WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research

2020 ANNUAL REPORT

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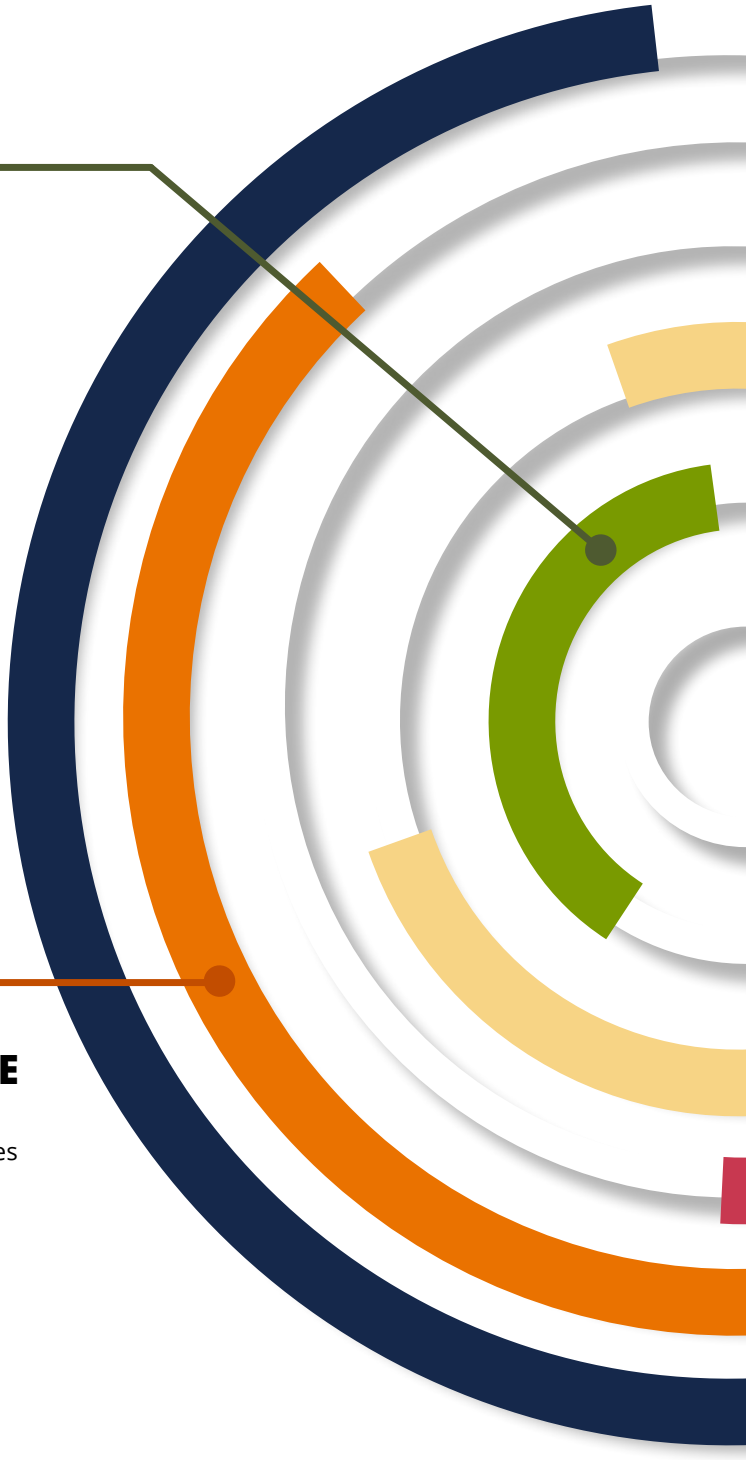

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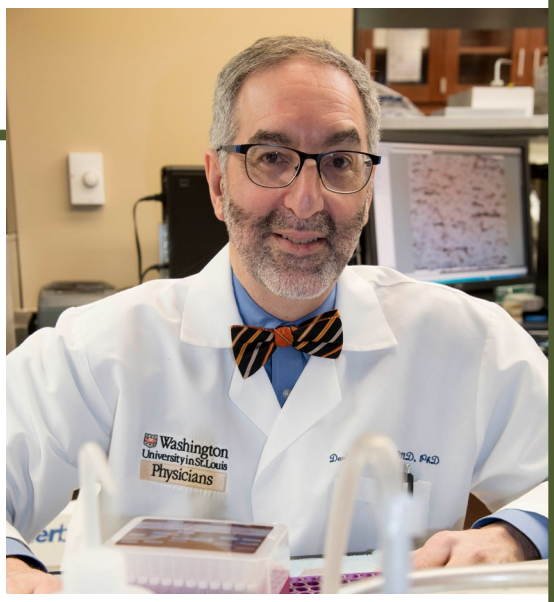
MESSAGE FROM THE DIRECTOR



It has been a year like no other. As we all have learned to adjust to life during the COVID-19 pandemic, we have also had to grapple with inherent racial inequities in our country. It is not an understatement to say that these times have served as a flashpoint, prompting deep re-examination, extraordinary accommodations, and renewed focus.

Over the past year, we have also had to make changes and adaptations. With great sadness, we made the decision to postpone the 2020 Washington University NF Center Research Symposium until it is safe for us all to gather again in person. In the clinic, we are now using telemedicine to care for our families with NF, while in the research laboratories, we have established ways to remain productive through virtual laboratory meetings and streamlined operations.

ADVANCING CLINICAL CARE

On a very positive note, this year witnessed the first Federal Drug Administration (FDA)-approved drug for Neurofibromatosis Type 1 (NF1). Based on promising studies spearheaded by Dr. Brigitte Widemann at the National Cancer Institute, the MEK inhibitor, Selumetinib, is now available to treat children and adults with growing plexiform neurofibromas.

In addition, we have seen remarkable progress in our understanding and management of brain tumors in people with NF1. Dr. Jasia Mahdi recently published a study on brain tumors in children with NF1 arising in locations other than the optic pathway, forming the foundations for future studies to develop practice care guidelines for these tumors. As a part of a larger international team, we also established new recommendations for the management of brain tumors in children and adults with NF1, as well as worked with the World Health Organization and National Institutes of Neurological Disorders and Stroke to update their resources on Neurofibromatosis.

These advances are important for our families whose children with brain tumors are cared for by Dr. Nicole Brossier, our pediatric neuro-oncologist specializing in the treatment of children with NF1-associated brain tumors

ADVANCING NF RESEARCH

In the laboratory, we celebrated the graduation of two star PhD students, Michelle Wegscheid and Xiaofan (Gary) Guo. Dr. Wegscheid is currently completing her medical training at the Washington University School of Medicine, and hopes to become a neurosurgeon-neuroscientist. In her most recent publication, Michelle used human induced pluripotent stem cells to demonstrate that different *NF1* mutations create different defects in human mini-brain development.

Dr. Guo is now a Neurology resident at Loma Linda University in California. Gary's major project was also published this spring, in which he found that *Nf1* optic glioma growth in mice is controlled by interactions between nerves and immune system cells, suggesting potential future avenues for brain tumor treatments. In addition, researchers in the NF Center identified new mutations in high-grade gliomas (Dr. Wing Wong) and malignant peripheral nerve sheath tumors (Dr. Angela Hirbe).

We have also been fortunate to attract several new members to our research team, including Kelly Hartigan (future MD-PhD trainee), Olivia Cobb (staff bioinformatician), Dr. Alex Chen (new postdoctoral fellow), Alice Bewley (bioinformatics student), and Ji-Kang Chen (visiting scientist).

RAISING NF AWARENESS

Using a combination of in-person and virtual tours, visitors to the NF Center learned how laboratory studies have advanced our understanding of the health problems affecting children and adults with NF. Furthermore, the NF Center has been able to pivot and transition all of its Complementary Care programs to a virtual format. Whether providing our toddler's with a virtual Beat NF program, participating in a virtual Club NF session, or continuing our Teen NF program via Zoom meetings; we continue to provide free, high-quality therapy programs to our NF families during these uncertain times.

Sincerely,

David H. Gutmann, MD, PhD, FAAN, FANA
Donald O. Schnuck Family Professor
Director, Washington University NF Center
Vice Chair for Research Affairs, Neurology

RESEARCH GRANTS

PEDIATRIC BRAIN TUMOR FOUNDATION

>> has awarded **DR. DAVID GUTMANN** a three-year drug discovery grant to study pediatric low-grade astrocytomas (PLGAs). This award will allow Dr. Gutmann to develop and characterize a series of human PLGA models that reflect the genetic diversity of these brain tumors in children.

NF1 RESEARCH INITIATIVE (NFRI)

>> awarded **DR. ANGELA HIRBE** a collaborative two-year grant along with Drs. David Largaespada and David Wood at the University of Minnesota, Dr. Christine Pratilas at Johns Hopkins University, and Sara Gosline at Pacific Northwest National Laboratory. The scientists will be using a comprehensive set of patient-derived xenografts they developed to test novel combinations of therapies for malignant peripheral nerve sheath tumors.

ALEX'S LEMONADE STAND FOUNDATION

>> awarded **ELIZABETH CORDELL, MD CANDIDATE** a Pediatric Oncology Summer Training grant to study the relationship between medical conditions and brain tumors. This award will enable Elizabeth to explore how immune conditions alter the tumor microenvironment in NF1 optic gliomas.

THE DEPARTMENT OF DEFENSE

>> awarded **DR. ANGELA HIRBE** a three-year grant to evaluate the utility of the protein TYK2 as a prognostic marker, as well as a therapeutic target in MPNST. Dr. Hirbe's lab will be evaluating novel compounds targeting TYK2 that were developed at Washington University in order to identify better therapies for this aggressive cancer.

ANA TRAVEL & POSTER PRESENTATION AWARD

>> The American Neurological Association (ANA) selected **DR. MICHELLE WEGSCHEID** to receive a travel award to attend the annual meeting to showcase her work demonstrating that patient *NF1* gene mutations have different consequences on mini-brain development. In addition, Dr. Wegscheid was selected as a poster presentation awardee for being one of the top scored poster presenters at the annual meeting.

PATIENT SPOTLIGHT: DANIEL

At six months of age, Daniel Crum was brought to the Washington University NF Clinical Program at St. Louis Children's Hospital and received a diagnosis of Neurofibromatosis Type 1 (NF1). Although both his father and grandfather had signs of NF1, they had gone without a formal diagnosis, and the news came as a shock. The Crum family immediately rallied around Daniel, and began seeing NF specialist, Dr. David H. Gutmann, every six months.

At two and half, Daniel's parents noticed that he had a lazy eye – it was then that he was diagnosed with a brain tumor called an optic pathway glioma (OPG). Through many years of chemotherapy and incredible difficulties, Daniel stayed strong, upbeat, and playful. His parents love that he never stopped playing and loving basketball, even in the midst of his treatments. At nine years old, his tumor stopped growing, reducing Daniel's NF checkups to once a year. Although this was an indescribably difficult time for Daniel and his family, they made it through with their faith and the support of their community. They now try to help everyone they meet better understand NF1 and those who struggle with it.

In spite of his diagnosis, Daniel thrived in middle and high school. Capitalizing on his love of sports, Daniel became involved in his school's basketball, football, and golf teams. Even though his vision was severely impaired, Daniel played golf for all four years of high school, winning an award for being the first blind student to do so. By the time he graduated, he had won two more awards – he was presented with the Rosemary Zander Award for his ability to go above and beyond what was expected of him, and his class of 2013 began a new award in his name, honoring his dedication and strength, called the Crum Perseverance Award.

After graduation, Daniel brought that love of sportsmanship and athletics to his current job at the Enterprise Center. There, he works in Press Dining to feed the numerous reporters, sports writers, cameramen, and retired athletes who come through the center.

Now 24 years old, Daniel absolutely loves his job and excels at every aspect of it. He gets to know each of his customers on a first name basis, and frequently works in other departments when they need extra help. Recently, Daniel got to see and touch the Stanley Cup at an event for season ticket holders, which was incredibly exciting. His parents are so proud of everything he has accomplished, most importantly, his perseverance and fortitude in pursuing his dreams.

DR. MORRIS NAMED SECTION HEAD OF PEDIATRIC GENERAL NEUROLOGY

We are delighted to announce that Dr. Stephanie M. Morris has been named Section Head of Pediatric General Neurology at the Washington University School of Medicine. In her newly appointed position, Dr. Morris will oversee clinical operations for pediatric general neurology. During the past several years, she has been caring for children and young adults with NF as co-Director of the NF Clinical Program at St. Louis Children's Hospital, and has extended her practice into the pediatric general neurology field with her Autism Clinic and as Director of the Fragile X Clinical Program.

Dr. Morris received her pediatric neurology training at Washington University, where she served as the administrative chief resident. Following her residency, she was a clinical research fellow working with Dr. John Constantino (Chief, Child Psychiatry) and Dr. David H. Gutmann (Director, NF Center) to study autism and developmental disabilities in children with NF1.

GUTMANN RECEIVES TWO AWARDS

ADVOCATE OF HOPE AWARD

David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor and Vice Chair for Research Affairs in the Department of Neurology at Washington University School of Medicine in St. Louis, received the Advocate of Hope Award from the National Neurofibromatosis (NF) Network. The NF Network is a nonprofit organization dedicated to helping people living with NF.

The Advocate of Hope Award honors Gutmann for his work in the field of NF and his compassion for NF patients. For more than 25 years, he has devoted his academic career to improving the lives of people with NF, through laboratory and clinical research. He established the NF Clinical Program at St. Louis Children's Hospital in 1994, which serves as a regional referral center for patients. In addition, he founded and directs the Washington University NF Center, one of the world's largest centers focused on accelerating the pace of scientific discovery and its application to the care of individuals with NF.

NEURO-ONCOLOGY AWARD

Dr. Gutmann also received the Abhijit Guha Award from the Society for Neuro-Oncology and the Section on Tumors of the American Association of Neurological Surgeons/Congress of Neurological Surgeons. The award honors an accomplished investigator who has achieved significant results both in the laboratory and in the clinic, and who has played an active role in mentoring the next generation of neuro-oncology professionals.

Dedicating his academic career to genetic causes of childhood brain tumors, specifically the neurofibromatosis (NF) cancer predisposition syndromes, his work on NF has broad implications for neuro-oncology, ranging from defining the cells of origin for these cancers to elucidating the role of immune cells in tumor formation and growth, and in vision loss linked to brain tumors. In addition, Gutmann and his colleagues have leveraged both human stem cells and genetically engineered mice to define the factors that underlie disease risk, with a goal of improving precision medicine for people with brain tumors.

FDA APPROVES FIRST THERAPY FOR CHILDREN WITH NF1

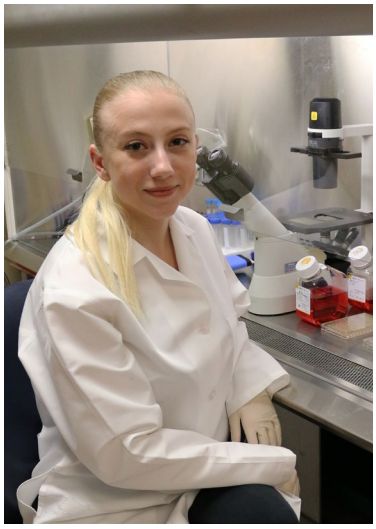
On April 10, 2020, the US Food and Drug Administration (FDA) approved the drug selumentinib (Koselugo) for people with Neurofibromatosis Type 1 (NF1) who are 2 years of age and older. The first of its kind drug will be used to treat symptomatic, inoperable plexiform neurofibromas. These tumors are often detected in young children, and may involve the eye socket, face, arm, leg, back, chest, or abdomen.

The FDA approval came after a clinical trial conducted by the National Cancer Institute showed that nearly two thirds of patients had a positive response to the drug, with at least a 20% reduction in tumor volume. Of these patients, most had responses that lasted 12 months or longer. However, no patients experienced complete disappearance of their tumor.

> *"These are exciting times for families affected with NF1", says NF Center Director, David H. Gutmann, MD, PhD. "This success is the result of decades of hard work by scientists, physicians, nurses, and patient advocacy groups."*

CORINA ANASTASAKI, PHD & MICHELLE WEGSCHEID, MD, PHD

In the recently published study in *Stem Cell Reports,* Corina Anastasaki, PhD, Michelle Wegscheid, PhD, and colleagues sought to determine whether different *NF1* gene mutations found in patients with NF1 have different effects on human brain cells. To achieve this, the authors used seven human induced pluripotent stem cell lines with different NF1 patient *NF1* gene mutations to grow different brain cell types, both as individual cell types, like nerve cells (neurons), but also as three-dimensional (3D) mini-brains (cerebral organoids). They definitively showed that while all mutations increased the production of support cells (astrocytes), mini-brains with different *NF1* mutations produced different numbers of neurons. This study opens the door to future investigations into how different *NF1* mutations cause different features in people with NF1.



A YEAR OF GROUNDBREAKING RESEARCH

During 2020, researchers in the Washington University NF Center made many groundbreaking discoveries. Additionally, we continue to expand the resources required to make these advances, including the NF1 Genome Project (~570 patient DNA samples), NF1 Clinical Research Database (~805 patients enrolled), and the NF1 Brain Trust (~32 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.

JASIA MAHDI, MD

Neurofibromatosis Type 1 (NF1) is one of the most common cancer predisposition syndromes, where children are prone to develop low-grade brain tumors. In order to better define the MRI features and natural history of non-optic pathway tumors (non-OPTs) in children with NF1, Dr. Jasia Mahdi conducted a retrospective cross-sectional analysis of 64 children with NF1 harboring 100 non-OPTs. Their findings showed that the majority of non-OPTs grew over time and caused medical problems. In addition, she also identified a small subset of children with a particularly aggressive form of brain tumor, which tended to arise in younger children. The researchers hope that these findings will improve the recognition and management of children with NF1.

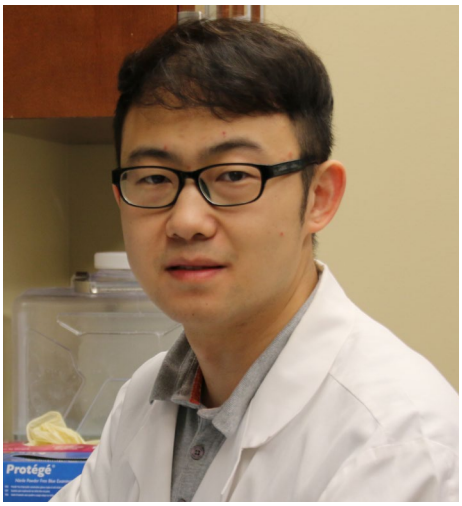
Currently, Dr Mahdi is a Beverly and Bernard Wolfe Fellow in Pediatric Neuro-Oncology at Stanford University & Lucile Packard Children's Hospital.

WING H. WONG, PHD

In a recent publication, spearheaded by Dr. Wing H. Wong, a former graduate student in Dr. Todd Druley's laboratory, in collaboration with NF Center director, Dr. David H. Gutmann, identified a new gene involved in the formation of malignant brain tumors, called glioblastomas, in people with NF1.

In this study, they performed whole-exome sequencing on multiple brain tumor samples from a young man with NF1 who died of a glioblastoma. Using this approach, they found that mutations in the *KMT2B* gene were the likely the cancer-causing genetic events in this young man. KMT2B belongs to a family of proteins that package DNA in the nucleus and are important for turning on and off the activity of DNA. Future research is aimed at understanding how mutations in KMT2B lead to brain cancer, especially in young adults with NF1.

XIAOFAN GUO, MD



Children with the genetic condition Neurofibromatosis Type 1 (NF1) can develop brain and nerve tumors. If a tumor develops within the optic nerve, which connects the eye and the brain, the child may lose his or her vision.

New research at Washington University School of Medicine in St. Louis indicates that the growth of these brain tumors is driven by nearby non-cancerous neurons and immune cells, and that targeting immune cells slows tumor growth in mice. The findings, published May 1 in *Nature Communications,* point to new potential treatments for low-grade brain tumors in people with NF1.

"The fact that nerve cells and immune cells interact to support a tumor is a new way of thinking about how tumors develop and thrive," said senior author David H. Gutmann, MD, PhD, FAAN, the Donald O. Schnuck Family Professor of Neurology and director of the Washington University Neurofibromatosis Center. "These tumors are arising in the nervous system, but until recently, few people had considered that the nerve cells themselves could be playing a role in tumor development and growth. These findings show that we have to consider nerve cells as participants, if not essential drivers, of cancer development."

NF1 affects about one in every 3,000 people. It is caused by any one of a variety of mutations in the *NF1* gene. While people with NF1 usually come to medical attention for birthmarks on their skin, nearly one in five children with NF1 will develop a brain tumor on the optic nerve, called an optic glioma.

To better understand what drives the development and growth of these brain tumors in people with NF1, first author Xiaofan Guo, MD, a graduate student in Gutmann's research laboratory, and colleagues studied mice with *Nf1* mutations and optic gliomas. The team previously had discovered that the tumor cells in optic gliomas are interspersed with immune cells that help drive tumor formation and growth. But there is also another cell type in the vicinity of the tumor: neurons.

Suspecting that neurons also might be contributing to tumor growth, the researchers examined human neurons with *NF1* mutations that had been grown from stem cells. They discovered that the neurons release a protein that activates immune cells, known as T cells, which then produce proteins that ultimately promote the growth of tumor cells. The findings jibe with data from people with low-grade gliomas. By analyzing two publicly available datasets, the researchers found that patients whose tumors had more of a kind of T cell, known as CD8+ T cells, had reduced overall survival.

Disrupting the communication between neurons, T cells and tumor cells potentially could slow the growth of tumors, the researchers said. In the new study, they removed T cells from mice with optic gliomas, or prevented T cells from getting into the brains of such mice. In both scenarios, the researchers found that the optic gliomas grew more slowly in the absence of T cells.

"What we have here is a new way of thinking about how neurons and immune cells interact to control tumor growth, adding important new insights to the emerging field of cancer neuroscience," Gutmann said. "We are excited about harnessing these critical interactions to develop new therapeutic strategies for childhood brain tumors."

- Written by Tamara Bhandari, Washington University School of Medicine – The Record

THE "EMERGING FIELD OF CANCER NEUROSCIENCE"

As an outgrowth of a seminal meeting at the Cold Spring Harbor Laboratory Banbury Center in December 2019, a white paper contributed to by Dr. David H. Gutmann, outlined the new field of "cancer neuroscience".

This emerging scientific discipline is built upon the idea that the nervous system normally controls the development, maintenance and plasticity of numerous organs throughout the body. However, the importance of nerve cells (neurons) to cancer is only just beginning to be appreciated. At this Banbury meeting, investigators studying a variety of different cancers showed that cancer formation, growth, and spread can be controlled by neurons.

The growing understanding of the importance of nerves to cancer is especially relevant to Neurofibromatosis, where most of the tumors arise in close association with nerves. Ongoing work in the Washington University NF Center is currently examining the key role of neurons in optic glioma and neurofibroma formation and growth.

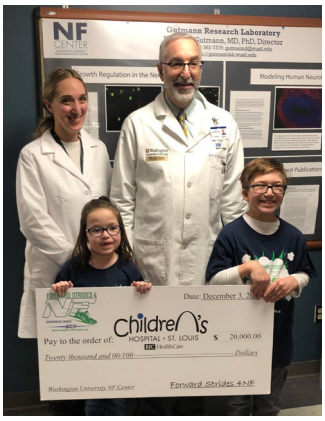
SUPPORT BEYOND THE CLINIC

PATIENT ENGAGEMENT

Our patients and their families are critical to the NF Center mission of providing exceptional care through groundbreaking research. Because of their generosity, we are able to conduct cutting-edge investigations and provide outstanding complementary care resources.

FuNFest is a family-friendly festival designed to promote awareness about NF and to raise funds for NF research. The event includes games, obstacle course, music, a live auction, and silent auction bidding.

FuNFest raised money to support laboratory research focused on developing personalized medicine approaches for people with NF1. The Washington University NF Center extends its heartfelt gratitude to Amanda and Brian Walk, who worked tirelessly to plan and direct this event.



Forward Strides 4NF is a charity started in 2016 by Gina Wilburn to honor her daughter and husband, who both have Neurofibromatosis Type 1 (NF1). This year the committee celebrated their 5th anniversary with a Superhero theme, and hosted over 200 registered walkers, with more than 30 volunteers. Entertainment at the event included an obstacle course slide, music, food and beverages donated from local restaurants, as well as superhero mascots to cheer participants at the finish line. Additionally, both a raffle and silent auction, which included many amazing items, have proven to be huge attractions every year.

The Washington University NF Center extends its warm gratitude and congratulations to the Forward Strides 4NF committee on their largest yearly fundraising total to date.

COURTNEY'S CORNER

Courtney Dunn is a physical therapist with over 25 years of experience in providing therapy services for children. She earned her Bachelor of Physical Therapy from the University of Missouri, Columbia in 1995 and her Doctorate of Pediatric Therapy in 2010. Courtney is currently part of the Washington University Neurofibromatosis (NF) Center team and is the Outpatient Therapy Manager at Ranken Jordan, a pediatric bridge hospital. Through Courtney's Corner Blog on the NF Center website, she will be exploring a variety of topics that support children with NF achieve the best version of themselves.

Courtney has provided therapy for children in a variety of settings, including inpatient rehabilitation, outpatient therapy, home health, early intervention, school settings, and in multidisciplinary clinics. Since joining the NF Center in 2010, she has spearheaded several clinical research studies examining motor skills in children with NF1.

Courtney's approach to PT involves treating the whole child: addressing sleep patterns, sensory modulation, strength, muscle balance, and coordination to support developing a healthy and active lifestyle. In this regard, Courtney has collaborated with members of the NF Center to create community-based complementary care programs. Beat NF, for preschool-aged children and Club NF, for school-age children, provide motor and social development through community partnerships throughout the St. Louis region.

COMPLEMENTARY CARE PROGRAMS

At the Washington University NF Center, we believe that the care of our families extends beyond the walls of the hospital. To supplement our medical services at St. Louis Children's Hospital, we have partnered with the St. Louis Children's Hospital Foundation and Jazz St. Louis to create complementary care programs for all age groups that address the ongoing needs of children with NF1.

BEAT NF (Ages 2 – 5 years)

Together with Jazz St. Louis education staff, the Washington University NF Center has developed this one-of-a-kind therapy program that specifically focuses on frequently delayed skills in young children with NF1. During each session, professional jazz musicians play live music, while the children review social engagement rules as a group, learn about a "mystery instrument", and engage in gross and fine motor therapy. Educators and musicians from Jazz St. Louis compose and play original music expressly written for these activities. In addition, Beat NF Team members carefully design each week's program to work on particular social and motor delays in toddlers with NF1.

During each session, toddler participants enjoy five weeks of a jazz music motor therapy curriculum utilizing jazz music and physical therapy to promote social, attention, and motor skills in toddlers with NF1, while also fostering healthy parent-child interactions, peer relationships, and jazz appreciation.

CLUB NF (Grades K – 8)

Through our partnership with St. Louis Children's Hospital, the Washington University NF Center proudly provides Club NF as a free, bimonthly, play-based therapy program for children with NF1. Each event is designed to address a specific set of skills often delayed in school age children with NF1. While the children are working on those skills with their therapists, parents have the opportunity to speak with NF specialists to learn more about NF1 and to implement the strategies used in Club NF activities.

Club NF aims to empower families and children with NF1 through the use of play-based therapy and education. By creating a safe, fun environment, families with NF1 learn more about this condition, as well as understand how to foster healthy communication and interactions with peers. Past Club NF events include: Schnucks Cooking School, Game Design, Glass Blowing, Penguin Encounters at the St. Louis Zoo, Dancing, and Ice Skating.

TEEN NF (Ages 13 – 18 years)

Our Teen NF program, led by St. Louis Children's Hospital Psychologist Dr. Kimberly Sirl, is open to all teenagers with NF1, with the objective of fostering positive interpersonal relationships at home, at school and in the community. Focusing on common challenging social situations that teens encounter, the goal of this program is to further social and conversational skills, encourage appropriate selection of friends, learn to read social cues, and enter/exit conversations with peers. Additionally, the program has been expanded to include peer support, social gathering opportunities used to practice learned social skills, and leadership development through volunteer opportunities.

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As we celebrate our successes in 2020 and look forward to 2021, we want to thank everyone who has supported our mission. We are particularly indebted to our partners at the St. Louis Children's Hospital Foundation and Schnuck Markets Inc.
Washington University NF Center 2020 Annual Report created and designed by Jennifer N. Traber.