers have developed a powerful tool to help identify cancer-causing mutations in patients' genomes.

The tool combines math and biology to find alterations in tumor cells that drive patients' cancer. The method is called cis-expression or cis-X and is publicly available on St. Jude Cloud and GitHub.

The method was developed to study DNA that does not encode genes but does regulate gene activity. This DNA makes up 98% of the genome. Until now, it has been difficult to search this DNA for mutations.

St. Jude researchers developed the tool to change that. Researchers used the method to identify known and novel oncogenes in leukemia and solid tumors, including in adult cancers.

"Cis-X is a fundamental change from existing approaches," says Jinghui Zhang, PhD, Computational Biology chair. "The method will help us develop a more complete picture of what causes cancer and advance treatment for children and adults."

*Nature Genetics* published a report on this work. [2](#)

ANN-MARGARET HEDGES



Jinghui Zhang, PhD

## St. Jude recognized as clinical care center for rare von Hippel-Lindau syndrome

### ST. JUDE HAS BEEN DESIGNATED

as a von Hippel-Lindau Clinical Care Center by the VHL Alliance. St. Jude is the first and only VHL Alliance-recognized Clinical Care Center dedicated solely to children.

Von Hippel-Lindau (VHL) syndrome is a rare genetic condition that can cause tumors in areas of the body that contain blood vessels, including the brain, spinal cord, eye and inner ear. Children with von Hippel-Lindau syndrome are at risk of developing multiple types of tumors during their lifetimes.

Doctors, nurses and genetic counselors in St. Jude Cancer Predisposition work with families to set up early detection, active surveillance and appropriate treatment for children with genetic diseases such as VHL. The team also collaborates with scientists to find new and better ways to help children who have a higher-than-normal risk of getting cancer. [2](#)

By Elizabeth Jane Walker



## Life after St. Jude Dakota's Dreams

Made possible in part by the Pediatric Cancer Genome Project.

**DAKOTA CUNNINGHAM** was nearly 4 years old when scientists launched an initiative that would one day help save his life.

As the preschooler romped and played, scientists in the Pediatric Cancer Genome Project rolled up their sleeves and set to

work. The project would eventually transform cancer diagnosis, treatment and research. It would also offer hope to the Cunningham family.

Seven years later, Dakota arrived at St. Jude Children's Research Hospital

### No more chemo

Dakota's family members, Breken, Tricia and Steve, join him in celebrating his last day of therapy.

*\*Photo was taken before the COVID-19 pandemic.*

with T-cell acute lymphoblastic leukemia (T-ALL). This disease occurs when genetic mutations prompt a buildup of the white blood cells called T cells.

Dakota enrolled in the TOTAL 17 clinical trial, which incorporates discoveries from the Pediatric Cancer Genome Project. Within the 3 billion base pairs of Dakota's genome, the scientists found issues with five genes. These gene changes—a fusion, a gain, a frameshift, a deletion—had huge implications for treatment.

Based on his genetic makeup, Dakota received a drug called bortezomib to attack his cancer cells.

"The doctors were able to make adjustments to tailor treatment specifically to what Dakota needed, not just cookie-cutter treatment," says his mom, Tricia Cunningham. "It saved my child. He's cancer free today, and it's 100% because of that."

Tricia says she and her husband, Steve, are grateful to the thousands of St. Jude patients who donated tissue samples and enrolled in clinical trials through the years.

"Dakota's treatment was developed as a result of all the research that was done in the past," Tricia says. "We hope what they learn from him will help others down the road."

In January of 2020, Dakota completed cancer therapy. Now 14, he has become an avid golfer and aspires to play for a Division I college.

"I don't know why I got cancer, but if nothing else, it gave me golf," he says.

Dakota also has a drive to help other patients facing cancer treatment.

"Let me tell you what I've been through," he says. "I know it sucks; I know it's hard. There are going to be days you think you can't make it, but you will."

"I needed somebody to tell me that," he continues. "Now I need to be able to say, 'You've got this.'" **1**

# A new era of discovery

As St. Jude celebrates successes generated by the Pediatric Cancer Genome Project, our scientists eagerly anticipate another milestone: completion of the St. Jude Advanced Research Center.

Scheduled to open in 2021, the state-of-the-art facility will help accelerate progress toward cures.





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DNA artwork provided by Alexis Paez Alfaro, Paola Rodriguez-Domenech and Lany Rullan-Soto.

