Mother and daughter share a Familial Foe

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Three decades after undergoing treatment at St. Jude, Katie Martin helps her daughter wage a similar battle.

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Revealing the Secrets of the Genome
With tiny trowels and delicate brushes, archaeologists sift through layer upon layer of sand, dirt or silt in their quest to unearth artifacts and better understand the past. With dedication, meticulous attention to detail and a little luck, the workers reveal long-buried secrets or fabulous treasures. But the greatest treasure for mankind is hidden inside each of us—the human genome. For children with cancer, the genome’s secrets hold the keys to health and hope.

About two-and-a-half years ago, scientists at St. Jude Children’s Research Hospital and Washington University School of Medicine in St. Louis joined forces on an expedition to explore the multilayered pediatric cancer genome. Like archaeologists, these researchers hope to uncover secrets that have eluded scientists for generations.

Investigators in the St. Jude – Washington University Pediatric Cancer Genome Project have already begun making exciting discoveries. The papers published thus far have provided the global scientific community with astounding details about cancers of the brain/nervous system, eye and blood. Researchers hope the findings will help them devise more effective ways to treat these diseases.

“The genome project is generating new insights into the genetic alterations that underlie some of the most aggressive childhood cancers,” says James Downing, MD, St. Jude deputy director, scientific director and site leader of the Pediatric Cancer Genome Project. “Those discoveries are pointing us toward new therapeutic options for children with these cancers.”

**Tools of the trade**

Scientists working with the Pediatric Cancer Genome Project are exploring uncharted territory. The team is sequencing the entire genomes of
both normal and cancer cells from 600 childhood cancer patients. By comparing differences in the DNA, scientists can identify genetic mistakes that lead to cancer.

Soon after the project began, St. Jude computational biologists realized they needed a new tool to pinpoint certain cancer-causing mutations that occur within the 3 billion base pairs of DNA in the human genome. Because such a tool did not exist, the scientists created one of their own.

Called Clipping Reveals Structure, or CREST, the computational method offered higher precision than other strategies for finding structural variations, which often involve chromosomal rearrangements or insertion or deletion of genetic material.

“Other tools missed up to 60 to 70 percent of structural rearrangements in tumors,” explains Jinghui Zhang, PhD, the Pediatric Cancer Genome Project’s lead St. Jude computational biologist. The new method created by Zhang and her colleagues is a boon to scientists worldwide who are combing through the vast sets of data in search of genomic treasure.

In January of 2012, top-tier journals began publishing initial findings from the project. The first papers appeared in such prestigious publications as Nature, Nature Genetics, Nature Methods and the Journal of the American Medical Association.

A rare subtype of leukemia

The initial findings emerging from the Pediatric Cancer Genome Project offer hope to children who face overwhelming odds. One such study involves a rare and often deadly form of leukemia.

Although the vast majority of patients with acute lymphoblastic leukemia (ALL) enjoy long-term survival, children with one particular subtype have a poor prognosis. Sixty to 70 percent of patients with early T-cell precursor ALL (ETP-ALL) fail to respond to therapy and succumb to their disease.

Researchers wanted to find out why that happens. The rare subtype of ALL was included in the Pediatric Cancer Genome Project because the disease was poorly understood and because the outcomes were so devastating. After sequencing genomes of this subtype, the researchers were excited to identify mutations unique to ETP-ALL. This kind of cancer appears to have more in common with acute myeloid leukemia (AML) than with other subtypes of ALL. The findings suggest that children with ETP-ALL may respond better to drugs that have been traditionally used to treat AML.

Work is already underway to develop laboratory models of human ETP-ALL and to use those models to identify AML drugs that may benefit children with the disease.

“We don’t have a definitive answer of what the best treatment will be, but we have a number of very important new options,” says Charles Mullighan, MD, MBBS, of St. Jude Pathology.

“We’re constantly reminded about why we’re doing this work,” Mullighan adds. “Every day we see children and families who are affected by these terrible diseases. It’s strong motivation to do work that will provide important basic scientific insights, ultimately benefiting patients and improving the outcome of treatment.”

Scientists worldwide turned their eyes to St. Jude when the initial paper was published.

“This is the first of a series of important discoveries on the genomic basis of childhood cancers that are emerging from the Pediatric Cancer Genome Project, which is on schedule to fully sequence 600 pediatric cancer genomes by 2013,” announced Dr. William E. Evans, St. Jude director and CEO.

An aggressive form of eye cancer

Illustrating the depth and breadth of the project, other findings soon followed in a spectrum of diseases. For instance, researchers studying the childhood eye cancer retinoblastoma identified the mechanism responsible for its aggressive nature. Retinoblastoma tumors also grow faster than other kinds of tumors. Although 95 percent of children with this disease...
In samples of diffuse intrinsic pontine glioma, Suzanne Baker, PhD (at left), and her team found a specific mutation that had never before been identified in other types of human cancer. Required for normal blood development, SYK has been linked to other cancers. Drugs targeting the SYK protein are already in clinical trials for adults with leukemia and rheumatoid arthritis. Dyer and his colleagues are working on an SYK inhibitor that can be delivered directly into the eye. The researchers have found that the drug is effective at killing retinoblastoma cells in the lab, and they hope to move it into Phase I studies soon.

New brain tumor discoveries

Another Pediatric Cancer Genome Project study sheds light on a cancer with one of the worst possible prognoses. More than 90 percent of children with a brain tumor known as diffuse intrinsic pontine glioma (DIPG) die within two years of diagnosis. There are no proven therapies for this aggressive tumor, which cannot be surgically removed because of its location in the brain stem.

“We didn’t really know what to expect when we sequenced the whole genome,” admits Suzanne Baker, PhD, co-leader of the Neurobiology and Brain Tumor Program. “This was an ideal tumor type for sequencing because so little is known about the tumor and there is such a great opportunity to improve outcome for these patients.”

Baker and her colleagues were astounded to discover that 78 percent of the DIPG samples they sequenced exhibited a specific mutation that had never before been identified in other types of human cancer.

“That’s a very exciting finding,” Baker says. “These mutations are found in the tumor DNA and not in the normal DNA from the same individual. That tells us the mutations give the tumor cells a selective growth advantage. This is important in turning a normal cell into a tumor cell.

“By helping us understand what goes wrong in the cell to make these tumors, the data may suggest new therapeutic approaches that would counteract the effects of this mutation.”

In samples of diffuse intrinsic pontine glioma, Suzanne Baker, PhD (at left), and her team found a specific mutation that had never before been identified in other types of human cancer.

Cancer of the nervous system

The genome project is also revealing why the same kind of cancer may endanger children of varying ages in drastically different ways. For example, if an infant, an older child and a teenager have the exact stage of neuroblastoma, a cancer of the nervous system, the patients will likely have dramatically different outcomes, depending on their ages. The survival rate for infants is 88 percent, with the rate plunging to 49...
To help speed further findings, St. Jude is sharing the information gleaned from the Pediatric Cancer Genome Project with researchers worldwide. In June of 2012, the hospital announced it was making all of its raw sequence data available—the largest-ever release of such data for free access by the global scientific community. This action more than doubled the volume of comprehensive whole genome information available from all human genome sources combined.

“Setting this precedent reflects a commitment to freely sharing information that has been a hallmark of St. Jude since we opened our doors 50 years ago,” says Dr. William E. Evans, St. Jude director and CEO. “The Pediatric Cancer Genome Project is a one-of-a-kind effort, so the information has the potential to accelerate disease research worldwide.”

Researchers internationally have already requested the raw data, which is made available at no charge. Because accessing and downloading the enormous file sets requires significant sophistication and equipment, these requests tend to be from genomics experts. However, St. Jude has also developed a way to enable a wide range of researchers to access and use the findings. An online tool titled Explore (http://explore.pediatriccancergenomeproject.org) makes much of the information accessible in a highly visual way. It enables researchers to more easily search for information of interest and drill down to greater levels of detail.

“Explore allows researchers to access the genome project’s unique, published data specific to pediatric cancers and to make discoveries of their own,” says James Downing, MD, the hospital’s deputy director, scientific director and site leader of the Pediatric Cancer Genome Project.
It’s a bittersweet visit for Justin Flowers, as he arrives at St. Jude Children’s Research Hospital for one of his final checkups in the sickle cell clinic. After 18 years at St. Jude, Justin is transitioning to adult care.

This fall, the St. Jude-Methodist Sickle Cell Disease Transition Clinic will be Justin’s new medical home. The clinic is aimed at reversing poor transition rates among teens and young adults. The program helps 18-year-olds make the leap from St. Jude to adult-care facilities of their choice.

“It’s scary when I think about leaving St. Jude because I’ve been here for so long. The staff is like my extended family,” Justin says.

His physician, Jane Hankins, MD, of St. Jude Hematology, enters Justin’s exam room and offers news about his progress.

“Your labs are good today. Your red blood cells look great,” says Hankins, who serves as medical director of the transition program, a joint effort with Methodist University Hospital in Memphis. “You’re picture perfect for where you should be with your type of sickle cell disease.”

Justin inherited a subtype known as hemoglobin SC. Without warning, his round, flexible red blood cells become stiff and banana-shaped, blocking blood flow to his organs and tissues. Often, the result is debilitating pain and lengthy hospital stays.

Grooming health advocates

Clinicians hope the transition program for 12- to 18-year-olds will become a national model for similar programs that encourage teens with sickle cell disease to continue their treatment as adults.

“Historically, many children nationwide haven’t made smooth transitions to adult sickle cell programs,” Hankins says. “They’ve ended up either dying or hopping from emergency department to emergency department until they’ve finally found suitable medical homes for their continued care. This may take many years and may have clinical, social and economic consequences for both the patients and for society in general.”

When Justin entered the hospital’s transition program, his family immediately immersed themselves in its educational offerings and tailored interventions.
It was the first step to addressing the underlying factors that can cause patients to abandon treatment. Such risk factors may include lack of follow-up adult care, medical insurance issues or lack of family support.

“I was encouraged early on to learn and write down everything about Justin’s treatment,” says his mother, Juanita Vann. “I have my own medical chart at home detailing his treatment since he was very young, and I plan to pass it down to him to continue as he transitions.”

Using a curriculum developed by the St. Jude Hematology department, the social worker, physician assistant, academic coordinator, psychologist and nurses on Justin’s transition team have guided him through the preparation period. This guidance facilitates a gradual shift in medical responsibility from the parents to the patient.

“We hope to have a new generation of well-prepared, more conscientious teenagers who will make responsible decisions about their health,” Hankins says. “By having a transition clinic that bridges well pediatric care to adult care, we can make teens feel comfortable about continuing their health care and give them fewer reasons to abandon their sickle cell treatment.”

Justin learned to communicate with adult care providers about his medical complications, immunization records and lab reports and began attending clinic visits on his own.

“I checked myself in, filled out my personal health record and answered questions about my blood type, the type of sickle cell disease I have and what precautions I should take if I go into a crisis when I’m alone,” he explains. “They also sent me to the genetic counselor, who quizzed me about the risks of having sickle cell disease.”

The curriculum also addresses peer relationships, nutrition, stroke risk, the benefits of exercise, and the effects of substance abuse on teens with sickle cell disease.

“Education is just as important as treatment itself,” says Justin’s case manager, Sheila Anderson, RN. “It helps patients follow the regimen that we plan for them and also makes them aware of when to seek medical attention. We want them to take control of managing their health.”

**Tailored interventions**

Since 2007, St. Jude has taken teenaged patients on tours of local adult sickle cell care providers. These tours offer teens a glimpse of life as adult survivors. They learn about available services, express their concerns about transitioning and hear testimonials from adults with sickle cell disease.

Since implementing the tour program, transition rates from St. Jude to adult care facilities have increased from less than 15 percent to more than 75 percent.

After transitioning, the focus shifts to compliance. Recognizing the affinity most teens have for technology, the transition team collaborated with the hospital’s Information Sciences staff to create a text-messaging system. This system encourages medication compliance for teens who take hydroxyurea, a drug that reduces the percentage of sickled cells.

Teens craft their own messages and decide how often to receive them. Justin draws his smartphone from his pocket and retrieves the text that alerts him every morning: “Hey you, take your medicine,” it reads.

Another technical lure is a virtual mentorship program. Adults with sickle cell disease undergo extensive training before embarking on an online mentoring program with teens. They communicate regularly with their mentees, reinforcing the importance of medication compliance and follow-up care.

**Looking to the future**

Thanks to the transition clinic, new data will be accessible to Hankins and her team as they cultivate the program and report their research findings to the medical community. Early signs indicate the clinic is proving effective.

“Several patients who left St. Jude at 18 had not identified an adult doctor or received the proper follow-up care,” Hankins says. “They heard about the transition clinic and called to schedule appointments. Now we have a seamless process for monitoring their progress once they leave St. Jude.”

Justin’s adult care treatment plan will mirror what he received at St. Jude. Hankins and Anderson will join him on initial visits and will assume a supportive role thereafter, as he consults with his adult doctor.

With his sights set on college, Justin is ready for the next chapter in his life and the responsibility of driving his own medical care.

“It will be different, but I’m ready,” he says. “This is something that my mom and St. Jude have prepared me for my whole life.”
Three decades have passed since Katie received cancer treatment at St. Jude. Now her daughter is waging a similar battle.

By Elizabeth Jane Walker
“Of course, we believe that Madeleine’s going to make it,” says her dad, “but at the same time, it’s good to know that what they learn from her will help other kids.”
Madeleine Martin has a rainbow on her tummy and a button on her chest. That’s how the precocious toddler explains the semi-circular scar on her abdomen and the catheter embedded just below her collarbone. In a voice of angelic innocence, Madeleine assures her parents that St. Jude is going to fix her tummy.

For 2-year-old Madeleine, that’s all she needs to know.

Déjà vu

The world is a bit more complicated for Madeleine’s mom, Katie. Thirty-three years ago, she, too, was a patient at St. Jude Children’s Research Hospital. Now Katie is reliving the experience through her daughter.

During a routine checkup in 1979, a pediatrician discovered a lump in Katie’s abdomen. Within days, surgeons had removed her right kidney along with a large, cancerous mass called Wilms tumor, or nephroblastoma. Doctors advised Jay and Mary Jellison to take their 18-month-old daughter to St. Jude for further treatment, which would include chemotherapy.

“We wanted the best care for Katie,” Mary says. “The doctors and staff of St. Jude offered hope to all children with cancer. It was a bonus that St. Jude paid for our gas, hotel room and meals; that was amazing. We got the best care, and we didn’t have to pay for any of it.”

Every two weeks, the family made the trek to Memphis so that Katie could receive chemotherapy and meet with her oncologist, Judy Wilimas, MD. Because the hospital did not have long-term housing available in the 1970s, the Jellisons drove home immediately after each checkup. Mary vividly remembers those seven-hour car trips. “The protocol was quite different then,” she says. “Katie would receive her chemo, and on the drive home she would start feeling nauseated, often getting sick in the car.”

As she matured, Katie enjoyed excellent health, but remained vigilant.

“Growing up, I was told to be cautious because I had only one kidney,” she recalls. “I wasn’t supposed to go horseback riding or do contact sports. I stopped soccer at the sixth grade.”

Eventually, Katie embarked on a career in health care. “I knew I wanted to be in the health field from the time I was itty bitty because I loved St. Jude so much,” she explains. “The whole reason I became a pediatric nurse practitioner is because of my experiences with the nurse practitioners there.”

Mother’s intuition

In 2009, Katie and her husband, Justin, welcomed a beautiful baby girl into their lives. Although Madeleine seemed perfect, Katie worried that the baby might develop cancer. Even though the odds of having a child with Wilms tumor were negligible, the possibility haunted Katie. Last fall, she traveled to Memphis to participate in St. Jude LIFE, an ambitious research project that aims to identify the long-term effects of childhood cancer and its treatment. During one appointment, Katie confided her concerns to Tim Folse, MD, of Oncology. “If it will make you feel better, Madeleine could have an ultrasound,” Folse told her. “Why don’t you talk it over with her pediatrician?”

After discussing pacifiers and potty training and sleep issues during Madeleine’s annual checkup, Katie broached the subject of an optional scan. An ultrasound was scheduled for October 12.

Justin knew Madeleine’s odds of having Wilms were miniscule. “While I was blowing leaves in the yard, I was thinking, ‘We’re just going to be throwing money away. They’ll find out everything’s fine, but I’ll write the check, and then we’ll have peace of mind,’” he recalls.

Madeleine’s mom, Katie (shown here with her older sister, Lisa) was just under 2 years old when doctors discovered she had Wilms tumor. More than 30 years later, Katie is now reliving those experiences as her own toddler undergoes treatment for the same kind of cancer.
The morning of the procedure was fraught with petty irritations. A fussy toddler. A misplaced insurance card. A traffic jam. After the procedure, both mother and daughter were exhausted. They waited for the results. And they waited. What was causing the long delay?

Finally, a technician called Katie to the phone. Madeleine’s pediatrician was on the line. To Katie’s amazement, the physician was crying. “I don’t know how to tell you this, but there’s a mass on Madeleine’s left kidney,” the doctor told Katie. “They think it’s Wilms because of your history.”

Double trouble

Soon the doctors arrived with worse news. They had detected lesions on both kidneys.

Madeleine’s grandparents were astounded when they heard the diagnosis. “Back in 1979 when we found out Katie had cancer, we were in total shock. This one was a double shock, plus déjà vu,” Mary Jellison says. “We had assumed that was all behind us. Now our daughter would have to go through the same thing that we had—only this one was even trickier, because they had found it on both of Madeleine’s kidneys.”

Justin, Katie and her parents unanimously agreed to request a referral to St. Jude—a decision based not only on the institution’s reputation for clinical excellence, but also on its research emphasis.

“Katie’s dad and I both work for research organizations,” Justin explains. “Of course, we believe that Madeleine’s going to make it, but at the same time, it’s good to know that what they learn from her will help other kids.”

When the family arrived in Memphis, Katie’s St. Jude physician provided Madeleine’s oncologist, Lisa McGregor, MD, PhD, with pertinent details about Katie’s treatment.

“When I said Katie’s name, Judy Wilimas went to a book where she had kept information on all of the old Wilms tumor patients,” McGregor says. “She immediately gave me a summary of the treatment that Katie had received three decades ago.”

Uppercut time

Madeleine soon began six weeks of chemotherapy treatments. Afterward, using the nephron-sparing procedures that he had helped pioneer, Surgery Chair Andrew Davidoff, MD, removed four masses from Madeleine’s right kidney and five from the left, while sparing as much healthy kidney tissue as possible. The operation was much more complex than the procedure Katie had undergone in 1979, which had involved complete removal of a kidney.

“Even though the imaging may look a little foreboding, more often than not, we’re now able to save normal kidney on both sides,” Davidoff says. “That was the case with Madeleine.”

Two masses on Madeleine’s left kidney were Wilms tumor; the others were nephrogenic rests, which are lesions that have a high likelihood of becoming cancerous. The operation left Madeleine with two-thirds of her left kidney and three-fourths of her right.

“She has more kidney than I have, which is wonderful,” Katie says.

Unlike her mom, Madeleine should one day be able to ride horses, play soccer and participate in any other sport she chooses.

“She’s not at greater risk than anyone else is of injuring her kidneys,” Davidoff explains. “I wouldn’t give her any activity restrictions.”

Because of the bilateral lesions and her genetic predisposition, Madeleine has a higher risk of recurrence than her mother did. To further explore the rare familial link, Christine Odom, a genetic counselor at St. Jude, set up a battery of genetic tests and coordinated the family’s enrollment in a Wilms tumor genetic study.

As a result of the increased risk factors, Madeleine is now receiving additional chemotherapy.

Justin compares his daughter’s treatment to a boxing match. “The initial chemo before surgery is like they’re just jabbing the cancer over and over in the
same spot,” he says. “They’re testing it, trying to get a reaction and softening it up. Then they do the surgery, and they come back and do some more of that jabbing, but they start mixing in different punches and getting it off balance—body blow, head shot, work the kidneys—get in there. It’s low dosage and then it’s a mix of drugs, and then at the end they give bigger doses. That’s what I call uppercut time. They’re throwing the biggest punches they can to knock it out.”

Symbol of strength
For the most part, Madeleine appears to be unconcerned about the epic battles occurring on her behalf. The tiny girl derives joy from the simplest actions—whether it’s singing “Twinkle, Twinkle, Little Star,” hurtling down a playground slide or judging the heft of a ball. She constantly delights friends, family and caregivers with her advanced language skills, her ebullience and her keen powers of observation.

Playing in the bathtub one evening, Madeleine begins rubbing soap across her scar. “What are you doing?” asks Katie.

“Madeleine wash scar off. Madeleine make tummy smooth,” the toddler responds.

“Sweetheart, you can’t wash off your scar; it’s part of you now, and it helped to make your tummy all better,” Katie gently explains. “It’s a beautiful scar, and it shows your strength and courage.”

Madeleine contemplates those words. A few weeks later, the little girl inspects her reflection in the mirror.

“Madeleine has a rainbow on her tummy,” she announces.

“Yes, that’s right! Madeleine has a rainbow on her tummy,” Katie exclaims, reaching out to hug her daughter. “And it’s the most beautiful rainbow I’ve ever seen.”

Enveloped in her mommy’s warm embrace, that’s all Madeleine needs to know.
A zestful exuberance marinates in the eyes of 17-year-old Nick Gagnon. His enthusiasm bubbles over as he explains the intricacies of cast-iron cooking and describes the cornucopia of cakes, cobblers, stews and vegetables that he has prepared. Nick discusses how the placement of coals on the top and bottom of a pot bakes food like a convection oven. Listening nearby, his mother, Suzette, smiles as Nick’s hands slice the air to illustrate the culinary method.

His excitement is a welcome sight—a cheerful scene in a dark drama that began in late 2010 when the teenager felt an unusual pain in his left leg. It’s a journey that led Nick to St. Jude Children’s Research Hospital, where he received treatment for a form of bone cancer and found an unexpected mentor in one of his favorite places: the kitchen.

A potful of hobbies

Although cooking is Nick’s passion, he has always had a well-rounded set of interests and hobbies. He played baseball, basketball and tried swimming before finding his athletic niche in the sport of rowing. As a member of the crew rowing team, Nick enjoyed the harmonious teamwork required to move a 60-foot, fiberglass boat through the calm rivers of his native Florida. Each day before practice Nick and his rowing club teammates carried the boats—some heavier than others—from the boathouse to the river dock. Before launching, the entire team participated in a strenuous
land workout of running, squats, push-ups and erging—a type of rowing simulation.

During a series of practices in October of 2010, Nick started experiencing pain in his left leg. Merely walking uphill to the boathouse became a painful task.

“My running performance started to drop, so my coaches asked if it was because I was getting bored with rowing. I said, ‘No, it just hurts,’” Nick says.

An X-ray in December of 2010 revealed a shadow on the upper portion of Nick’s femur. A magnetic resonance imaging (MRI) scan revealed a spot about 9 centimeters long. A local orthopedic oncologist performed a biopsy and diagnosed an osteoid osteoma, a benign bone tumor. Surgeons removed the tumor and replaced it with bone cement. Within two months, Nick was walking without the aid of crutches, but, more importantly, without pain.

Thinking this was a minor blip to his busy teenage schedule, Nick again poured his energy into the activity that spurred his love of cooking—the Boy Scouts. As a 12-year-old scout, Nick had discovered cast-iron cooking, also known as the chuck wagon style.

Last fall, Denise Hale (at left) and Nick Gagnon teamed up to help cook a thank-you meal for St. Jude staff.
that was popularized by late 19th century settlers of the American West. After his recovery, Nick’s main focus soon became his Eagle Scout project, which involved constructing raised garden beds at the local middle school where his mother served as a science teacher. Nick anticipated that the school’s students would eventually use the garden for various projects and experiments while he would satisfy the requirements to attain the scouts’ highest honor.

During the project’s planning stages in May of 2011, the pain in Nick’s leg returned. Assuming that he had not recovered fully from the osteoma removal, doctors placed Nick in physical therapy, which only made the pain worse. In July—just days after his 17th birthday and weeks before the beginning of his senior year of high school—an X-ray revealed a shadow near the same area as the previous one. An MRI of the femur indicated a spider-web pattern emanating from a central spot.

“When I saw that, I thought to myself that there was no way that could be removed,” Suzette says.

**Recipe for success**

Nick’s doctor sent results of a second biopsy to St. Jude. A team of physicians diagnosed osteosarcoma, a bone cancer that affects 400 children and adolescents under the age of 20 each year. After thorough research, Suzette and her husband, Greg, obtained a referral to St. Jude, where Nick’s cousin had been successfully treated for non-Hodgkin lymphoma a decade earlier.

“I thought that if we were going out of state, we were going to St. Jude because not only do they offer osteosarcoma treatment, but our niece had been treated there,” Suzette says.

Nick enrolled in the OS2008 protocol, which combines chemotherapy drugs with bevacizumab, a drug that slows the growth of new blood vessels. By choking off the blood supply to a tumor, bevacizumab helps prevent the cancer’s spread to other parts of the body. The drug has improved the efficacy of chemotherapy in adult patients with various types of cancer. St. Jude is building upon that base to conduct the novel trial in osteosarcoma patients, whose five-year survival outcome is magnified from 30 to 75 percent if the cancer has not spread at the time of diagnosis.

Nick’s cancer was confined to one area, but he still faced 10 weeks of intensive chemotherapy before undergoing limb-sparing surgery. Thirty weeks of additional chemotherapy would follow the operation.

“Decades ago, if you had osteosarcoma, your limb was amputated. A high percentage of those patients had the tumor come back in their lungs,” says Nick’s attending physician, Lisa McGregor, MD, PhD, of St. Jude Oncology. “From this, we know that even if we cannot see tumor and we just amputate, it’s most likely that the tumor has spread to somewhere else in the body. We administer chemotherapy after surgery to take care of any last tumor cells that still might be there.”

Because the chemotherapy was so intense, Nick had few opportunities to return home during treatment. Suzette resigned from her teaching position to stay during.

During a Boy Scout trip several years ago, Nick prepared the meat for his troop’s supper. Nick is now completing his Eagle Scout project, which encompasses construction of raised garden beds for a local middle school.
with him. The teenager stayed in the hospital during treatments so that clinicians could ensure his body flushed out the drug to prevent organ damage. Nick needed almost all of the days between treatments for his body to fully recover.

Michael Neel, MD, of St. Jude Surgery performed Nick’s limb-sparing operation in November 2011, which required the removal of his upper left femur within four inches of the knee. Neel inserted a titanium rod to complete the procedure, which is comparable to a hip-replacement surgery.

Cooking up a storm

After the surgery, Nick worked with therapists in Rehabilitation Services to become accustomed to the prosthesis in his upper leg. He was also able to further his culinary foundation. His passion for food was well known around the hospital, so when TV personality and chef Giada de Laurentis visited St. Jude to film a Thanks and Giving segment for NBC’s TODAY show, he was a natural fit to help out. Airing on Thanksgiving Day, the segment featured Nick and other patients sharing their stories and preparing a “thank-you” meal for St. Jude physicians and scientists.

During the segment’s filming, St. Jude Executive Chef and Director of Culinary Operations Miles McMath learned of Nick’s ambitions. The two quickly bonded over culinary conversation. McMath, also a fan of chuck wagon cooking, says Nick’s enthusiasm is both impressive and inspirational.

When he sees Nick and Suzette in the hospital, McMath takes time from his busy schedule to talk food.

“It’s always nice to be able to mentor someone who has a passion for food like Nick does,” McMath says. “He would be feeling bad from the chemotherapy, and the only thing that would make him feel better would be talking about food. Just imagine what kind of passion he’ll have when he’s feeling better: He’ll be incredible!”

Nick also participated in other cooking projects and events at the hospital during his treatment. He returned home to Florida in May to undergo further therapy with the goal of returning to the kitchen in the near future. He has received an extension to complete his Eagle Scout project and has plans to enroll in a culinary program at his local community college after high school graduation.

“I love to cook,” Nick says. “You get to experiment and see what works and what doesn’t. There’s always something new to try.”

The Food Services department at St. Jude has the exciting and challenging task of feeding patients who are not always hungry due to illnesses or treatment. Partnering with the hospital’s Clinical Nutrition department, Food Services seeks ways to ensure that patients not only eat, but do so in a healthy manner.

Patients can request meals that satisfy their regional or international tastes. If approved by Clinical Nutrition, Executive Chef Miles McMath and his team whip up creations ranging from Cajun gumbo to a Mexican flauta or Memphis-style barbecue.

Since patients aren’t always hungry at the traditional times of day, the department has adopted the growing food preservation method of sous-vide (French for “under vacuum”) to seal in a meal’s taste and freshness. Food is prepared, then vacuum sealed in plastic bags in small portions and frozen. If a patient craves a meal at 3 a.m., a staff member thaws it through steaming and then serves the meal nearly as fresh as when it was prepared.

McMath’s staff welcomes feedback from patients and families to learn what works and what does not. Food Services staff members get to know the faces they feed through activities that allow patients to create parfait treats or make their own pizzas.

Many patients have dietary limitations or have problems tasting some foods. These scenarios bring out the prodigious talents of the hospital’s four executive chefs.

“I love being creative and being challenged as a chef,” McMath says. “It’s easy to make a customer happy by cooking with some really good ingredients, but here at St. Jude, it takes technique more than ingredients to be successful. It involves using all those basic fundamentals that we learned starting out as chefs and applying them to each situation creatively.”

St. Jude Executive Chef and Director of Culinary Operations Miles McMath found a kindred soul in Nick. “It’s nice to be able to mentor someone who has a passion for food like Nick does,” McMath says. “He would be feeling bad from the chemotherapy, and the only thing that would make him feel better would be talking about food.”
A sleepy little town on the banks of the mighty Mississippi River may seem far removed from a scientific research project of historic proportions. But Port Gibson, Mississippi, is the home of Joc Carpenter, who has guided the Madison Charitable Foundation to become a key supporter of the St. Jude Children’s Research Hospital – Washington University Pediatric Cancer Genome Project.

From his back deck overlooking the river, Joc describes how his desire to help improve the lives of children led him to earmark a sizeable gift from the foundation for the groundbreaking genome research taking place in Memphis.

“The research that St. Jude is doing and the data that will be accumulated from this project are unbelievable,” he says. “To think that St. Jude is poised, through this research, to double the knowledge that has been gained over the last 50 years is truly exciting.”

Joc’s business partner of 35 years, Wiley Hatcher, formed the Madison Charitable Foundation in 2007 from the proceeds of the sale of his oil and gas pipeline engineering company. These men, along with two other associates, became equal trustees of the foundation, each being allowed to direct grants as they see fit. Joc has the greatest respect for his former partner. “I believe giving to others is a learned trait,” Joc says, “and watching Wiley has taught me a lot about giving.”

A self-described advocate for children’s causes, Joc says choosing St. Jude as a major beneficiary was an easy decision. “It’s hard to go anywhere and not meet someone who has been affected by the work of St. Jude,” he observes.

Shortly after making the initial contribution to St. Jude, the cause of fighting childhood cancer became much more personal to Joc and his wife, Leigh Ann. In the fall of 2009, their great-nephew became a Hodgkin lymphoma patient at St. Jude.

Today, the little boy has completed his treatment and is doing well, making Joc’s decision to support St. Jude even more meaningful and spurring him to make an additional donation through the Madison Foundation to fund a matching gift for the hospital. “I wanted to encourage others to help the children of St. Jude too, and offering funds for matching seemed like a great way to do that,” Joc explains.

The Carpenters are proud of their involvement with the Pediatric Cancer Genome Project, and they eagerly track the progress of the research through their St. Jude representative, Leslie Davidson. “Leslie keeps us well informed as discoveries are happening,” Joc says. “We are in awe of the work that St. Jude is doing.”

Through his experiences with the Madison Charitable Foundation, Joc has found truth in the adage, “To give is better than to receive.”

“It’s a very gratifying job,” says Joc of his trustee position. “Being able to provide financial support and seeing how it can make a difference in the lives of so many people—it does your heart good.”
All of the children at St. Jude Children’s Research Hospital are warriors.

Kevin Washburn knows that is true because his son Ethan has been fighting since January 2010, when tests revealed the presence of acute lymphoblastic leukemia, the most common childhood cancer.

Ethan was immediately referred to St. Jude, where the 7-year-old began a three-year chemotherapy treatment plan that put his cancer into remission.

Now Kevin is a warrior, too, competing in a Warrior Dash competition produced by Red Frog Events, LLC. Chicago-based Red Frog, a leader in the active entertainment industry, recently made St. Jude its national charity partner and has already raised more than $2 million by encouraging participants in the Warrior Dash, Great Urban Race and Beach Dash events to raise money for St. Jude.

Most people who compete in Red Frog events are fun-loving professionals in their 20s or 30s. “It’s been unbelievable, seeing the passion our participants have for what St. Jude does,” Kunkel says.

Inspired by the TV show The Amazing Race, Kunkel’s brother-in-law Joe Reynolds started Red Frog in 2007 with eight Great Urban Race events. Touted as a wacky urban adventure, the race requires teams to solve 12 clues and complete challenging tasks while exploring a city. Kunkel joined the company in 2009.

Red Frog has seen tremendous growth and, in 2011, won the U.S. Chamber of Commerce DREAM BIG Small Business of the Year Award. That year, the company also decided to make St. Jude its national charity partner.

St. Jude will also partner with Red Frog in its newest endeavor, the Firefly Music Festival, planned for July in Dover, Delaware, through the Music Gives to St. Jude Kids program.

“We feel it’s a privilege to be working with such a truly world-changing organization,” says Kunkel, “and we are excited to continue to grow our efforts to continue to provide lifesaving treatment to the kids of St. Jude.”

Making the Leap

Red Frog Events commits to St. Jude as a national charity partner.

By Leigh Ann Roman

For more information, visit www.stjude.org/warriordash.
Four St. Jude faculty members have recently won national and international honors for their achievements.

In March of 2012, Dr. William E. Evans, director and CEO, received the pharmacy profession’s highest recognition, the Remington Honor Medal. Presented by the American Pharmacists Association, the award honors Evans for his research with anticancer agents and pharmacogenomics, as well as his leadership contributions to St. Jude.

The American Society of Clinical Oncology presented the 2012 Pediatric Oncology Award to Ching-Hon Pui, MD, Oncology chair. The honor recognizes Pui’s many contributions to better understanding the biology and treatment of leukemia, as well as his role in improving survival rates for the disease.

Brenda Schulman, PhD, of Structural Biology was named to the 2012 class of new Fellows and Foreign Honorary Members of the American Academy of Arts and Sciences. Schulman was elected for her contributions to understanding a major form of cellular regulation. Studies by Schulman’s laboratory have helped explain the structure and function of a family of enzymes known as ubiquitin-like proteins, which help regulate cell division.

Guillermo Oliver, PhD, of Genetics was elected a fellow in the American Association for the Advancement of Science. Oliver was chosen for his contributions to the field of developmental biology and the lymphatic vascular system.

Inherit the risk

St. Jude scientists have pinpointed genetic factors that increase Hispanic children’s risk of having acute lymphoblastic leukemia (ALL) and of dying from the disease.

Researchers studying a gene called ARID5B linked a number of common variants of the gene to an increased risk of developing pediatric ALL and having the cancer return after treatment. Investigators found that Hispanic children were up to twice as likely as their white counterparts to inherit a high-risk version of ARID5B.

“For years we have known about ethnic and racial disparities in ALL risk and outcome, but the biology behind it has been elusive. Therefore, it is truly exciting to be able to not only pin down the biological basis but to find that the same gene might be responsible for both differences,” said Jun Yang, PhD, of Pharmaceutical Sciences. Yang was corresponding author of a report on this study, which appeared in the Journal of Clinical Oncology.

The findings set the stage for exciting research in understanding how genetic, environmental and other factors combine in ALL, especially in the context of racial and ethnic disparity. Yang said additional work is needed to translate these findings into new clinical tools.
How sulfa drugs kill bacteria

More than 70 years after the first sulfa drugs helped to revolutionize medical care and save millions of lives, St. Jude scientists have determined at an atomic level the mechanism these medications use to kill bacteria. The discovery provides the basis for a new generation of antibiotics that would likely be harder for bacteria to resist and cause fewer side effects.

The work focused on sulfa drugs and their target enzyme, dihydropteroate synthase (DHPS).

“The structure we found was totally unexpected and really opens the door for us and others to design a new class of inhibitors targeting DHPS that will help us avoid side effects and other problems associated with sulfa drugs,” said Stephen White, DPhil, Structural Biology chair. White was corresponding author of a paper on this study that appeared in the journal Science.

Co-author Richard Lee, PhD, of Chemical Biology and Therapeutics, added: “Now we want to leverage this information to develop drugs against the opportunistic infections that threaten so many St. Jude patients.”

When chemotherapy is best

An international study found that bone marrow transplants are not the best option for some young patients with acute lymphoblastic leukemia (ALL) whose disease does not go into remission after the initial weeks of intense chemotherapy known as induction therapy.

The largest study ever of such patients identified a subset of young children who achieved 10-year survival rates of 72 percent after additional chemotherapy rather than bone marrow transplantation. The patients are among the estimated 85 percent of children with ALL whose cancer begins in white blood cells destined to become B cells. These patients were 1 to 6 years old at diagnosis and had favorable leukemic cell genetic abnormality. This subset represented about 25 percent of the patients for whom initial remission induction had failed.

Results of the study, which involved more than 44,000 patients from the U.S., Europe and Asia, appeared in the New England Journal of Medicine.

“Induction failure is a rare event, affecting just 2 to 3 percent of all pediatric ALL patients,” said the study’s corresponding author, Ching-Hon Pui, MD, Oncology chair.

“But these children are at very high risk for a bad outcome and were always considered candidates for bone marrow transplantation. These results tell us that induction failure should no longer be considered an automatic indication for a transplant.”
Research Highlights

A protein’s surprising functions

St. Jude scientists have rewritten the job description of a protein called TopBP1 after demonstrating that it guards early brain cells from DNA damage. Such damage might foreshadow later problems, including cancer.

Researchers showed that cells in the developing brain require TopBP1 to prevent DNA strands from breaking as the molecule is copied before cell division. Investigators also discovered that stem cells and immature cells known as progenitor cells involved at the beginning of brain development are more sensitive to unrepaired DNA damage than progenitor cells later in the process. Although more developmentally advanced than stem cells, progenitor cells retain the ability to become one of a variety of more specialized neurons.

“Such DNA strand breaks have great potential for creating mutations that push a normal cell toward malignancy,” said Peter McKinnon, PhD, of Genetics. McKinnon is senior author of a report on this research that appeared in the scientific journal Nature Neuroscience. Results of this study offer new insights into normal brain development, DNA damage repair mechanisms and cancer biology.

Story of lymphatic system expands

A century after the valves that link the lymphatic and blood systems were first described, St. Jude scientists have detailed how those valves form and identified a gene that is critical to the process.

The gene is Prox1. Earlier work led by Guillermo Oliver, PhD, of Genetics, showed Prox1 was essential for formation and maintenance of the entire lymphatic vasculature. A network of vessels and ducts, the lymphatic vasculature helps maintain the body’s fluid balance and serves as a highway along which everything from cancer cells to disease-fighting immune components moves. Oliver is senior author of the new study, which appeared in the scientific journal Genes & Development.

The new research suggests that Prox1 is also essential for proper formation of the one-way valves that control movement of fluid and nutrients from the lymphatic system into the blood stream. Researchers found evidence that the Prox1 protein also has a critical role in formation of the venous valves.

“Understanding how valves form is crucial to efforts to develop treatments for valve defects that affect both children and adults,” said the paper’s first author, R. Sathish Srinivasan, PhD, of Genetics. Those defects are linked to a variety of problems, including lymphedema and deep vein thrombosis.

Good FORTUNE

St. Jude has been recognized by FORTUNE magazine as one of the “100 Best Companies to Work For” for the second consecutive year. Employees again ranked pride in the hospital’s mission—finding cures, saving children—as one of the top reasons St. Jude is a great place to work.

“Our employees look at the work they do at St. Jude as much more than a job,” said Dr. William E. Evans, director and CEO. “As we celebrate our 50th anniversary this year, we are reminded that one of the keys to our success has been attracting outstanding people and giving them a place to do their best work. Employees embrace the mission and espouse the culture of St. Jude, which is one of collaboration, compassion, innovation and quality in all we do.”
The importance of form and function

Scientists have discovered that a protein vital for cell survival and immune balance also has another form with a different function. This finding could yield an additional cancer treatment strategy.

Safeguarding cell survival and maintaining a balanced immune system are only two tasks of the myeloid cell leukemia sequence 1 (MCL1) protein. Nearly 20 years after MCL1 was discovered, scientists have identified a second form of the protein that works in a different location in cells and performs a different function. This newly identified version is shorter and toils inside rather than outside mitochondria where it assists in production of chemical energy that powers cells. The research appears in the journal Nature Cell Biology. Investigators say that the finding will likely aid the development of cancer drugs.

“We believe this newly identified form of MCL1 that works inside the mitochondria is probably essential for tumor cell survival. If that proves to be correct, then strategies to block the protein from getting into mitochondria offer a new therapeutic approach for cancer treatment,” said the paper’s senior author, Joseph Opferman, PhD, of Biochemistry.

Equal access helps close the gap

A new analysis from St. Jude adds to evidence that equal access to comprehensive treatment and supportive care typically translates into equally good outcomes for most young African-American and white cancer patients.

Racial disparities in cancer survival are widely recognized among African-American patients of any age. These patients are less likely than their white counterparts to become long-term cancer survivors. However, researchers found no significant difference in survival rates between African-American and white children treated at St. Jude for virtually all cancers during a 15-year period ending in 2007.

While this and previous studies have highlighted the success of St. Jude in closing the gap, investigators reported that the disparities persisted for many other U.S. pediatric cancer patients.

“This study shows that with outstanding medical care and psychosocial support African-American patients should not necessarily fare worse than white patients,” said Oncology Chair Ching-Hon Pui, MD, lead author of a report on this study that appeared in the Journal of Clinical Oncology.

An event to remember

Patients and siblings recently had the opportunity to dress up and celebrate during the hospital’s 2012 Teen Formal. Prior to their journey down the red carpet, the partygoers prepared for the big night. Girls had their hair, make-up and nails done while the boys donned sharp-looking tuxedoes before boarding limousine buses bound for the hospital. Events such as the Teen Formal, organized by Child Life staff, provide a fun respite for teen patients who might otherwise miss this rite of passage while undergoing treatment. Navigating the red carpet while acknowledging the applause of families and staff are Morgan Harris (seated) and her sister, Breanna.
Perspective

Opening Doors to New Discoveries

The parent of a former patient explains why he supports the Pediatric Cancer Genome Project.

Allan McArtor and his wife, Grace, learned about St. Jude 38 years ago, when their daughter, Kelley, underwent treatment there. Now Allan chairs the Pediatric Cancer Genome Project’s fundraising campaign.

My wife, Grace, and I first walked through the doors of St. Jude Children’s Research Hospital in 1974, when our 2-year-old daughter, Kelley, needed treatment for a brain tumor.

For a parent with a sick child, walking through those doors hasn’t changed. Families today still receive a warm reception from top-quality people—clinicians, researchers, administrators and volunteers—who are absolutely committed to the hospital’s mission. It’s still all about hope.

But what’s behind those doors has changed immensely in the past 38 years.

It’s staggering to consider the sophistication of what goes on at St. Jude today. One of those aspects is the St. Jude Children’s Research Hospital – Washington University Pediatric Cancer Genome Project.

In spite of scientific advances, we still have a poor understanding of the origins of childhood cancer. The Pediatric Cancer Genome Project takes the incredible computing power and knowledge base of genome science and applies it specifically to pediatric cancer.

This is breakthrough stuff. When I heard about it, I knew that I wanted to be a part of it.

As the parents of a St. Jude patient, my wife and I were impressed with the level of care and compassion our daughter received at the hospital. We were also impressed with the research that goes on there. Kelley lost her battle when she was 8 years old, but tissue from her tumor is still preserved in the hospital’s tissue bank. St. Jude scientists had the foresight to keep those samples, hoping that they would be able to use them someday. The Pediatric Cancer Genome Project is sequencing the entire genomes of normal and cancer cells from more than 600 patients. Although we’ll never know for sure, we hope that perhaps Kelley is contributing to this study.

That’s the thing about St. Jude. Not only do the children receive the best treatment, but the scientists learn valuable lessons from each of those children, whether they survive or not.

I encourage everyone to invest just a little time in learning more about the Pediatric Cancer Genome Project. Sometimes, when I talk to people from other cities, they say, “Well, I’m committed to the children’s hospital here in our area.” And I say, “Great! Then you know how important it is to improve treatment. Information from the Pediatric Cancer Genome Project is shared freely worldwide, so you’ll contribute to your hospital’s knowledge base by investing in this remarkable St. Jude project.”

Scientists in the project already are making exciting discoveries (see page 2). The results speak for themselves. I can’t think of a better place to put your efforts than by helping St. Jude with the Pediatric Cancer Genome Project.

Allan McArtor, chair of the Pediatric Cancer Genome Project fundraising campaign, is a longtime member of the ALSAC/St. Jude Professional Advisory Council and was named the 2012 Cardinal Stritch Donor of the Year. Currently chairman of Airbus Americas, McArtor’s career has included service in the Air Force as well as senior leadership positions at FedEx, Legend Airlines and the Federal Aviation Administration.
Brennan was diagnosed with a rare form of acute myeloid leukemia that did not respond to standard treatment. St. Jude doctors pioneered a treatment plan that is giving him a chance at life, and Brennan’s parents will never receive a bill for his care.

Create a legacy gift that will help St. Jude continue its lifesaving mission so that one day children like Brennan can realize their dreams.
Golfer Nick O’Hern offers pointers to St. Jude patient Courtney Davis during the 2012 FedEx St. Jude Classic. Founded in 1958 as the Memphis Open, the tournament has realized donations totaling more than $25 million since 1970, when St. Jude became its sole beneficiary. Attendance at the 2012 event was the largest in the history of the tournament.