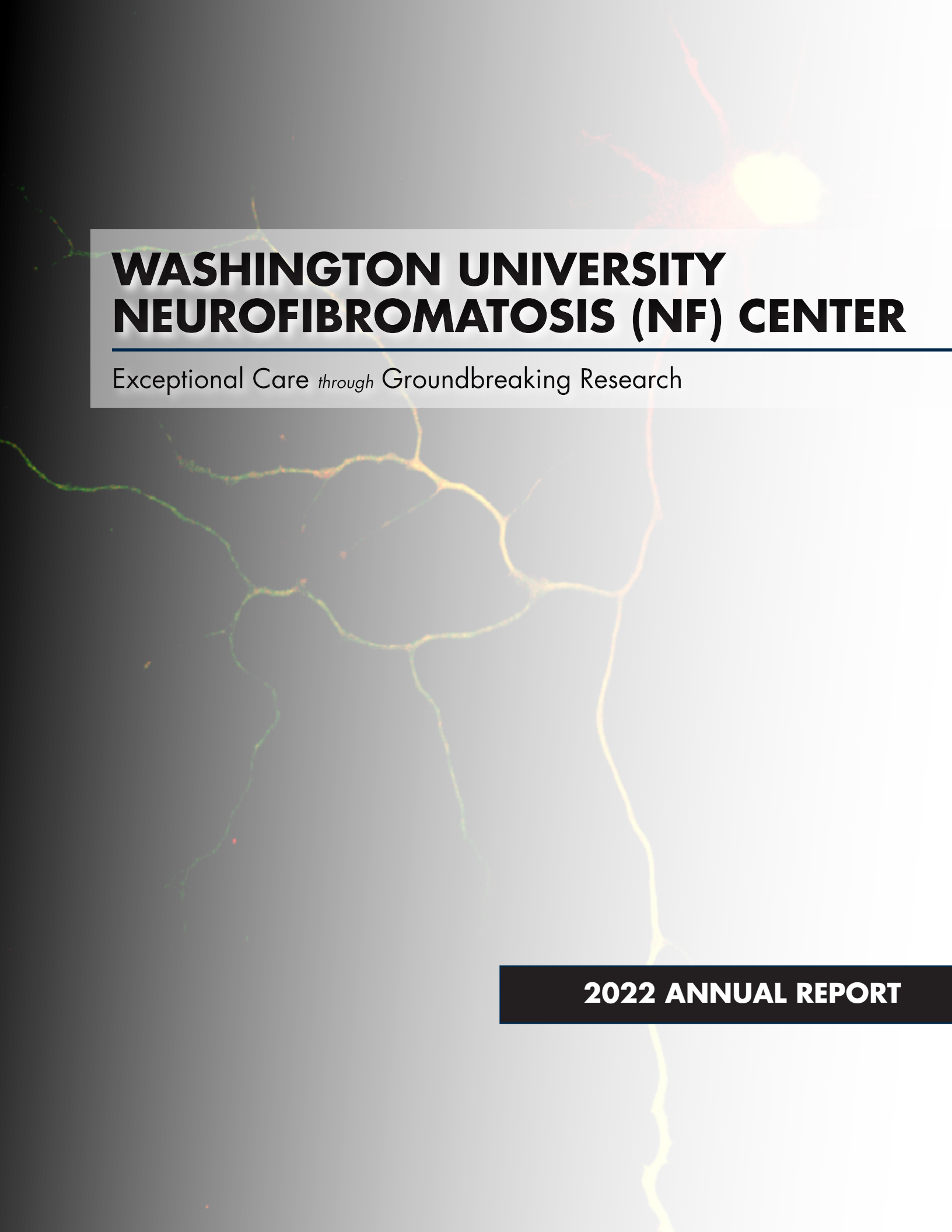
# WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research



## 2022 ANNUAL REPORT

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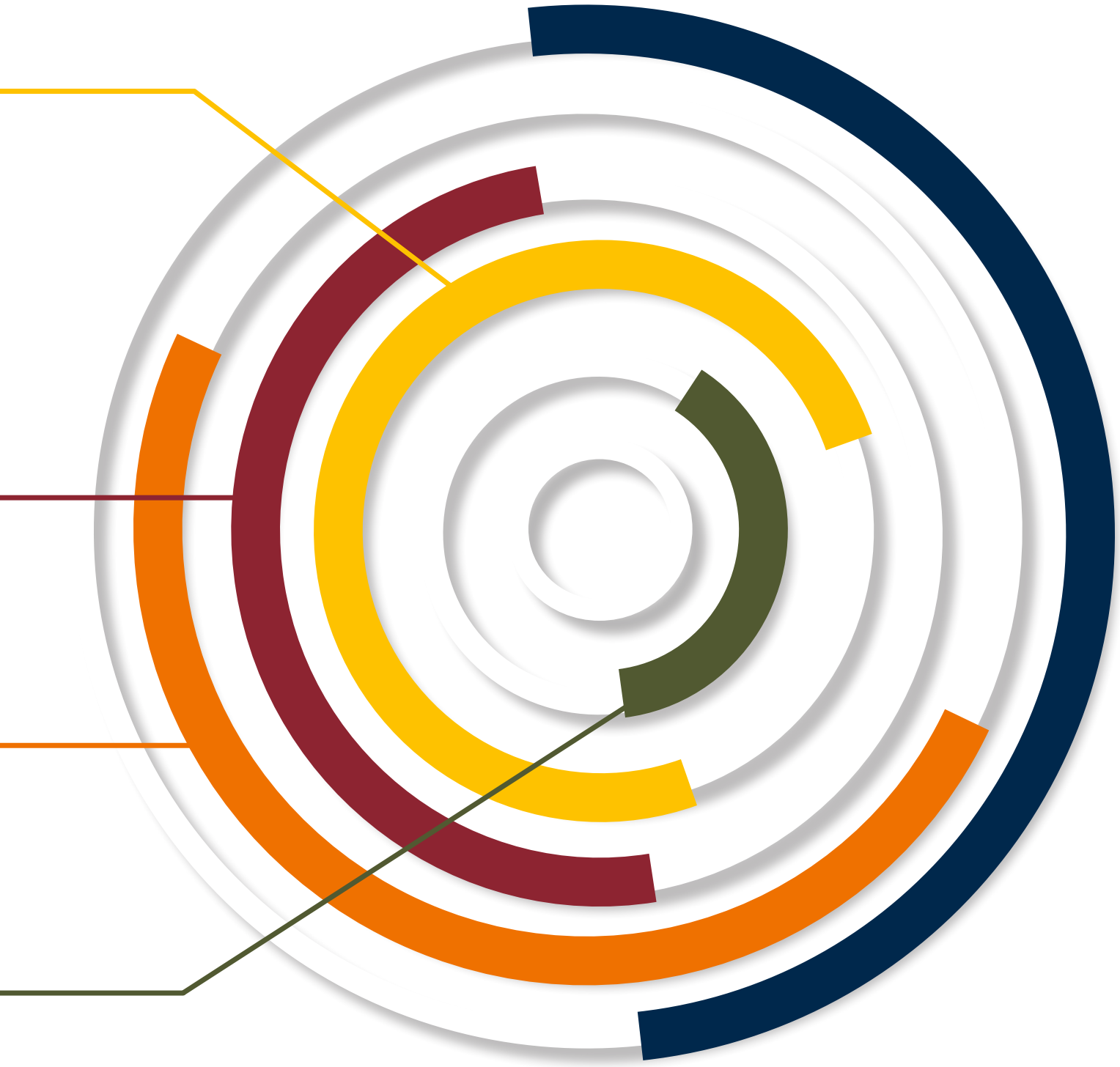


# MESSAGE FROM THE DIRECTOR

It has been another exciting year for us in the Washington University NF Center. We have recruited several new members to our clinical and research teams, and made a number of seminal advances in both the clinic and the laboratory.

## ADVANCING CLINICAL CARE

This year, we welcomed Dr. Sheel Pathak, Assistant Professor in Neurology, to our clinical care team. As a pediatric neurologist, Dr. Pathak brings tremendous experience in developmental delays and autism. Together, Dr. Pathak and I will be training a new future member of our clinical team, Dr. Nino Kerashvili. Dr. Kerashvili is an expert in the care of both children and adults with neurologic problems. Following the completion of her neurogenetics training, she will spearhead the development of our transition to adult care program. In addition, Madeline (Maddy) Scherr joined the NF Center as our NF Center Coordinator. She is working closely with our community partners to expand Music Heals, Club NF, and Totally TEEN activities. Under her leadership, we have begun to optimize our NF clinical hospital-based and out-of-hospital resources.

In addition, Dr. Angela Hirbe and her colleagues have made seminal advances in the genetics of cancers in adults with NF1. She found that one of the earliest genetic changes in malignant peripheral nerve sheath tumor (MPNST) development involves a gain of chromosome 8. Working with a large international team, Dr. Gutmann contributed to the establishment of revised criteria for NF2 and Schwannomatosis – an important milestone in providing uniform standards for the diagnosis of these conditions. Ms. Kyra Rosen, a former Washington University NF undergraduate scholar, examined the reasons why children do not return for their recommended follow up appointments in the NF Clinical Program. Additionally, in collaboration with our colleagues in the Institute for Informatics at Washington University, we employed machine learning to identify predictive risk factors for optic glioma and attention deficit.

Lastly, together with Drs. Mohamed Abdelbaki, Chief of Pediatric Neuro-Oncology, and Margaret Shatara at St. Louis Children's Hospital, we have expanded our international virtual NF tumor board to provide consultations on clinical management for colleagues in seventeen different countries worldwide.

## ADVANCING NF RESEARCH

In the laboratory, there were many exciting advances. Drs. Amanda Costa and Jit Chatterjee used single cell RNA sequencing to identify the non-cancerous cells in *Nf1* mouse optic gliomas, and leveraged these findings to show that blocking immune cell function during tumor evolution completely blocks optic glioma formation. In addition, Dr. Chatterjee worked with Dr. Michael Holtzman, an expert in asthma, to reveal that asthma blocks *Nf1* mouse optic glioma formation. His detailed study uncovered the mechanism by which asthma changes T cells to damage the lungs, but impairs non-cancerous cell support of brain tumor development.

Based on our landmark study last year with Drs. Michelle Monje and Yuan Pan at Stanford showing that nerves can control *Nf1* optic glioma formation in mice, Dr. Corina Anastasaki demonstrated that neurons are also important for continued tumor growth. This most recent study revealed that *Nf1*-mutant neurons are more excitable than normal neurons, and that blocking their hyperactivity reduces the production of a key molecule critical for *Nf1* optic glioma progression. She also identified a new growth factor made by *NF1*-mutant neurons that controls neurofibroma growth. Combining these observations, Dr. Anastasaki demonstrated that repurposing a drug used to treat epilepsy in children reduced the growth of both *Nf1* mouse optic gliomas and plexiform neurofibromas.

We have also been fortunate to recruit several new trainees to our research team, including Anna Gabrielsen (future neuroscience PhD trainee), Ethan Hillis (MSBIS graduate student), and four new Washington University NF undergraduate scholars (Chloe Kernan, Hannah Wang, Lara Marco Y Marquez, and Karen Gao). The NF Scholars Program was made possible by generous support from ForwardStrides4NF. Lastly, we also congratulate Dr. Stephanie Morris, former Pediatric NF Clinical Program Director, on her new position at the Kennedy Kreiger Research Institute in Baltimore.

Sincerely,

David H. Gutmann, MD, PhD, FAAN, FANA
Donald O. Schnuck Family Professor
Director, Washington University NF Center

# RESEARCH GRANTS

## • NATIONAL CANCER INSTITUTE

Awarded **Dr. David Gutmann** a five-year grant to study how nerve cells control optic glioma formation and growth in collaboration with Dr. Michelle Monje at Stanford University.

## • HOPE CENTER

Awarded **Dr. Terence Kummer** and **Dr. David Gutmann** a two-year grant to explore the link between brain injury and brain tumor formation.

## • GILBERT FAMILY FOUNDATION

Awarded **Dr. David Gutmann** a three-year grant to develop new humanized models of malignant brain tumors arising in young people with NF1.

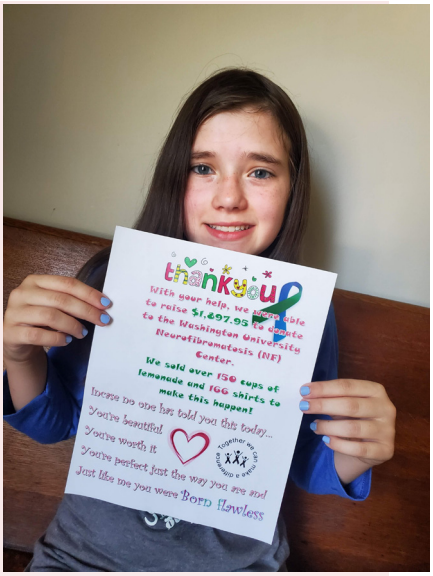
## • DEPARTMENT OF DEFENSE

Awarded **Dr. Angela Hirbe** a three-year grant to examine the role of chromosome 8 loss in NF1 malignant peripheral nerve sheath tumor formation and progression.

## • GILBERT FAMILY FOUNDATION

Awarded **Dr. David Gutmann** a three-year grant to investigate why children with NF1 lose vision from optic gliomas.

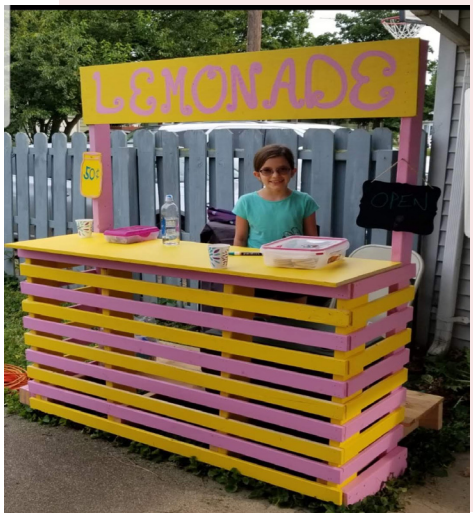
# PATIENT SPOTLIGHT
## *MARLI JOHNSON*




Marli was 6 months old when I (her mom) discovered her first café-au-lait spot. I took her to our pediatrician, Dr. Jennifer Hulsen, who promptly checked Marli head to toe for other café-au-lait spots and freckling in her underarms and groin, while explaining NF and the potential for a diagnosis. At that time, Marli only had a couple café-au-lait spots, and no freckling or other signs or symptoms that would point to NF. Dr. Hulsen decided, at that time, that the best course of action was watchful waiting. For the next couple of years, we kept a careful eye on her integumentary system for potential progression. Around the age of three, Marli had approximately 12 café-au-lait spots and Dr. Hulsen suggested that we see Dr. Gutmann at the Washington University Neurofibromatosis (NF) Center.

The NF Center team has always been so excellent with Marli Grace! "Everyone is so nice. I like how they make me feel so comfortable," says Marli. Early on, the team recognized her ankle pronation and immediately helped us order the appropriate orthotics. They have also been great with referring to physical therapy to help her find relief and new ways to build her core strength. She always looks forward to coming and seeing everyone in the NF Center. You all, especially Dr. Gutmann, make her feel like she is the only patient in the office. The care, attention, and love that she receives from the NF Center team lights up her heart in such a special way.

Since receiving her NF diagnosis, we have been so fortunate that Marli has not had severe or debilitating challenges. Her biggest issues have been ankle, knee, and hip pain that is aggravated with activity. This has made her apprehensive to pursue some endurance sports that interest her. Marli would argue that her biggest challenge is her short stature; however, we think she is perfect! She does experience social anxiety which is finally slowly improving.




When Marli was in 3rd grade, she filled out a paper that prompted her to write out her goals for the next five years and her lifetime. We were elated to see that she had written down that she wanted to "raise money for other kids with NF." She has stayed true to that goal. Currently, Marli and I have been making badge reels out of medicine bottle caps, as well as hosting a lemonade stand to help support the fight towards ending NF. As she grows, Marli wants to continue to raise money for NF research and to raise awareness within our community and beyond. She indicates, "I want to be known at St. Louis Children's Hospital as someone who has helped others with NF". She ultimately wants to inspire others to step outside of their comfort zone and find confidence in what makes them unique. "I want to be successful...to have a good job, and a healthy, happy family," says Marli.

*Written by Stevi Johnson (Marli's mother)*

## INTERNATIONAL EXPERTS REVISE THE NF2 AND SCHWANNOMATOSIS DIAGNOSTIC CRITERIA

A collaboration of international experts has recently reached a consensus for revising the diagnostic criteria of NF2 and Schwannomatosis. The strategy used 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 necessary to diagnose NF2 and Schwannomatosis.

## GUTMANN INDUCTED INTO THE ASSOCIATION OF AMERICAN PHYSICIANS

David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor and Director of the Neurofibromatosis Center at Washington University, was inducted into the Association of American Physicians (AAP). The AAP is an honorary medical society founded in 1885 by Sir William Osler for "the advancement of scientific and practical medicine". Election to the AAP is an honor extended to physicians with outstanding credentials in basic or translational biomedical research. Dr. Gutmann was inducted for his contributions to neurofibromatosis and related disorders at the 2022 joint American Society for Clinical Investigation/AAP meeting in Chicago.

## DR. CORINA ANASTASAKI PROMOTED TO ASSISTANT PROFESSOR

Corina Anastasaki, PhD, was promoted to the rank of Research Assistant Professor in the Department of Neurology at the Washington University School of Medicine. Dr. Anastasaki obtained her PhD from the University of Edinburgh before completing her postdoctoral research fellowship in the laboratory of David Gutmann.

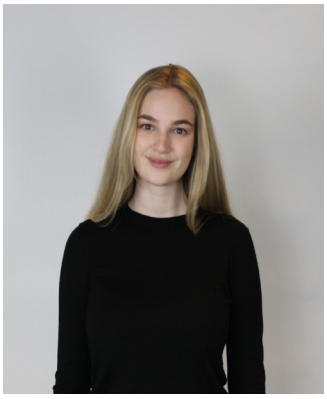
During her postdoctoral fellowship training, she pioneered the use of human induced pluripotent stem cells to study NF1. Dr. Anastasaki has made numerous advances using this technology, including identifying abnormalities in human brain development and a new gene involved in autism, as well as developing the first humanized mouse models of brain and nerve tumors in NF1. Dr. Anastasaki will continue to lead our efforts to understand human brain and tumor development in her new role in the Washington University NF Center.

## THE NF CENTER WELCOMES FACULTY MEMBER: DR. SHEEL PATHAK

Dr. Pathak, MD, is an Assistant Professor of Pediatrics and Neurology. He has worked in the St. Louis area in private neurology practice, and as a member of the faculty at Washington University. He has a special interest in treating patients with neurodevelopmental disorders and movement disorders, as well as has experience managing behavioral conditions and disorders of attention. In addition, he will be assisting in the training of future NF clinical member, Dr. Nino Kerashvili, who will spearhead the development of our adult transition to care program. Dr. Pathak currently sees patients for consultation and follow up in the NF Clinical Program at St. Louis Children's Hospital.

# A YEAR OF GROUNDBREAKING RESEARCH

During 2022, researchers in the Washington University NF Center made many groundbreaking discoveries. We continue to expand the resources required to make these advances, including the NF1 Genome Project, NF1 Clinical Research Database, and the NF1 Brain Trust. In addition, we launched a new program aimed at developing humanized mouse models of brain tumors in collaboration with our colleagues in Neurosurgery. These critical resources only exist because of the enthusiastic involvement of our families.



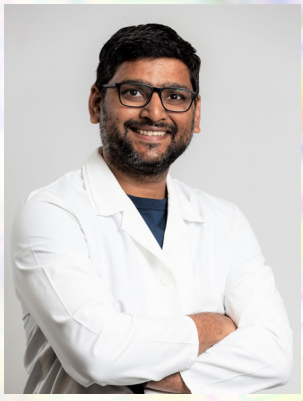
## NF CENTER UNDERGRADUATE EXPLORES PREDICTORS OF PATIENT RETURN

Ms. Kyra Rosen, a recent graduate from Washington University, used mathematical modeling to define the factors that predict patient return to the NF Clinical Program. Using electronic health record data, Rosen was able to identify some of the reasons why children seen in a large NF referral clinic, do not return for their follow up appointments after an initial consultation. She found that children who received a diagnosis of café-au-lait spots only, were from rural areas, were older, or who lived farther from the hospital, were less likely to return to clinic. These findings support the implementation of tailored communication and monitoring interventions to improve the care for children with NF1.

## ADVANCED INFORMATIC METHODS REVEAL NEW INSIGHTS IN NEUROFIBROMATOSIS TYPE 1

Dr. Philip Payne, Director of the Institute for Informatics, and his colleagues, Drs. Aditi Gupta and Randi Foraker, joined forces with Drs. Stephanie Morris and David Gutmann, to use electronic health records data and advanced informatic methods. They were able to develop classification models to predict a diagnosis of optic pathway glioma and attention deficit. This study opens the door to larger explorations across institutions and the potential to create risk assessment algorithms for future use to predict what medical problems might arise in children and adults with NF1.

## ASTHMA MAY REDUCE RISK OF BRAIN TUMORS — BUT HOW?



Dr. Jit Chatterjee, PhD, a postdoctoral fellow, took on the challenge of investigating the association between asthma and brain tumors. Working with co-author Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine and Director of the Division of Pulmonary & Critical Care Medicine, Chatterjee studied mice genetically modified to carry a mutation in their *Nf1* genes and form optic pathway gliomas by 3 months of age. Chatterjee exposed groups of mice to irritants that induce asthma at 4 to 6 weeks of age, and treated a control group with saltwater for comparison. Then, he checked for optic pathway gliomas at 3 and 6 months of age. The mice with asthma did not form brain tumors.

Further experiments revealed that inducing asthma in tumor-prone mice changes the behavior of their T cells. After the mice developed asthma, their T cells began secreting a protein called decorin. In the airways, decorin is a problem. It acts on the tissues that line the airways and exacerbates asthma symptoms. But in the brain, Chatterjee and David H. Gutmann, MD, PhD, discovered that decorin is beneficial. There, the protein acts on immune cells, known as microglia, to block their activation by interfering with the NFkappaB pathway. Activated microglia promote the growth and development of brain tumors. Treatment with either decorin or caffeic acid phenethyl ester (CAPE), a compound that inhibits the NFkappaB pathway, protected mice with *Nf1* mutations from developing optic gliomas. The findings suggest that blocking microglia activation may be a potentially useful therapeutic approach for brain tumors.

*Originally written by Tamara Bhandari. Washington University School of Medicine: WUSM News Release, December 10, 2021. Edited for space.*

## EPILEPSY DRUG STOPS NERVOUS SYSTEM TUMOR GROWTH IN MICE

Researchers at Washington University School of Medicine in St. Louis have discovered that neurons carrying a mutation in the *Nf1* gene are hyperexcitable and that suppressing this hyperactivity with lamotrigine, a drug approved by the Food and Drug Administration to treat epilepsy, stops tumor growth in mice.

"Tumors are very common in people with NF1," said senior author David H. Gutmann, MD, PhD. "We have shown that we can block the growth of NF1 tumors by shutting off neuronal hyperexcitability. We have done it now a couple of different ways, and there is no question that repurposing antiepileptics is an effective way to inhibit tumor growth, at least in mice. This underscores the critical role that neurons play in tumor biology."

Last year, Gutmann and Michelle Monje, MD, PhD, a professor of neurology at Stanford University School of Medicine and a Howard Hughes investigator, showed that light induces increased neuronal activity in the eyes of *Nf1*-mutant mice, which then causes tumors to form on the optic nerve that connects the eyes and the brain. In the new study, they — along with first author Corina Anastasaki, PhD, an assistant professor of neurology at Washington University, and co-author Lu Q. Le, MD, PhD, a professor of dermatology at the University of Texas, Southwestern Medical Center — investigated how increased neuronal activity leads to tumors in people with NF1.

The researchers studied neurons from mice with and without *Nf1* gene mutations. At baseline, neurons from mice with tumor-causing *Nf1* mutations fired electrical impulses more frequently than neurons from normal mice. These hyperexcitable neurons then released molecules that increased the growth of brain and nerve tumors. The researchers discovered that this was the result of a dysfunctional ion channel that changed the baseline electrical activity inside the neurons.

They also studied mice with an *Nf1* mutation seen in people with NF1 who do not develop brain or nerve tumors. Anastasaki found that neurons from mice with this specific *Nf1* mutation are not hyperexcitable and do not develop tumors – providing the first explanation for why this group of patients with NF1 lack optic gliomas or neurofibromas.

Hyperexcitable neurons are also a feature of epilepsy, and the epilepsy medication, lamotrigine, targets the same ion channel disrupted in hyperexcitable *Nf1*-mutant neurons. The researchers gave lamotrigine to a group of *Nf1*-mutant mice that develop optic nerve tumors. Compared to mice receiving placebo, mice that had received the drug had smaller tumors, which no longer were growing.

Apart from suggesting a new way to treat NF1 tumors, these findings also suggest a new way of thinking about the origins of the disorder's cognitive symptoms. "The mutation in the *Nf1* gene changes the basic biology of the neuron," Gutmann said. "During development, neurons form first and tell the rest of the brain how to develop. If you have a mutation that affects how neurons behave, that may change everything about how the brain gets set up during development. Nothing we have tried so far to prevent learning disabilities has worked. Maybe this discovery could lead to new treatments for the learning and cognitive problems in children with NF1."

*Originally written by Tamara Bhandari. Washington University School of Medicine: WUSM News Release, June 15, 2022. Edited for space.*

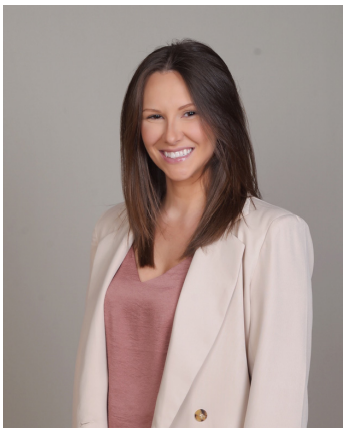
## TARGETING THE IMMUNE SYSTEM BLOCKS OPTIC GLIOMA FORMATION IN MICE

Postdoctoral fellows, Drs. Jit Chatterjee and Amanda Costa, teamed up to determine when immune cells, specifically microglia and T cells, first appear in optic gliomas and when these immune cells produce small signaling molecules that support optic glioma progression. By blocking these signaling molecules, called chemokines or cytokines, during the times when they are first expressed, Chatterjee and Costa showed that mice did not develop optic gliomas. Moreover, these effects were long-lasting, with mice not showing any evidence of tumor formation months after initial treatment. These exciting findings suggest that *Nf1*-optic glioma formation and progression can be prevented by interrupting immune system cell function, opening the door for more refined approaches to treating brain tumors arising in children with NF1.

# SUPPORT BEYOND THE CLINIC

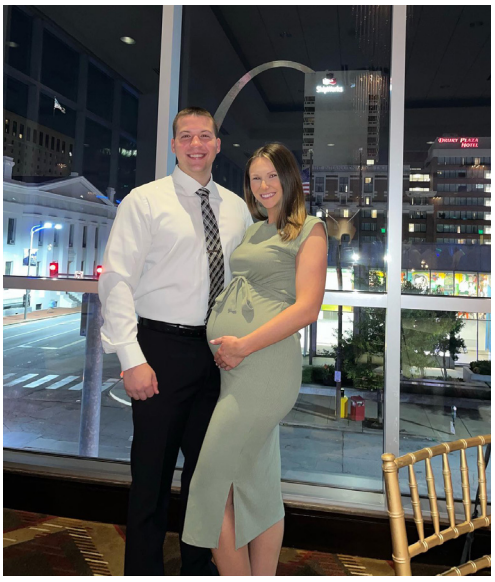
## MEET MADELINE (MADDY) SCHERR

### NF CENTER COORDINATOR AND OCCUPATIONAL THERAPIST



Maddy is a licensed Occupational Therapist (OT) who received her Masters of Science degree in Occupational Therapy from Brenau University. She brings a wealth of experience in pediatric outpatient occupational therapy and the care of children with autism, attention deficits, behavioral concerns, and childhood developmental delays. Additionally, she has experience developing and promoting newly established pediatric therapy programs.

Maddy joined us in March 2022 as our new Washington University Neurofibromatosis (NF) Center Coordinator and Occupational Therapist. In this role, she provides evaluations and consultations for our children in clinic, directs our complementary care programs (Club NF and Totally TEEN), maintains the NF Center social media platforms, and assists in recruiting research participants. She is excited to use her occupational therapy training/education and program development experience simultaneously to create programs and services that will enhance patient care and the overall goals of the NF Center Clinical Program.



She believes in treating the patient as a whole. Maddy indicates that each person has unique talents and gifts. Sometimes, patients need guidance exploring those talents, or assistance overcoming barriers to reach their goals. When people are given the appropriate tools to succeed, they have greater likelihood of achieving their full potential.

Born and raised in St. Louis, Maddy and her fiancé are excited to be welcoming their first child this fall. In her free time, she enjoys unwinding with family and friends by hiking, swimming, and traveling.

## THE THERAPY VAULT

We are excited to announce the launch of our new online therapy blog, The Therapy Vault. On the NF Center website, families now have access to therapy resources from the comfort of their own home. Every month, our physical and occupational therapists write about a variety of topics intended to support children with NF1 and ultimately help them become the best version of themselves. Examples of past topics include: picky eating, summer activities for promoting healthy childhood development, confidence building, and selecting appropriate shoe attire.

The goal of The Therapy Vault is to provide NF Center families with tools needed to help foster the growth of children with NF1. We hope to add an additional therapist to the blog team in the near future to further highlight speech and language therapy concerns.

# 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.

## MUSIC HEALS (Ages 2 – 5 years)

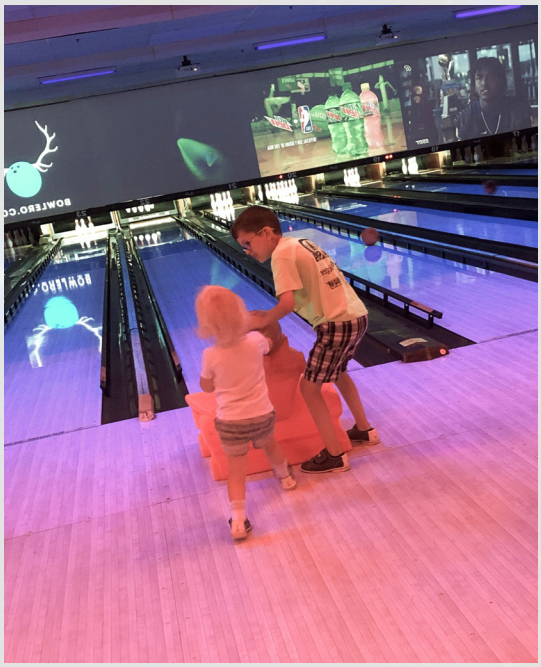
Formerly known as "Beat NF," Music Heals is a jazz music-motor therapy program designed for young children with NF1. The curriculum is designed to promote social, attention, and motor skills, while fostering healthy parent-child interactions, peer relationships, and jazz appreciation. During each session, professional jazz musicians play live music, while 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 specifically written for these activities.

With the intention of reaching a larger audience, Music Heals successfully transitioned to Jazz St. Louis. Music Heals will continue to collaborate with the Washington University NF Center.

## CLUB NF (Grades K – 8)

Through our partnership with St. Louis Children's Hospital, the Washington University NF Center proudly provides Club NF - a 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 physical and occupational therapist, parents have the opportunity to speak with NF specialists to learn more about NF1 and how to integrate therapy activities at home.

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. Now that we have returned to in-person events, examples include cooking, bowling, ice skating, and glass making.



## TOTALLY TEEN (Ages 13 – 18 years)

In collaboration with the St. Louis Children's Hospital Foundation, we are pleased to introduce Totally TEEN (Thrive. Engage. Educate. Neurofibromatosis). This social and life skills therapy program was developed to build on the early successes of our former teenage program, "TEEN NF." The goal of Totally TEEN is to improve conversational and executive function skills, and to begin preparing teenagers for the transition to adulthood.

Led by Maddy Scherr, NF Center Occupational Therapist, in collaboration with Dr. Kimberly Sirl, a neuropsychologist at St. Louis Children's Hospital, Totally TEEN sessions focus on handling embarrassing feedback and bullying, choosing appropriate friends and social activities, exploring career interests, money management, and food preparation. Each event will be held at a different location across the Greater St. Louis area, such as Topgolf, the Science Center, and Schnucks Cooking School.

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**nfcenter.wustl.edu**

As we celebrate our successes in 2022 and look forward to 2023, 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. The Washington University NF Center 2022 Annual Report was created and designed by Madeline Scherr.