TABLE OF CONTENTS

MESSAGE FROM THE DIRECTOR
Learn how the NF Center is providing exceptional care through groundbreaking research, as highlighted by NF Center Director, David H. Gutmann, MD, PhD.

RESEARCH GRANTS
Groundbreaking research requires funding from numerous sources, including the federal government, private foundations, and individual donors. We appreciate the generous support we have received from each of these important sources over the past year.

PROVIDING EXCEPTIONAL PATIENT CARE
Discover the difference that the patient care team at the NF Center Clinical Program at Barnes-Jewish Hospital and St. Louis Children’s Hospital is making in the lives of our patients and their families.

A YEAR OF GROUNDBREAKING RESEARCH
Get a first-hand look at the discoveries made by NF Center researchers and their collaborators, and learn more about early-phase findings that bring us closer to offering personalized care for individuals with NF.

SUPPORT BEYOND THE CLINIC
Explore the array of NF Center complementary care programs we offer for children with NF1, providing outstanding care beyond the clinic walls, and supporting patients from early childhood through adulthood.

PAGES 3 - 4

PAGES 5 - 6

PAGES 7 - 8

PAGES 9 - 10
ADVANCING CLINICAL CARE
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In addition, Dr. Angela Hirbe and her colleagues have made seminal advances in the genetics and early detection of cancers in adults with NF1. She and Dr. Aadel Chaudhuri performed the first integrated molecular and clinical analysis of low-grade brain tumors in children with NF1, providing a clear picture of the genetics of these common pediatric cancers. Similarly, Dr. Gutmann and his colleagues worldwide have contributed to the establishment of revised criteria for NF1 and Legius syndrome – an important milestone in providing uniform standards for the diagnosis of these conditions.

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As we conclude our second year of physical distancing, wearing masks, and adapting to virtual interactions, we reflect back on how much we have accomplished in the face of adversity and change. In the Washington University NF Center, we have developed new programs, made impactful research advances, and expanded our clinical care team.

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PATIENT SPOTLIGHT: CARTER HOSS

Carter prefers to be active and outside, playing baseball, basketball, soccer, and nerf games with his little brother. He always looks forward to fishing with his grandpa or baking with his grandma, and has a particular passion for meeting new people and trying new things. He is a reliable friend to his classmates, often standing up for his peers in the face of bullying and serving as a go-to resource for anyone who needs a laugh. When Carter’s little brother was nervous for his first day of Kindergarten, Carter reassured him, wisely remarking that everyone has to start somewhere. His mom describes him as “ready to defeat the world.”

It was that caring and go-getter attitude that spurred Carter’s participation in Walk 4 NF. Walk 4 NF is an annual fundraising event held in several midwestern locations. Its mission is to end NF by funding research and raising awareness. Participants put together their own fundraising teams before coming together to walk, enjoy live music, hear speeches, and connect with other members of the NF community. Carter’s team, called Carter’s Cardinals, first participated in Walk 4 NF in 2020. Though that event was virtual, Carter hugely enjoyed the strong sense of community and belonging it generated and was super excited to be featured in an official NF Midwest video played at the event’s conclusion.

For the 2021 Walk 4 NF, held in Columbia, MO, Carter increased his fundraising goal, motivated both by the opportunity to help the NF community and his ambition to outdo himself. Not only did Carter meet his goal, but he also won second place in fundraising overall, raising more than twice his original objective. Additionally, he interacted with over 200 people in the NF community - he loved talking with a diverse group of individuals affected by NF, especially those older than him, with wisdom to share. Carter’s parents particularly enjoyed talking to other parents of children with NF, exchanging stories and advice. Carter and his family are determined to continue their participation in Walk 4 NF for years to come – where Carter will focus on raising a little bit more every year.

For Carter and his family, the joy of participation in both Walk 4 NF, and Club NF comes from the sense of community present in these events and the feeling of accomplishment that they offer. Carter walks away knowing that he produced tangible change, that he actually did something, and that he is never alone in doing so. For these reasons, the Hoss family strongly encourages all families affected by NF to get involved, both in these events and in all others like them. As put by mother, Moriah, knowing that the money goes “toward something near and dear to our hearts” is the ultimate reward.

Carter Hoss is a goofy, caring, and fun-loving sixth grader. He has also raised over $1500 to benefit NF Midwest through participation in the organization’s annual Walk 4 NF event. Both aspects of Carter stem from his drive to constantly improve himself and the world around him, always on a mission to help however he can.

Carter first visited the Washington University NF Clinic Program at St. Louis Children’s Hospital as a toddler after his pediatrician referred him to Dr. David H. Gutmann. At this time, he received a diagnosis of NF1. Since then, Carter has been an enthusiastic participant in Club NF, the Washington University NF Center’s school-aged free therapy program – he has enjoyed going ice-skating and swimming in particular.

INTERNATIONAL EXPERTS REVISE THE NF1 DIAGNOSTIC CRITERIA

A collaboration of international experts has recently reached a consensus for revising the diagnostic criteria of NF1. The method for determining the new measures included a Delphi method involving global experts. Additionally, non-NF experts, patients, and advocacy groups were invited to participate in the evaluation process. The consensus results have determined the minimal clinical and genetic criteria to diagnose NF1 and Legius Syndrome. This report was published in Genetics in Medicine.

PROVIDING EXCEPTIONAL PATIENT CARE

NF CENTER AND CHILDREN’S TUMOR FOUNDATION (CTF) SYNODOS TEAM PUBLISH LANDMARK GENOMIC STUDY OF NF1 BRAIN TUMORS

Dr. Michael Fisher at Children’s Hospital of Philadelphia and Dr. David Gutmann from the Washington University NF Center spearheaded an internal consortium effort to define the genetics of low-grade brain tumors in children with NF1.

In their study, involving 25 centers worldwide, they characterized the genetic changes seen in these tumors, and analyzed the importance of these alterations to patient outcome. Low-grade gliomas from 70 children with NF1 were studied, revealing additional genetic changes beyond NF1 gene mutation. One of these changes involving a mutation in the fibroblast growth factor receptor (FGFR1) was shown to increase the growth of NF1-mutant mouse tumor cells.

This report was recently published in Acta Neuropathologica.
MICHELE WEGScheid, MD, PhD
Neurodevelopmental disorders are often caused by losses of large pieces of chromosomes containing many genes. This is also true for a subset of individuals with Neurofibromatosis type 1 (NF1) who have severe developmental delays and intellectual disabilities. These NF1 patients often harbor a large deletion involving the NF1 gene on chromosome 17q11.2, termed a total gene deletion (NF1-TGD).

To understand why children with this chromosomal deletion have such profound neurodevelopmental deficits, Dr. Michelle Wegscheid, a former MD-PhD student in the laboratory of Dr. David Gutmann, teamed up with her colleagues in the NF Center to use patient-derived human induced pluripotent stem cells (hiPSCs) to generate a neural progenitor cell line (CRLF3) or “mini-brains.”

In a new report recently published in the journal Cell Reports, Dr. Wegscheid, along with Dr. Corina Anastasaki, Kelly Hartigan, Olivia Cobb, Jennifer Traber, and Dr. Stephanie Morris, identified both neural stem cell growth and neuronal maturation abnormalities in NF1-TGD hiPSCs. While the increased NSC proliferation resulted from decreased NF1/RAS regulation, they showed that the neuronal differentiation, survival and maturation defects were caused by decreased expression of a gene called cytokine receptor-like factor 3 (CRLF3).

Importantly, they demonstrated a higher autism burden in NF1 patients harboring a mutation in the CRLF3 gene, thus establishing CRLF3 as a new causative gene within the NF1-TGD locus responsible for hCOs brain abnormalities and autism in children with NF1.

A YEAR OF GROUNDBREAKING RESEARCH
During 2021, 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 (~589 patient DNA samples), NF1 Clinical Research Database (~820 patients enrolled), and the NF1 Brain Trust (~35 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.

NICOLE BROSSIER, MD, PhD
In a recent study published in the journal of Clinical Investigation, Dr. Lu Le, Professor of Dermatology at the University of Texas-Southwestern, joined forces with Drs. Corina Anastasaki and David Gutmann at the Washington University NF Center to develop a human model of neurofibromatosis. By taking advantage of human stem cell engineering methods, called CRISPR, the team developed a series of NF1 patient-specific human induced-pluripotent stem cell (hiPSCs) lines that they used to create human Schwann-like cells. They found that implanting human NF1 Schwann-like cells in the nerves of mice resulted in the formation of bona fide tumors; those kept in the dark during a critical period of development did not.

As part of this study, the researchers used mice with mutations in their NF1 gene. Such mice start developing low-grade tumors of their optic nerves around 9 weeks of age, and virtually all have tumors by 12 weeks to 16 weeks old. Since the neurons in the optic nerve become active when exposed to light, the researchers investigated whether they could reduce neuronal activity — and, thereby, tumor formation — simply by keeping the mice away from light. They raised mice from age 9 weeks to 16 weeks in the dark and then checked for tumors. Further experiments verified the crucial role of light exposure and narrowed down the critical window to age 6 weeks to 12 weeks. None of the mice reared in the dark during that time frame developed tumors by 24 weeks of age. Putting mice older than 12 weeks, when the tumors already had formed, into darkness slowed tumor growth but did not shrink them.

First author Yuan Pan, PhD, who first worked with Gutmann at Washington University and is now a postdoctoral researcher with Monge, showed that the link between light and tumors requires a protein called neurologin 3. When their optic nerves are stimulated, mice with NF1 mutations release abnormally high levels of neurologin 3. Blocking the protein with a drug or genetically modifying mice to eliminate the neurologin 3 gene resulted in fewer and smaller tumors.

“All of this is teaching us that we may have ignored one really important cell type in nervous system cancers: the neuron,” said co-lead author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology at Washington University and the director of the university’s NF Center. “As neurologists, we have been treating overactive neurons for decades with drugs. One of the directions our laboratories are pursuing is repurposing some of those drugs to see if we can shut off unwanted activity, maybe just for a short developmental period, and prevent brain tumors from forming. And there are other points at which we could intervene as well: by limiting light exposure, by targeting neurologin 3 or inhibiting some other step in the pathway. It has really opened our eyes.”

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SUSAN E. MALONEY, PhD
As part of an investigation into shared motor impairments across genetic liabilities for intellectual and developmental disorders (IDDs) by Maloney and Joseph Dougherty, in collaboration with the Gutmann laboratory, recently discovered altered gait development in mice harboring a patient-derived NF1 gene mutation. This new study conducted a comprehensive analysis of gait across a critical developmental window in which gait matures in the mouse model. NF1 mutant mice exhibited altered spatial, temporal, and postural subcomponents of gait compared to their control littermates, which persisted into adulthood. In addition, the pattern of disruption to gait development in this NF1 model was also observed in a mouse model of Williams Syndrome, another IDD that features motor deficits. Overall, their findings indicated that IDDs may share features of atypical gait yet differ in resolution or persistence of these abnormalities. Therefore, gait may serve as a helpful outcome variable in studies of therapeutic efficacy in the long-term treatment of IDDS.
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, Jazz St. Louis, and the St. Louis Science Center 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 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 virtual Club NF events include: Schnucks Cooking School, Katmai National Park Ranger Talk and JR Ranger Badge, and JR Vet Lab with the Loggerhead Marinelife Center.

TEEN NF (Ages 13 – 18 years)
Our Teen NF program, led by St. Louis Children's Hospital neuropsychologist 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/exist conversations with peers. Additionally, the program has been expanded to include peer support, social interaction opportunities used to practice learned social skills, and leadership development through volunteer opportunities. Partnering with the St. Louis Science Center, Teen NF also offers Life Skills and Career Building classes to help prepare patient families for adulthood.
As we celebrate our successes in 2021 and look forward to 2022, 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 2021 Annual Report created and designed by Jennifer N. Traber.