


# NF NEWS

THE NEWSLETTER OF THE CHILDREN'S TUMOR FOUNDATION  
FALL 2022

CHILDREN'S  
TUMOR  
FOUNDATION  
ENDING NF  
THROUGH RESEARCH

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Extraordinary Spirit



The annual NF Conference, hosted by the Children's Tumor Foundation, took place in Philadelphia, PA, on June 21-24 at the Loews Philadelphia Hotel. The largest meeting of its kind, this four-day event took place in-person and virtually, attracting more than 650 leading specialists from a wide range of scientific disciplines and clinical backgrounds, all focused on improving the lives of NF patients.

# FROM the President

Annette Bakker, PhD



**T**hank you from all of us at the Children's Tumor Foundation (CTF). Your support is the reason we continue to be the leading private funder of research for all manifestations of NF, and I am proud to consider each of you a partner in our efforts.

In June, our NF Conference brought together more than 650 NF researchers, clinicians, and experts to learn about the latest in NF research. This newsletter shares details and highlights from the annual meeting, including advancements in immunotherapy as a possible treatment for NF, studies in whole-body MRI, and potential supplements showing some efficacy in NF1 patients.

Other important topics included updates about CTF-funded studies in gene therapy and our investments in pain studies for schwannomatosis. Also presented were the revised diagnostic criteria for NF2 and

schwannomatosis, which will improve diagnosis and care.

As the fall season begins, our fundraising efforts are underway as the Foundation's programs offer people of all ages opportunities to participate in the fight to end NF. Our Shine A Light NF Walk, Cupid's Undie Run, and NF Endurance programs have numerous upcoming events around the country that will make a difference in the lives of those with NF.

I hope you will also join us in person or virtually for our National Gala, which will take place in New York City's Gotham Hall this year. Registration for the virtual program is a beautiful way for our global community to come together.

My gratitude goes out to all of you, our friends and donors, researchers and clinicians, patients and caregivers. Special thanks to all of you who have joined the NF Legacy Society, like Carolyn Meyer-Tolliver, who you will read about in this newsletter, and who is helping ensure our work will continue for generations to come. Our united efforts are paving the way to more treatments and better lives for all who live with NF.

Sincerely,

Annette Bakker, PhD  
President

## IN THE MEDIA:

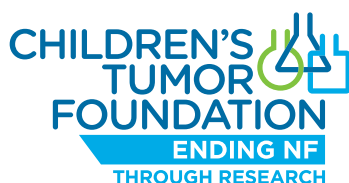
### CTF President Annette Bakker appeared on *Office Hours*

**C**TF President Annette Bakker appeared as a guest on the *Office Hours* broadcast, hosted by sports executive, entrepreneur, and investor, David Meltzer. David Meltzer's late-night entrepreneurial show is available in more than 100 countries around the world, and features the brightest minds, billionaires, and entrepreneurs talking about success, failure, and everything in between.

Dr. Bakker shared with Meltzer, "There are scientific problems and there are system problems. For the scientific problems, you need science brains. For the system problems, you just need to have people who speak logic[ly]... and make sure your incentives are in the right place. This is the BRIDGE initiative."

This great conversation continued as they spoke about drug development, technology, the pharmaceutical industry, and business working together to end NF. Click [HERE](#), and jump to 30:05 for President Annette Bakker's portion of the episode.

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## Jaishri O'Neill Blakeley, MD

RECEIVES THE CHILDREN'S TUMOR FOUNDATION FRIEDRICH VON RECKLINGHAUSEN AWARD

At this year's NF Conference in Philadelphia, the Children's Tumor Foundation announced the recipient of the 2022 Friedrich von Recklinghausen Award, Jaishri O'Neill Blakeley, MD.

Dr. Blakeley is a Professor in Neurology, Oncology and Neurosurgery (Neuro-oncology) at Johns Hopkins University, Director of the Johns Hopkins Comprehensive Neurofibromatosis Center, and Director of the Neurofibromatosis Therapeutic Acceleration Program (NTAP), which she co-founded in 2012 to dramatically shift the landscape of NF1 clinical care via necessary, efficient, and expert discovery, translational, and clinical research.

Dr. Blakeley has been one of the most significant thought leaders in the NF field for many years, notably in clinical trial design and outcome measures in both REINS (Response Evaluation in Neurofibromatosis Studies) and the NF Clinical Trials Consortium. She has also made important contributions to the DHART SPORE program. Overall, Dr.

Blakeley has made powerful contributions to the understanding of all types of neurofibromatosis and schwannomatosis. Through her involvement with all funding entities of NF, Dr. Blakeley has established herself as a model of collaboration, which has been transformative for the community.

Of additional significance is her tireless efforts to support the development of junior investigators through the Francis S. Collins Scholars Program, underscoring her commitment to mentorship and training. And of course, Dr. Blakeley is deeply respected and loved by her patients, to whom she is totally dedicated, treating not just the patient but the person.

The Children's Tumor Foundation, along with her colleagues and peers, is proud and thrilled to recognize Dr. Blakeley with the 2022 Friedrich von Recklinghausen Award, not only for her many outstanding achievements throughout her years in the field, but also for her dedicated efforts in supporting the entire NF community. Please join us in congratulating Dr. Blakeley for this well-deserved honor.

**T**he Children's Tumor Foundation Friedrich von Recklinghausen Award is given to individuals in the professional NF community who have made significant contributions to neurofibromatosis research or clinical care. It is named after Friedrich Daniel von Recklinghausen (1833-1910), the German physician who first described 'von Recklinghausen's disease' – what we now know as neurofibromatosis type 1.

## 2022 NF Conference Poster Session Winners

Poster sessions are an opportunity for researchers to showcase their work in basic and clinical sciences to an audience of NF researchers. At this year's NF Conference, a panel of judges selected the top posters, and the investigators were invited to present their work in front of the full conference. Listed here are the winning posters at the 2022 NF Conference in clinical and basic sciences.

### CLINICAL SCIENCE

- Inka Ristow, MD**  
**University Medical Center Hamburg**  
*Characterization of Benign, Atypical, and Malignant Peripheral Nerve Sheath Tumors in Patients with Neurofibromatosis Type 1 Using Diffusion-Weighted Magnetic Resonance Imaging*
- Taylor Sundby, MD**  
**National Cancer Institute**  
*Machine Learning Integration of Multimodal Cell-free DNA Features Enhances Detection of Peripheral Nerve Sheath Tumors*
- Madeleine Franchi, MS**  
**University of Alabama at Birmingham**  
*Parents' Perspectives of Disclosing a Pediatric Diagnosis of NF1 to their Children*

### BASIC SCIENCE

- (tie) Miriam Mansour, PhD Student**  
**Institute Mondor de Recherche Medicale**  
*Exploring Mechanisms Governing Initiation and Progression of Plexiform Neurofibromas Using Prss56Cre, Nf1/fl/fl Mouse Model*
- (tie) Catena Kresbach, MD**  
**University Medical Center of Hamburg**  
*Molecular and Clinical Refinement of Atypical Neurofibroma*
- Krizelle Alcantara, MS**  
**Nationwide Children's Hospital**  
*In Vitro Modeling of Neurofibromatosis Type 2 (NF2) to Explore Potential Therapies in the Context of Patient-Specific Mutations*

## YOUNG INVESTIGATOR AWARDS 2022

The Children's Tumor Foundation is pleased to announce the funding of nine Young Investigator Awards (YIA) for the 2022-2024 cycle, an investment of \$800,000 in innovative research projects.

### **SIMGE ACAR**

Washington University

#### ***Global Protein Changes Associated with Chr8 Gain in MPNST***

Malignant peripheral nerve sheath tumors (MPNST) are one of the common malignancies in individuals with NF1 and are associated with poor overall survival. Unlike plexiform neurofibromas, MPNSTs have an extra copy of chromosome 8 (Chr8q gain), which is hypothesized to induce genome-wide perturbations that specifically promote cancer progression. This study will analyze cells with Chr8q gain along MPNST samples from patients to test the above hypothesis and to characterize the molecular changes caused by this phenomenon.



### **HALEY HARDIN**

University of Central Florida

#### ***Evaluation of BRD4 Inhibitors for Use in Combination with Kinase Inhibitors for NF2 Schwannomas***

NF2 tumors respond to treatment with MEK inhibitors but eventually develop drug resistance. This study will evaluate a MEK-BRD4 inhibitor combination therapy for drug response in NF2 compared to MEK inhibitor monotherapy. Specifically, this study will investigate the drug resistance mechanism by examining the role of BRD4 in regulating the expression of resistance-mediating genes and will test various MEK-BRD4 inhibitor combinations to identify new drug combinations for NF2.



### **CHARLENE ILTIS**

Memorial Sloan Kettering Cancer Center

#### ***Characterization of the Molecular Mechanisms Conferring Resistance to Treatment on NF1-associated MPNST***

MPNSTs in the context of NF1 are often the result of malignant transformation of benign precursor lesions including plexiform neurofibromas. The proposed project will characterize a rare MPNST population with stem-cell like properties that is essential for tumor initiation and relapse, and elimination of which promotes tumor shrinkage and abolishes tumor relapse. This study can provide deeper insights into MPNST development and new therapies for targeting them.



### **TONCI IVANISEVIC**

Vlaams Instituut voor Biotechnologie, Belgium

#### ***The Role of LZTR1 in Schwannomatosis Development and Progression***

Pathogenic variants in the LZTR1 gene account for up to 40% of the cases of familial schwannomatosis. However, the molecular mechanisms by which these variants predispose to schwannomas are still unknown. This project will perform multi-omic analyses of an LZTR1-deleted schwannoma model to identify the interactions between the RAS/MAPK and Hippo pathways during schwannoma development and progression. It will also develop clinically relevant 3D models of schwannomatosis to assess candidate drugs as monotherapy or in combination with Hippo pathway inhibitors.



## PAUL JONES

Washington University

### ***Early Detection and Model Development of NF1-MPNST Using Liquid Biopsy of cfDNA***

MPNSTs are the leading cause of death in NF1 patients but current methods to detect them, especially the early-stage ones, and track their progression are insufficient. This project aims to develop an assay based on cell-free DNA analysis that will more sensitively detect early-stage MPNST formation. It will further apply this assay in mouse models to understand tumor evolution, treatment response, and resistance mechanisms.



## ERICA LEIF

Alliant International University

### ***The Impact of Self-Determination Theory on Increasing Health-Promoting Behaviors in Adults with NF1***

NF1 is a complex health condition with multiple clinical manifestations including debilitating chronic pain. By applying the self-determination theory, which suggests autonomy, competence, and relatedness as main psychological needs for growth and change, this study will investigate NF1-associated pain and the contribution of a wide range of factors to successful self-management of pain.



## NAMRATA RAUT

Cincinnati Children's Hospital Medical Center

### ***The Role of Schwann Cells in the Onset of Pain due to NF1***

The majority of NF1 patients experience moderate to severe neuropathic pain. However, the underlying mechanisms of pain development are not fully understood. The proposed study will examine the specific cell types and mechanisms involved in neuropathic pain development in NF1. Using preclinical mouse models, this study will test whether growth factors produced by Schwann cells together with select immune cell populations that infiltrate the affected peripheral nerves contribute to neuropathic pain-like behaviors.



## NIPUNIKA SOMATILAKA

The University of Texas Southwestern Medical Center

### ***From Cold to Hot: Reprogramming Tumor Microenvironment to Target NF1 Malignancies***

MPNSTs associated with NF1 respond poorly to chemotherapy and radiotherapy. Immunotherapy drugs are also not effective against MPNSTs because these tumors are 'cold,' lacking T cells and other immune cells near or within the tumor. The present study aims to reprogram the MPNST microenvironment such that they are converted from non-T cell 'cold' tumors into T cell-rich 'hot' tumors. This will be achieved by activating the STING-IFN pathway using known small molecule agonists. This study will then test various combinations of STING agonists and immune checkpoint blockers to determine their efficacy in treating MPNST.



## DEREK WONG

University Health Network, Canada

### ***Integrated Analysis of Plasma Whole Genome Sequencing for the Early Detection of Malignant Tumours in Patients with NF1***

The clinical manifestations of NF1 are diverse and range in severity from mild (e.g., skin discoloration) to very serious (e.g., cancer). Clinicians need new ways to identify NF1 patients requiring heightened surveillance or treatment. The objective of this study is to develop an assay that utilizes cell-free DNA (cfDNA) to monitor NF1 disease severity and identify tumors with malignant potential. This assay will integrate two technologies that enable more thorough genetic and epigenetic profiling of cfDNA and will potentially allow physicians to deliver personalized, risk-adapted care to NF1 patients.



## Revised Diagnostic Criteria for NF2 and Schwannomatosis

This June, the Children’s Tumor Foundation announced the landmark publication of updated diagnostic criteria for the genetic disorders neurofibromatosis type 2 (NF2) and schwannomatosis in *Genetics in Medicine*, the official journal of the American College of Medical Genetics and Genomics. The publication results from an extensive, multi-year collaborative effort of leading NF experts from around the globe. It aims to improve the diagnostic accuracy of NF2 and schwannomatosis in patients, ultimately reducing misdiagnosis and improving care for those patients.

Significantly, among other significant changes, the term “schwannomatosis” was proposed in this publication as an umbrella term for NF2 and schwannomatosis, further classifying each type of schwannomatosis by the gene containing the disease-causing pathogenic variant (formerly called a gene mutation).

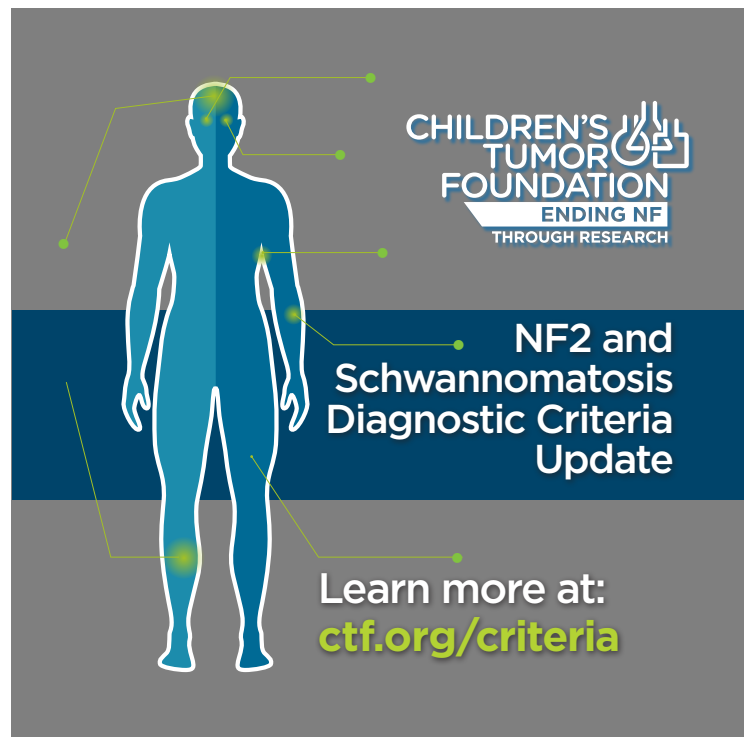
The updated diagnostic criteria for schwannomatosis classify each disorder according to the specific gene harboring a pathogenic variant. Therefore, NF2 is now termed NF2-related schwannomatosis. What was previously referred to as “schwannomatosis” is now termed either *SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, schwannomatosis-NOS (not otherwise specified), or schwannomatosis NEC (not elsewhere classified).

The original diagnostic criteria for NF1 and NF2 were established in 1987, and the diagnostic criteria for schwannomatosis was established in 2005. Since that time, there has been an explosion of knowledge about these genetic disorders, including the discovery of the genes that cause NF1, NF2, and schwannomatosis, as well as the technological development of genetic testing.

### Virtual Workshop on NF2 and Schwannomatosis

In April, the Children’s Tumor Foundation hosted a full-day virtual workshop with expert clinicians, surgeons, researchers, and pharma representatives to assess the current landscape of care, biology, and drug discovery

for all types of schwannomatosis, including NF2-related schwannomatosis, known as NF2. Recordings of this event may be viewed on the Resource Library portion of the CTF website at [ctf.org/education](https://ctf.org/education).



There has been some confusion and overlap in the diagnosis of all types of neurofibromatosis and schwannomatosis, and the updated criteria intend to improve patient care by reducing misdiagnosis:

- 9% of patients with a clinical diagnosis of schwannomatosis actually had NF2 upon genetic analysis
- 1-2% of patients with a clinical diagnosis of NF2 actually had schwannomatosis upon genetic analysis
- Significant overlap in features of schwannomatosis with mosaic NF2 patients
- No mention of the *LZTR1* gene or other genetic features in previous criteria
- A new awareness of the hybrid nerve sheath tumor (a close relative of schwannoma and neurofibroma) for use in the diagnosis of schwannomatosis

Additional information about this update, including a link to the publication in *Genetics in Medicine*, the researchers leading this effort, helpful explainer sheets and more (including the previously announced criteria for NF1, Legius syndrome, and mosaic NF1) can be found at [ctf.org/criteria](https://ctf.org/criteria).



## Focused Ultrasound Foundation and CTF Partner on NF Study

**T**he Focused Ultrasound Foundation and the Children's Tumor Foundation have established a partnership to advance innovative, noninvasive treatments in pediatrics. For more than 15 years, the Focused Ultrasound Foundation has been dedicated to advancing the development and adoption of focused ultrasound. Likewise, for over 40 years, CTF has been a leader in driving research, expanding knowledge, and advancing care for the NF community.

To launch the partnership, the two organizations are co-funding an early-stage laboratory study to investigate focused ultrasound's role in addressing NF2-related schwannomatosis, or NF2.

"Treatment options for NF2 patients are limited to high-risk surgery, chemotherapy, or radiation therapy, which carry high risks of morbidity. The development of more nonsurgical treatments, like focused ultrasound, offer much promise in more effectively and safely helping patients," said Tracy Galloway, Children's Tumor Foundation Board of Directors Chair. "On a personal level, it's devastating to see what NF2-related tumors can do to a person, like my daughter, who just underwent her third brain surgery, this time to remove a vestibular schwannoma located at the juncture where the hearing, balance, and facial nerves come together. Her recovery is ongoing, but she lost her hearing and developed other side effects, and it would be our greatest hope to not have to subject patients to severe surgeries and their devastating after effects. Though this journey has been tough for us personally, we know new options are on the horizon and we are proud to partner with the Focused Ultrasound Foundation and Dr. Tyrone Porter in order to help as many patients as quickly as possible. We believe this could be a real game-changer in improving the quality of life of those living with NF2."

The principal investigator for the study is Tyrone Porter, PhD, a Donald J. Douglass Centennial Professor in Engineering and an expert in image-guided drug delivery in the Department



Tyrone Porter, PhD

of Biomedical Engineering at the University of Texas at Austin. He and his team will use focused ultrasound to deliver a drug commonly used for lung cancer to a preclinical model of NF2. The drug will be wrapped in a special thermosensitive liposome packaging, and researchers hope to determine whether this packaging will lessen the drug's systemic side effects. If this is the case, it may be possible to increase the local concentration of the drug and thus enhance its effectiveness.

"Thermosensitive liposomes have proven to be an effective tool for localized delivery of anticancer agents to solid tumors, predominantly in adult patients," said Dr. Porter. "Focused ultrasound allows for triggered drug release specifically in the tumor, thus minimizing systemic exposure and the associated toxic effects. We believe this treatment strategy can be equally effective against pediatric brain tumors."

"This study is a first step toward addressing some of the unmet needs in the pediatric field," said Focused Ultrasound Foundation Chairman Neal F. Kassell, MD. "The Foundation recognizes the tremendous impact that focused ultrasound could have on young patients because it avoids surgery and radiation therapy and has fewer side effects than more traditional treatments. We are honored to partner with CTF and Dr. Porter on this project."

In August 2020, the Focused Ultrasound Foundation and CTF first collaborated to host a webinar and virtual panel discussion that introduced focused ultrasound to the NF research community.

To watch a recording of this webinar, go to [ctf.org/news](https://ctf.org/news)

"Thermosensitive liposomes have proven to be an effective tool for localized delivery of anticancer agents to solid tumors, predominantly in adult patients... Focused ultrasound allows for triggered drug release specifically in the tumor, thus minimizing systemic exposure and the associated toxic effects. We believe this treatment strategy can be equally effective against pediatric brain tumors."

**—TYRONE PORTER, PHD**  
University of Texas at Austin

## 2022 NF Conference Highlights

Organized by Conference Co-Chairs **Thomas De Raedt, PhD**, (Children’s Hospital of Philadelphia) and **Laura Papi, MD, PhD**, (University of Florence-Italy, Careggi University Hospital-Florence), this year’s program was the first in-person meeting since 2019, with virtual gatherings since that time. The meeting focused on growing the NF scientific and clinical community, assessing what can be learned from other disease communities, and applying the best of those ideas to NF. In this way the field can facilitate new discoveries and accelerate the path from discovery to clinical benefit. This focus was represented by the invited keynote speakers from outside the NF field.

### NF Clinical Care Symposium

The Clinical Care Symposium is a satellite half-day meeting specifically tailored to the NF and schwannomatosis clinical communities to address the current state of patient care, provide a forum for case studies, and to address other topics pertinent to running an NF clinic. This year’s symposium was moderated by **Nicole Ullrich, MD, PhD**, and included updates on CTF’s NF Clinic Network (NFCN), Clinical Care Advisory Board (CCAB), and the NF Registry, followed by additional topics and case presentations.

**Scott Plotkin, MD, PhD**, from Massachusetts General Hospital (MGH) and Chair of the CCAB, launched the symposium by recognizing the efforts of the group’s NFCN subcommittee, which oversees the network that now includes 68 NFCN clinics, after over a decade of development by the CCAB and CTF. He mentioned other highlights of the work of the CCAB, including studying the effects of COVID-19 infection on people with NF, presenting monthly Virtual Case Conferences, and addressing the need

for the delivery of guideline-concordant NF care.

**Pierre Wolkenstein, MD, PhD**, of Hopital Henri-Mondor in Paris, spoke about CTF-Europe’s EU Clinical Care Advisory Board, which includes members from all over Europe. Its current focus is to provide complete, continuous NF medical education through a program called International NF Educational Resources, or **INFER**, which is creating a series of online medical lectures by leading NF experts and can be accessed live or as video recordings.

Following this, **Heather Radtke, MS, CGC**, manager of CTF’s NF Clinic Network (NFCN), gave an overview of the network and its recent accomplishments. The network accepted its first two Canadian clinics this year, bringing the total of NFCN clinics to 68, which together saw nearly 20,000 patients last year. Ms. Radtke also described the NF Collective, a group of NF organizations from all over the U.S. who work together on ways to improve the lives of individuals with NF, under

the medical direction of **David Viskochil, MD, PhD**, of the University of Utah. The Collective recently completed work on a “Transition to Adult Care” resource for young adults and their caregivers and is currently working on a Classrooms that Care Program to provide school educational activities that build empathy for those facing health challenges.

**Pam Knight, MS**, senior director of CTF’s Clinical Program, reviewed the NF Registry and its progress over the last decade, during which membership grew to include 10,000 individuals. To date, the Registry has recruited patients for more than 60 clinical trials and research studies. Improvements underway will provide more precise metrics to allow CTF to improve outreach strategies, and enhance both recruitment effectiveness and the use of de-identified data for research.

**Kaleb Yohay, MD**, presented an updated version of his classic presentation, “Using a Business Plan Model for Funding Your Clinic,” demonstrating his accounting-based approach to

*Continued on page 16*



# stories

OF NF



## Blake Anthony Ellis

NF1

When Blake was around one year of age, we brought him to a pediatrician and asked questions about the spots we were seeing on him. She told us they were fine, nothing to be worried about.

We ended up getting a new pediatrician for Blake and he noticed the café-au-lait spots right away and we were sent to an assortment of doctors.

My son has gone through so much already, at just two years old. He has had nonstop ear infections since he was just a one-year-old, and you'd never know it unless the doctor told you. He's such a happy, well-mannered, and well-behaved child. He is so bright and full of life, and he has exceeded everyone's expectations. He always has a smile.

It brings a fear of his future since NF is a progressive disease; it makes you double-think common situations... Is this because of NF1? Will he have trouble learning? Why is he not doing that correctly? More than anything, I just want him to be happy.

## Seth Gelwasser

NF2

I was diagnosed with neurofibromatosis type 2 (NF2) in March 2002 at age six months. I was brought to medical attention because my eyes didn't focus the way eyes typically focus. My family took me to a retinal surgeon at Cleveland Clinic Cole Eye Institute. The surgeon said I had a retinal hamartoma, a possible NF2-related tumor. During the next months I had multiple surgeries and a retinal detachment which resulted in my being blind in my right eye. Following up on the possibility that I had NF2, the retinal surgeon referred us to a pediatric neurologist with a background in NF at the Cleveland Clinic Neurological Institute. The doctor noted I had several "lumps" on my skin, and I underwent a brain MRI that same month which was clean. In June 2002, a punch biopsy of a scalp lesion showed that it was a plexiform schwannoma, common with NF. Although the brain tumors typical of NF2 were not yet seen on the scans, my neurologist diagnosed me based on my skin and eye findings. That early diagnosis allowed me to have the advantage of being closely monitored.



No one ever wants to hear that they or someone they love has a rare disease that has no cure. I've been blessed to have the courage and strength to jump over the hurdles with which NF2 has challenged me. Also, I'm blessed to have an amazing medical team at Cleveland Clinic who provide excellent care and refer me for opinions to NF experts at other medical facilities. Without the support of my family and friends I don't know how I would get through every appointment, scan, or infusion, as well as my multiple surgeries and frequent hospital admissions.

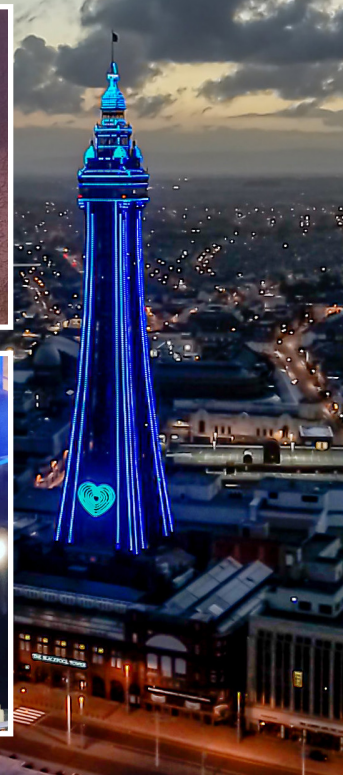
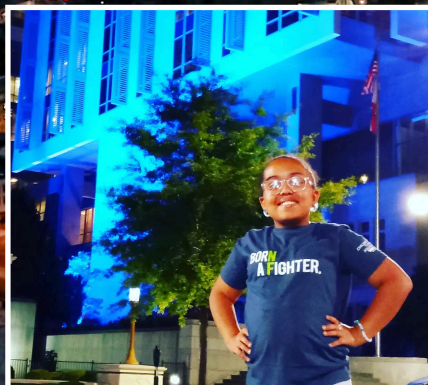
NF2 has caused many challenges over the past 20 years. I've lost vision in my right eye. I've had various surgeries for spinal cord tumors and a nerve graft in one arm. When I was eleven, my spine and brain tumors grew aggressively, and I needed lumbar spine surgery in 2012 and cervical spine surgery in 2013. These surgeries have affected my gait, endurance, and strength. Recent brain surgery affected my equilibrium. I have to use a cochlear implant and hearing aid and my remaining hearing is at risk. These physical challenges have affected me mentally and emotionally.

I've had to deal with many difficult situations and be part of a lot of scary, frustrating, and sad conversations. NF2 is very hard to live with. I can't drive or play sports. I've had to change my career goals. I consider every day, birthday, family event, minor victory, or family vacation as a gift. I've learned to not dwell on the bad things that happen and accept that not everything goes our way. It's important to be thankful for what we have and enjoy the moment.

# Awareness Month HIGHLIGHTS

## MAKE NF VISIBLE

The Children's Tumor Foundation continued our Make NF Visible theme throughout May NF Awareness Month, asking the NF community: What is something about your NF that people can't see? And what is something about you that people can't see because of your NF? Increased media coverage about the NF community supported this theme, including local and national coverage on television, radio, blogs, and podcasts.



## NF AWARENESS AROUND THE WORLD

Across the country, volunteers secured proclamations for NF Awareness month in 18 states and 22 cities. Families and friends joined our efforts on all CTF social media channels and created individual Facebook fundraisers throughout May to support the CTF mission.



## NATIONAL BILLBOARD CAMPAIGN

Our thanks to Lamar Advertising, who helped the Children's Tumor Foundation Make NF Visible through a national PSA digital billboard campaign to celebrate NF awareness month. Adding to the billboards secured by local NF families, 111 billboards in 27 markets featured an NF awareness message.



New York City's  
One World Trade Center

## SHINE A LIGHT

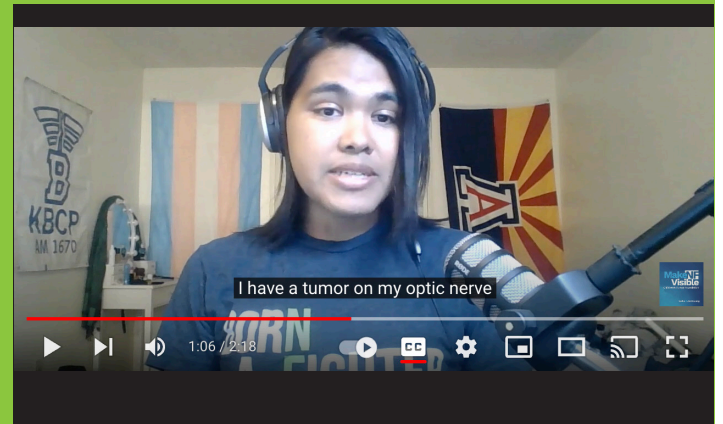
The annual Shine a Light on NF campaign brings NF awareness into the community by lighting up buildings, bridges, monuments, and homes in blue and green. Together with our partner NF organizations, this year 578 participating locations in 14 countries worked to Make NF Visible by Shining a Light on NF. To view a list of our participants and partners, go to [ctf.org/shinealight](https://ctf.org/shinealight).



## MAKING NF VISIBLE ON TVS & PHONES

Our thanks to **LG Ads Solutions** and **VIZIO** for running PSAs and ads on World NF Day in support of Make NF Visible.

## MAKE NF VISIBLE VIDEO GALLERY



Nearly 50 NF Heroes from around the world responded to our call for individuals to tell their NF stories through self-submitted videos. View these powerful video submissions all year long at [youtube.com/makenfvisible](https://youtube.com/makenfvisible).

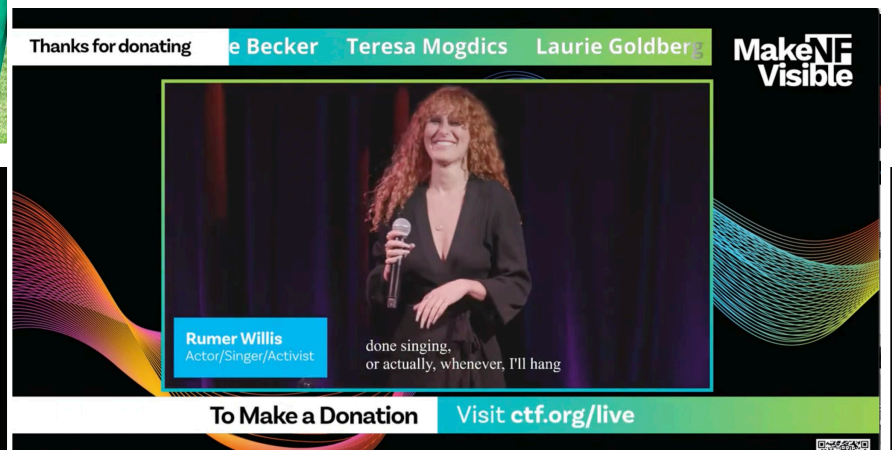
View our 2022 NF Awareness Recap video at [ctf.org/nfawareness](https://ctf.org/nfawareness)

## WEARING BLUE AND GREEN

NF Heroes showed their pride as part of our social media campaigns for two specific days significant to the NF community, Wear Blue & Green on May Seventeen and Wear Green & Blue on May Twenty-Two.



## MAKE NF VISIBLE: A WORLD NF DAY LIVE EVENT



On May 17, World NF Awareness Day, we came together to ensure the world knows about NF. Live streaming on YouTube, this event was hosted by actor/producer Jonathan Sadowski and included celebrity musical guest Rumer Willis. The evening was filled with stories of NF Heroes and raised more than \$280,000 to end NF.

Carolyn and her son, Jeff. "At the time of this picture, he was still symptom-free, and we did not think things would change the way they did. It is difficult to predict what NF will do."



“ There has been significant improvement over the past 40 years in our knowledge about what NF is and an encouraging start to finding treatments, but there is a long way to go. I hope to be able to increase my monthly donations as well as increase my legacy donation. ”

CAROLYN MEYER-TOLLIVER

doctor told me he suspected that Jeff had NF, he said to me that Jeff had Proteus Syndrome, which was more widely known as the elephant man's disease and is not NF. Over the years, CTF has increased the knowledge of NF tremendously, particularly in the past fifteen years. But the treatments for NF are still in the development stage, and there is nothing yet that seems to work for MPNSTs. There has been significant improvement over the past 40 years in our knowledge about what NF is and an encouraging start to finding treatments, but there is a long way to go. I hope to be able to increase my monthly donations as well as increase my legacy donation.

## Extraordinary Spirit **CAROLYN MEYER-TOLLIVER**

### AN NF LEGACY SPOTLIGHT

**The Children's Tumor Foundation NF Legacy Society consists of individuals who have ensured the future of NF research by including the Children's Tumor Foundation in their wills and estate plans. Longtime donor and NF Legacy Society member Carolyn Meyer-Tolliver spoke to us about the reason she gives and the importance of leaving a legacy.**

#### **CTF: How has NF impacted you and your family?**

**Carolyn Meyer-Tolliver:** My son Jeff was diagnosed with NF1 in 1982 at eight years of age because of his café au lait spots. He had no other symptoms until he reached his early 20s. While a student at the University of Florida, he developed severe pain in his left leg. His doctor at the University found a large tumor on the femoral nerve in his left leg. Removal of the tumor confirmed a diagnosis of NF1; however, the tumor was benign, and Jeff was able to go back to the University and finish his BA and his MA degrees. At 30 years of age, he was living in Maryland, and his doctors at Johns Hopkins

University found another tumor in his left leg, which turned out to be an MPNST - a malignant peripheral nerve sheath tumor.

I had been donating to the Children's Tumor Foundation every year since his diagnosis. Jeff had been working with CTF, telling people about the disease and helping raise funds for NF research by participating in various events. When the diagnosis became MPNST, I increased my donations, and Jeff worked tirelessly fundraising for CTF. Jeff had multiple surgeries and constant pain until his death twelve years ago at age 35. As my finances increased over the years, I have routinely increased my yearly donations and have talked to people about NF whenever the opportunity arises.

#### **Why do you think leaving a legacy gift is important?**

When Jeff was diagnosed, CTF was then called the National Neurofibromatosis Foundation, or NNFF, and it was only four years old. Very few people knew about the disease. When Jeff's

#### **What is your hope for the future of CTF?**

I hope that CTF can continue the growth that it is experiencing now. The research into the causes of NF and the development of treatments is vital. Making NF visible and the increase of NF organizations around the world is critical. It is also essential that the general public learns about NF and understands the needs of people with the disease. There are so many variables in the symptoms of NF, from nothing visible to extreme disfigurement. It might be easier to get support for research if everyone with NF developed external signs, but those like my son with no visible symptoms can also suffer severe pain and die at an early age.

By making a special legacy gift to the Children's Tumor Foundation, you will play an essential role in ensuring our work continues. Your planned gift is an investment in the organization's long-term future, ensuring that the Children's Tumor Foundation will continue to lead the way in the fight to end NF.

**To learn more about leaving a legacy and including CTF in your will or estate plan, please contact the Foundation at [info@ctf.org](mailto:info@ctf.org), or call us directly at 1-800-323-7938.**

# CUPID'S UNDIE RUN

Each February, thousands of undie runners in cities across the U.S. come together, whether it be in-person or virtually, to support those affected by NF. Cupid's Undie Run starts as a fun party, then we jog it out with a mile(ish) run/frolic, and ends with an EPIC dance party!

Cupid's season kicks off in the Fall with a launch in early October. For more information, to register, or to bring Cupid's to your city, please visit [cupids.org](http://cupids.org)



Cupid's Undie Run finished strong at the end of February 2022, raising more than \$1.75 million in 37 cities. A special thanks to Joe Boxer and Love, Tito's, our national partners, and to all our local sponsors, volunteer Event Directors, and many participants and fundraisers. Together you made this season extremely fun and successful!

## February 2023 Cities

Atlanta	Denver	Phoenix
Austin	Detroit	Pittsburgh
Baltimore	Jacksonville	Durham
Boise	Kansas City	Reno
Boston	Los Angeles	SF Bay Area
Buffalo	Minneapolis	St. Louis
Charleston	Nashville	St. Petersburg
Chicago	NY City	Virginia Beach
Cincinnati	Orlando	Washington, D.C.
Cleveland	Philadelphia	Wilmington

To register, go to [cupids.org](http://cupids.org)



## SPECIAL EVENTS



CHILDREN'S TUMOR FOUNDATION

# GALA

2022

MONDAY, NOVEMBER 14

GOTHAM HALL, 1356 BROADWAY, NEW YORK CITY

FOR TICKETS & ADDITIONAL INFORMATION: [ctf.org/gala](http://ctf.org/gala)

## Honoring

2022 HUMANITARIAN AWARD  
Rachel B. Tiven

2022 INNOVATION IN MEDICINE AWARD  
Allan Belzberg, MD, FRCS, FAANS  
Johns Hopkins Medical Center

2022 CTF CHAMPION AWARD  
Aubrey Rothrock III and  
Squire Patton Boggs

2023 NATIONAL AMBASSADOR  
Michele Holbrook

# SHINE A LIGHT NF WALK

**Shine a Light NF Walk** season kicked off with a bang! The Cincinnati and Utah Walks got the 2022 season started, with the remainder of our Walks scheduled between August and November. Cincinnati had over 400 people gather together at the first walk of the season and raised more than \$100,000 to end NF. Utah enjoyed a beautiful evening with friends and family celebrating their NF Heroes. Both events returned to an in-person format after two years of being virtual, and the smiles on the faces of those in attendance showed the exuberance of gathering together again. With more than 20 walks to go, we invite you to join us by registering at [shinealightwalk.org](http://shinealightwalk.org).

We extend a special thanks to our National Presenting Sponsor, **Alexion**, for supporting our Shine a Light Walk program this year and helping us get closer to our goal of raising \$1.6 million to end NF!

Shine a Light Walk is also an opportunity to make an impact in the fight to end NF. In 2021, our teams raised more than \$1.5 million to fund critical NF research and improve diagnosis and treatment for patients. We are setting our sights even higher in 2022!

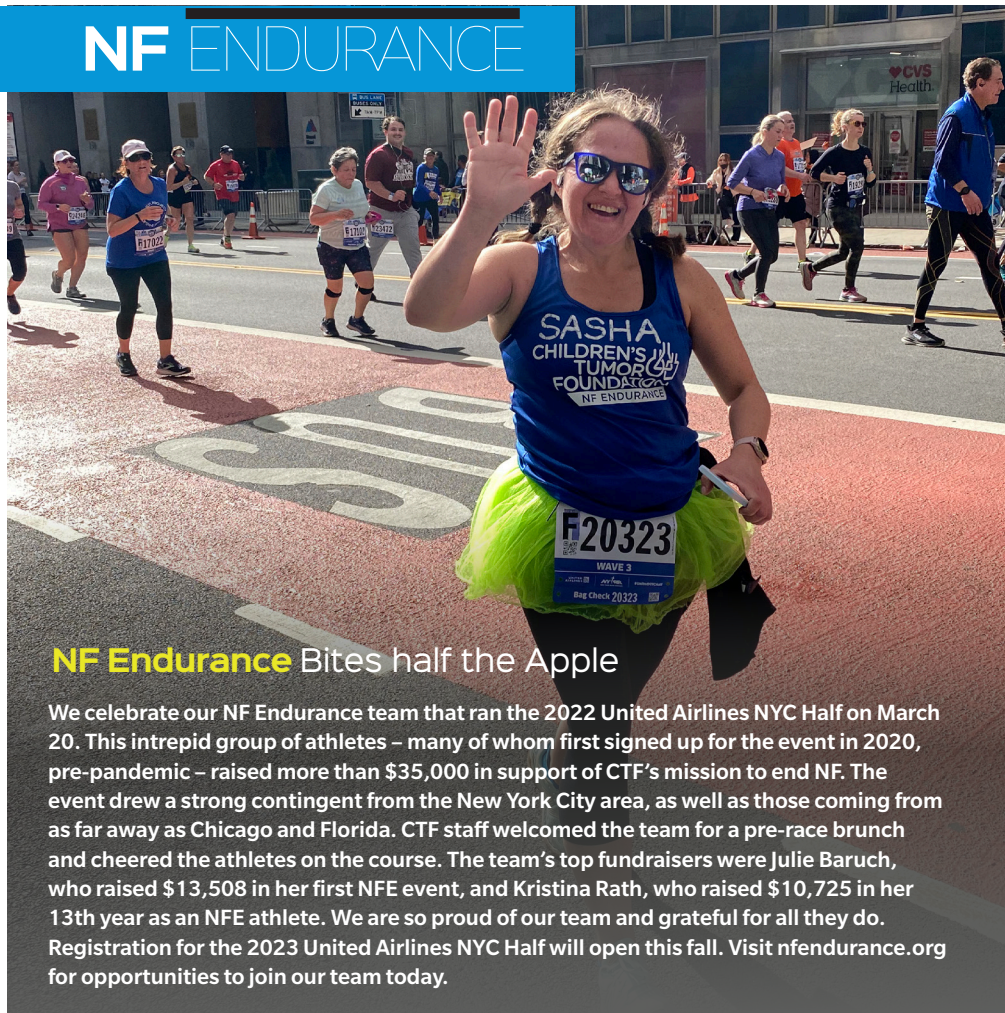


## UPCOMING WALKS

Register today at [shinealightwalk.org](http://shinealightwalk.org)

9/10/22	Virginia
9/10/22	Minnesota
9/17/22	Chicagoland
9/24/22	Denver
9/24/22	South Dakota
9/24/22	Kansas City
9/24/22	Buffalo
10/1/22	San Antonio
10/1/22	Philadelphia
10/8/22	Rochester
10/8/22	Carolinas
10/15/22	Atlanta
10/22/22	Southern California
10/22/22	Long Island
11/5/22	New Jersey
11/12/22	Houston
11/13/22	Arizona
11/13/22	Florida

# NF ENDURANCE



## NF Endurance Bites half the Apple

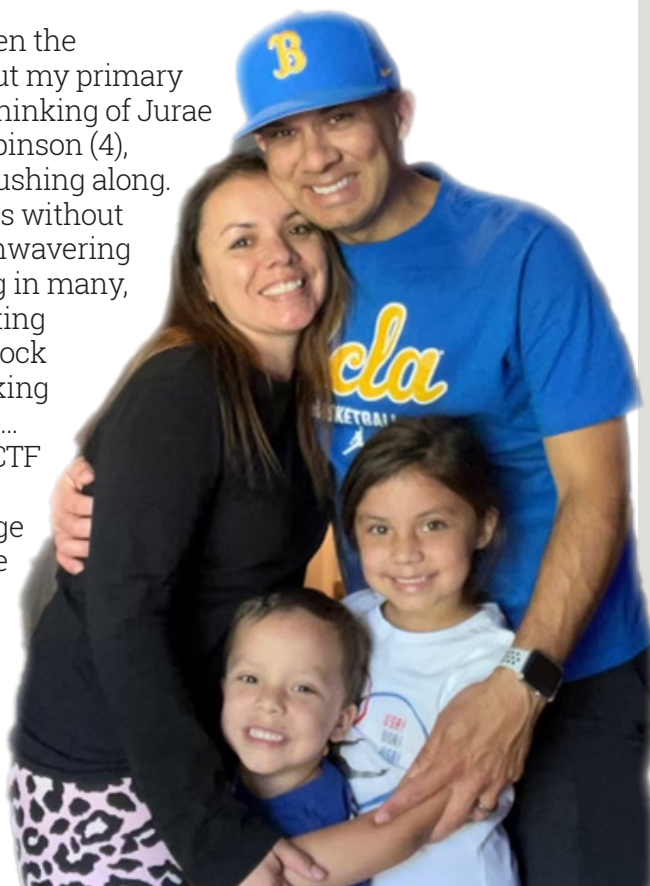
We celebrate our NF Endurance team that ran the 2022 United Airlines NYC Half on March 20. This intrepid group of athletes – many of whom first signed up for the event in 2020, pre-pandemic – raised more than \$35,000 in support of CTF's mission to end NF. The event drew a strong contingent from the New York City area, as well as those coming from as far away as Chicago and Florida. CTF staff welcomed the team for a pre-race brunch and cheered the athletes on the course. The team's top fundraisers were Julie Baruch, who raised \$13,508 in her first NFE event, and Kristina Rath, who raised \$10,725 in her 13th year as an NFE athlete. We are so proud of our team and grateful for all they do. Registration for the 2023 United Airlines NYC Half will open this fall. Visit [nfendurance.org](https://nfendurance.org) for opportunities to join our team today.

## ATHLETE SPOTLIGHT: JONATHAN SANDOVAL

“Many things move me when the training miles get tough, but my primary motivation is my family. Thinking of Jurae (6) and my NF1 Fighter, Robinson (4), always helps to keep me pushing along. I also couldn't do any of this without my wife, Nikole, and her unwavering support. While I am putting in many, many hours and miles getting ready for races, she is the rock at home with the kids, making sure it all remains possible... Being able to give back to CTF in honor of my son is an absolute honor and privilege and it helps to motivate me every single day.”

—JONATHAN SANDOVAL

Jonathan is running both the TCS New York City Marathon and the Bank of America Chicago Marathon with NF Endurance in honor of his son, NF Hero Robinson.



## 2023 NF ENDURANCE EVENTS:

**United Airlines NYC Half – March 19**  
Half marathon run through the streets of NYC

**Los Angeles Marathon – March 18-19**  
Marathon and 5K road races that launch from Dodger Stadium

**Flying Pig Marathon – May 7**  
Select from multiple distances – marathon, half marathon, 10K, 5K, and many combinations – at Cincinnati's premier road race

**TD Five Boro Bike Tour – May 7**  
Ride the car-free streets of New York City in this unique event

**Colfax Denver Marathon – May 21**  
Run a marathon, half marathon, 10-miler, 5K or team relay in the mile-high city

**BMW Berlin-Marathon – September 24**  
Add at notch to your Abbott World Marathon Majors star at this 2023 event

**Bank of America Chicago Marathon – October 8**  
The flat streets of Chicago make for a fast race at this world-class 26.2 mile race

**TCS New York City Marathon – November 5**  
Join NFE for 2023's largest marathon in the greatest city in the world

**El Tour de Tucson – November 18**  
Head to the desert for a 102, 63, or 32-mile tour, or a family-friendly fun ride

Contact Lydia Vanderloo at [lvanderloo@ctf.org](mailto:lvanderloo@ctf.org) or 646-738-8544 for more information.

capturing the financial value an NF clinic offers to its institution through referrals to surgery, radiology, laboratory services, consultation fees, and inpatient fees.

Next, **Jaishri Blakeley, MD**, director of the NF clinic at Johns Hopkins, shared the results of a study initiated in response to questions raised by the NF patient community about COVID-19 and how it might differentially affect their health. To understand more about the frequency and severity of COVID-19 in people with any form of NF, the CCAB collaborated with the NF Open Science Initiative (NF-OSI, part of Sage Bionetworks). Reassuringly, the analysis found that having NF does not appear to increase either the risk of COVID infection rates nor the risk of developing severe complications.

**Gareth Evans, MD**, chair of the U.K.'s nationally funded NF2-related schwannomatosis and schwannomatosis service at the University of Manchester, explored the potential impact of the new NF2 and SWN diagnostic criteria, and genetic testing through a case study of a patient with a solitary schwannoma. Because many of the diagnostic criteria include the presence of at least two tumors, a patient with one tumor will need additional evidence and testing for a diagnosis. Dr. Evans reported the prevalence of schwannoma-predisposition genes in people under 25 years old presenting with an apparently solitary schwannoma. Exon sequencing of *NF2*, *SMARCB1*, and *LZTR1* in these patients revealed that 19% of those in this cohort of 157 had a pathogenic variant in *NF2*, with 14% being mosaic. An *LZTR1* variant was found in 6%, *SMARCB1* in 4%, and no variant was detected in 70%.

Finally, the case conference portion of the program presented three case histories involving cutaneous neurofibroma. The cases were presented by **Carlos Romo, MD**, assistant professor at Johns Hopkins. Expert panel discussants included **Dr. Wolkenstein**, **Dr. Blakeley**, **Rox Anderson, MD**, a dermatologist and laser treatment researcher at Massachusetts General Hospital, and

**Michelle Manahan, MD**, a plastic and reconstructive surgeon at Johns Hopkins University.

Emerging from the discussion were observations that cutaneous, subcutaneous, plexiform, and paraspinal tumors, while histologically similar, have different severities and prognoses, a fact that should be clearly communicated to the patient or parent. The panel discussed options other than electrodesiccation or surgical approaches for removing cutaneous neurofibromas, including innovative laser techniques. Developing clinical trials and potential treatments for cNF hold promise, the panel stated, but must confront difficulties with quantifying tumor burden, defining the goal (prevention or removal), and considering whether to use systemic or topical drugs.

## OPENING KEYNOTE AND NEW OPPORTUNITIES

The official kick-off of the 2022 Children's Tumor Foundation NF Conference was a keynote given by **Nevan Krogan, PhD**, professor of cellular and molecular pharmacology at the University of California, San Francisco (UCSF). Dr. Krogan's scientific vision is to integrate data from various domains of genetics, biology, and proteomics to define new molecular networks that better describe diseases. The idea is that most diseases are not monogenic (caused by a pathogenic variant in one gene, i.e., *NF1* or *NF2*) but involve other key mutations, which need to be considered. This complex network uncovers previously unknown targets to exploit for drug discovery. Krogan's lab has tested this approach successfully by identifying new targets for breast, head, and neck cancer and applying the platform's power to interpret other cancer mutations. This approach to data integration was taken to combat SARS-CoV-2 infections and could be applied to NF and uncover new treatments or therapies.

At the end of his presentation, a key message was that pivotal discoveries are made only by collaborating and sharing data with no

restrictions. The current incentive system for medical research is competitive in nature and self-restrictive. This precludes others from participating with new ideas, slowing down the collaboration process and limiting the number of solutions that could solve the problem.

The silver lining for COVID-19 was that it showed the world that if personal interests, bureaucratic issues, or regulatory hurdles are removed, collaboration can run at full speed and progress can be very fast. If it took only nine months to approve an emergency vaccine for COVID-19, why can't we have the same output for other diseases? Why can't a network of researchers collaborate in the same way to solve cancer or NF or any other disease?

## Opportunities for the Scientific Community in Basic and Clinical Science

Intending to incentivize collaboration, the conference co-chairs, **Thomas De Raedt, PhD**, and **Laura Papi, MD, PhD**, presented four opportunities after Dr. Krogan's talk to the scientific community. The session aimed at engaging the audience in active discussion and vote on the most appealing topic. CTF would then work to organize a follow-up workshop-style gathering focused on the opportunity that received the most votes. The four topics were:

1. State of the art preclinical testing
2. An NF cBioPortal instance: improving access to published data
3. Leveraging and learning from external consortia and networks
4. Artificial intelligence and machine learning in clinical care and research

A speaker introduced each topic and provided examples of other communities that created similar collaborations with clear benefits. At the end of the conference, opportunity number three won the most votes, reflecting an interest in creating a framework for successful collaboration by following other scientific communities' footprints.



## Opportunities for the NF Community: Clinical Research

**Laura Papi, MD, PhD**, moderated the session. Her work is on the genetics of inherited tumor predisposition syndromes such as *NF2*-related schwannomatosis (NF2), schwannomatosis, and genetic predisposition to breast and colon cancers. Dr. Papi and her team are currently exploring the role of genetic modifiers in schwannomatosis.

**Georgia Chenevix-Trench, PhD**, chief of the cancer genetics lab at Queensland Institute of Medical Research-Berghofer, Brisbane, Australia, presented “CIMBA: Consortium of Investigators of Modifiers of BRCA1/2.” With nearly 90 participating centers worldwide, CIMBA has collected a large number of samples with associated family history, DNA, pathology, survival data, and clinical history. It used genome-wide association studies (GWAS) and genotyping to search for candidate modifiers of breast and ovarian cancer in multiple-case families with BRCA1 or BRCA2. Two variants were found to influence breast cancer risk in BRCA1, and three variants were associated with breast cancer risk in BRCA2, which could influence medical management. Dr. Chenevix-Trench discussed how a similar approach might help explain the variable penetrance of NF and lead to identifying genetic biomarkers that may indicate the need for more frequent screening for those at higher risk. In the following months, CTF will work with the group of researchers who showed interest in creating a similar framework in NF to assess the next steps.

**Eugene Jon Koay, MD, PhD**, presented “Applications of Machine Learning and Radiomics for Pancreatic Cancer: Early Detection and Therapeutic Interventions.” Dr. Koay is a physician-scientist at the University of Texas MD Anderson Cancer Center, where he leads the Cancer Physics and Engineering Laboratory Center. He discussed using artificial intelligence (AI) systems with image analysis to establish mathematical models in pancreatic cancer. These models could be applied to identify patient-specific

parameters to enable early detection, predict treatment response to improve outcomes in this and other cancers, and provide a roadmap that NF researchers could follow. He described how his group uses the physical properties of the tumor revealed by imaging to use features such as morphology, cell proliferation and migration ratios, and perfusion defects in developing algorithms to predict tumor biology. This approach enables early detection and personalized treatments. The National Cancer Institute (NCI) Division of Cancer Prevention is building an image repository for team data science that can be used to build such algorithms.

A panel discussion with **Brigitte Widemann, MD**, National Cancer Institute; **Gareth Evans, MD**, University of Manchester, UK; and **Michael Fisher, MD**, Children’s Hospital of Philadelphia, brought out the need to increase data sharing and aggregate information from biorepositories, both image and tissue, to have annotated samples for meaningful AI analysis.

## KEYNOTE #2 AND TUMOR ATLAS SESSION

Imagine you could navigate and explore tumors the same way you explore google earth, sitting in front of your computer just moving and clicking around with your mouse. Imagine you could zoom in, visualize the most miniaturized features, and see the connections between different elements and cells the same way you check countries, cities, and the roads that connect one place to another. The lab of **Sandro Santagata, MD, PhD**, Harvard University, has built visual maps of tumors that can be explored like Google Maps, at different scales and with a lot of information that describes how these complex tissues and cell networks function. Dr. Santagata explained that the tumor maps are not yet at the Google Earth level, but rather at the level of the first attempts at drawing an earth map back in the 15th century. Even still, the sophistication of such a great tool requires many researchers’ work, open sharing of data, and extensive collaboration. Taking this tool to the next level, the group

is now implementing a 3D map that will allow the use of multiplexed tissue imaging to reveal the spatial biology of cancer. This will be obtained by layering different maps on the same spatial region. With these maps, researchers can uncover responses to treatment, predict outcomes, and better define the basic biology of tumors. Each layer is represented by a different data type (WGS, RNAseq, proteomic, metabolomic, etc.) that can be explored, analyzed, and connected with clinical features and outcomes, constituting a powerful tool to interpret complex interactions. The future is training pathologists and operating room personnel to collect tissue in a way that preserves its characteristics. Standard protocols must be defined for tissue procurement that must be followed by all who wish to collaborate and contribute their data to the atlas.

Following the inspiring presentation of Dr. Santagata, **Steve Angus, PhD**, from Indiana University and **Kathrin Bernt, MD**, from Children’s Hospital of Philadelphia co-chaired the session on the NF1 tumor atlas. This session dove deep into the latest basic science discoveries in NF1, highlighting the complexity of this disease across the multiple tumor manifestations it can develop.

The first speaker, **Niousha Ahmari, PhD**, post-doc in the lab of Dr. Nancy Ratner at Cincinnati Children’s Hospital, reported on studies highlighting the effect of SHP2 inhibitors, a class of compounds that increase the immune response in NF1 tumors. Previous MEK and SHP2 combo studies in mice showed no additive or synergistic effect of the two mechanisms, reporting no substantial difference in using single agents or the combination on tumor volume. Dissecting the mechanism of action, Dr. Ahmari showed evidence that tumors treated with SHP2 inhibitors significantly increased the accumulation of some T cells. T cells are part of the immune system and help protect the body from infection; when appropriately activated, T cells are effective in fighting cancer. In NF1 plexiforms, this effect could be exploited in combination

with immunotherapy as a strategy to activate T-cells to attack and shrink the neurofibromas.

Cutaneous Neurofibromas (cNF) are the most common NF1 tumor with 95% penetrance and a variable phenotype in patients. The lab of **Eduard Serra, PhD**, at Germans Trias i Pujol Research Institute (IGTP) in Barcelona, Spain, has studied the cellular mechanisms of cNF for years, unraveling critical effects that could be used to combat these tumors. In his report this year, the researchers learned that Schwann cells, the cells from which cNF develops, require a close interaction of different cell types to develop and proliferate cNF. Having reproduced such effects in the lab using cell co-cultures, they also identified a critical mechanism that could be disrupted, cause cell death, and reduce proliferation. Co-treatment of Ogerin, a small molecule inhibitor of GPR68 involved in the cAMP pathway, with selumetinib, an FDA-approved MEK inhibitor for the treatment of inoperable plexiform neurofibromas, induced the most striking effects in cell models of cNF. The results bode well for the future investigation of this new combination drug intervention in animal models of cNF that the group is planning to run.

**David Gutmann, MD, PhD**, from Washington University in St. Louis, reported interesting results that could impact NF1 optic pathway gliomas (OPG) treatment. OPG is the most common brain tumor in children with NF1. OPGs are low-grade gliomas that generally develop on the optic nerve and could affect vision and cause other morbidities. The latest research showed that a type of neuron called retinal ganglion cells that populate the optic nerve is involved in a series of complex mechanisms that regulate their excitability status and a cascade of events that ultimately sustain the growth of OPG tumors. The interruption of this mechanism of events using the drug Lamotrigine showed attenuation in OPG tumor progression, validating the researchers' hypothesis. Lastly, Dr. Gutmann reported an interesting observation that not all germline

mutations are equal and that different *NF1* mutations have different effects on neuron-mediated glioma formation and growth. The development of OPG tumors could be specifically linked to the specific effect of that mutation on neurons.

## GENE THERAPY SESSION

The gene therapy session began with an introductory talk by **Deeann Wallis, PhD**, from University of Alabama at Birmingham. Dr. Wallis presented an overview of the various gene therapy strategies at the DNA, RNA, and protein levels, and the pros and cons of each in the context of NF1.

**Gary Brenner, MD, PhD**, from Massachusetts General Hospital (MGH) presented a gene therapy strategy for schwannoma treatment that utilizes adeno-associated virus (AAV) delivery of the pro-apoptotic gene ASC. The AAV-ASC vector killed schwannoma cells very effectively with minimal toxicity, showed resolution of tumor-associated pain, and the efficacy was not altered by pre-existing AAV immunity.

**Akiko Yoshinaga, PhD**, from MGH presented a gene replacement approach for schwannoma therapy that involved the intratumoral injection of an AAV vector carrying the *NF2* gene. This vector restored merlin activity in cells lacking the *NF2* gene and suppressed schwannoma growth in mouse models, providing another potential gene therapy option for NF2.

The presentation by **Cameron Church** from University of Alabama at Birmingham focused on exon skipping using antisense oligonucleotides (ASO) as a therapeutic approach for NF1. Exon 52 of *NF1* gene was shown to be non-essential for *NF1* function and ASOs designed to skip mutated exon 52 restored *NF1* expression and Ras signaling. Thus, patients with mutations in *NF1* exon 52 can benefit from exon skipping therapy. The presentation by **Dr. Erik Westin, PhD**, also from University of Alabama at Birmingham, showed how delivery of nanoparticles encapsulating *NF1* cDNA into rat mammary

gland tumors stopped tumor growth and also reduced tumor size, thus identifying *NF1* nanoparticles as another potential therapeutic strategy.

## NF2 AND SCHWANNOMATOSIS SESSION

**Long-Sheng Chang, PhD**, from Nationwide Children's Hospital reported on "Orthotopic Xenograft Models and Potential Treatments for NF2-Deficient Meningiomas." In his presentation, Dr. Chang discussed the identification of eIF4A, an important target for tumor cell growth, that can be effectively inhibited by a new class of drugs showing potent growth-inhibitory activity on both NF1 and NF2 tumors. Initial experiments in NF1 MPNST and NF2-related SWN vestibular schwannoma and meningioma models (both in cells and animal models) showed promising activity for this class of compounds, reducing tumor growth and increasing DNA damage response and apoptosis, a method the body uses to get rid of unneeded or abnormal cells. These initial results still require more investigation to gather the necessary efficacy and safety evidence required by the FDA to initiate a clinical trial in humans.

**Scott Plotkin, MD, PhD**, from Massachusetts General Hospital, presented the revised diagnostic criteria and nomenclature for NF2 and schwannomatosis, a process involving worldwide experts in these diseases, including the patient community, and took about five years to complete. The previous criteria were established in 1995, and advancements in the knowledge of these diseases and the availability of genetic testing were two very important factors that triggered the scientific community to reassess the old criteria. With the updated nomenclature, schwannomatosis is now the recommended umbrella term for both NF2 and schwannomatosis since they share a genetic predisposition for schwannoma formation. Molecular analysis is clinically indicated for all patients suspected of schwannomatosis (except those with bilateral

vestibular schwannoma). The types of schwannomatosis are classified and referred to according to the specific gene variant. Neurofibromatosis type 2, or NF2 is now called “NF2-related schwannomatosis”, and the general term for schwannomatosis is now specific to the gene variant identified, to include: *SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, schwannomatosis not otherwise specified (NOS), and schwannomatosis not elsewhere classified (NEC). Note that when referred to the gene, names are italicized, when referred to the gene product, or the protein produced by the gene, the names are not italicized

A retrospective study conducted by **Gareth Evans, MD**, from the University of Manchester, UK, of 266 NF2-related schwannomatosis (NF2) irradiated patients showed a significant increase in malignant progression or new primary malignancy developing in these patients. After years of anecdotal reports of malignant transformation for patients undergoing irradiation of their tumors, the study looked at data from 1969 until recent years to gather enough statistical significance to clarify this important evidence. Dr. Evans reported that the risk of developing malignancy or malignant progression in the *NF2-related SWN* population was 5-6%, a number that requires serious evaluation when considering such an approach, especially in the young population, as the risk is higher (up to 7.5%) in patients 25-years-old or younger.

**Robert F. Hennigan, PhD**, from Cincinnati Children’s Hospital Medical Center, reported on recent advancements in understanding the NF2 protein function and its network of interactions with other molecules or proteins. This critical information allows us to gain insights into the consequences of its loss in developing NF2-related schwannomatosis (NF2). A protein called PIP2 regulates the tumor suppressor function of Merlin (NF2) and represents a mechanism to activate Merlin. This new interactor of the NF2 protein will be further investigated and could

generate new hypotheses to enhance the tumor suppressor activity of Merlin. (<https://doi.org/10.1101/2021.11.11.468247>)

One of the hallmark features for all schwannomatoses, as well as NF1, is pain. Pain is highly variable among patients, puzzling researchers to understand the possible causes for such variation. **Sheila Mansouri, PhD**, from Princess Margaret Cancer Center, Toronto, Canada, presented the results of a study conducted to identify the molecular hallmarks of pain in schwannomatosis. This project, called **Synodos for Schwannomatosis**, analyzed a cohort of 165 tumors from 72 patients using a platform of genomic sequencing and analyses to correlate findings with clinical and molecular characteristics, uncover molecular mechanisms of pain in schwannomatosis and compare painful from non-painful tumor molecular profiles. The study unveiled that there are key genomic alterations in schwannomatosis and relative to non-syndromic schwannomatosis. It also showed key associations between pain and gender, tumor location, *LZTR1* mutation, and copy number variations. The significance of this study is that it will allow the testing of personalized therapeutic modalities for the treatment of pain depending on the patient’s genetic makeup.

The session concluded with **Larry Sherman, PhD**, from Oregon Health and Science University, which reported on the protein *SMARCB1* and its function in regulating the transcription of factors that directly mediate pain in schwannomatosis patients. In his findings, Dr. Sherman concluded that patients with *SMARCB1* compared to *LZTR1* mutations appear to experience different types of pain, likely through distinct mechanisms. Some schwannomatosis tumors secrete specific proteins called cytokines that are normally produced during inflammatory processes. Patients with *SMARCB1* mutations could benefit from pain relief by targeting IL6, a specific cytokine that plays a critical role in pain generation or progression. Targeting other secreted proteins that are common to

Schwann cells could also be beneficial for pain relief, and further research is warranted in this field to characterize this approach better.

## KEYNOTE #3 AND IMMUNOTHERAPY SESSION

The immunotherapy session began with a keynote lecture by **John Maris, MD**, from Children’s Hospital of Philadelphia. The first half of Dr. Maris’s talk focused on the discovery of the cell surface protein GPC2 as an oncoprotein in neuroblastoma and how it can be targeted by immune-based therapies such as antibody-drug conjugates and chimeric antigenic receptor (CAR) T cells. Both methods have shown strong efficacy with minimal toxicity in preclinical studies and have potential for development into clinical trials. Dr. Maris subsequently presented a novel strategy to recognize and target oncogenic proteins that are inside cancer cells and are typically not targetable. A new type of engineered CAR T cells called peptide-centric CARs (PC-CAR) were developed specifically to recognize a peptide from the *PHOX2B* gene implicated in neuroblastoma, and showed potent tumor killing. This technology has potential to significantly expand the immunotherapy field and make it available for more patients.

**Antonio Iavarone, MD**, from Columbia University Medical Center highlighted the differences in the tumor microenvironment of NF1 gliomas. He presented evidence for the presence of a low grade NF1 glioma subgroup that are ‘high immune’ type characterized by increased T lymphocytes, neoantigens, and other immune signatures. This category of low-grade glioma are potentially good candidates for immunotherapy.

## KEYNOTE #4 AND PAIN SESSION

**David Pang, MD** from Guys’ and St Thomas’ Hospital NHS Trust, UK, gave a keynote lecture on NF and long term pain, highlighting the various receptors and biological pathways that are known to be involved in pain. He discussed how these receptors are being studied for NF and how pain can be influenced not only by these

biological pathways, but also psychological and social factors. NF pain could fit into a wider category of pain state called central sensitization state, whereby the pain's signaling is a hyperactive mode, and pain signals are being turned on despite the fact that no real injury exists.

Indeed, such hypersensitivity in *NF1* was also an important teaching of a talk by **Namrata Raut, PhD**, Cincinnati Children's Hospital, who demonstrated how *NF1* depletion in mice Schwann cells affects pain signaling independently from the presence of a tumor.

**Frank Buono, PHD**, of the Yale School of Medicine presented an ongoing trial co-funded by CTF which involves the use of the iCanCope mobile app as a tool to monitor and manage NF1-related pain through cognitive-behavioral therapy and mind-body alternative approaches. Such a tool could also find applications in NF2 and non-NF2-schwannomatosis pain.

A presentation on an ongoing clinical trial at Massachusetts General Hospital for pain in non-NF2-schwannomatosis by Jennifer Da highlighted the necessity to involve many different centers in order to reach a meaningful number of patients, as well as the need for deeper involvement of the patients in the design of such trials.

Lastly, **Angelica Sandstrom, PhD**, Massachusetts General Hospital, discussed the various brain imaging techniques that could be applied to study NF pain.

## CLINICAL PLATFORM SESSION

**Scott Plotkin, MD, PhD**, from Massachusetts General Hospital provided interim results of brigatinib, a ALK tyrosine kinase inhibitor, in 20 NF2-related SWN patients with progressive tumors enrolled in the INTUITT-NF2 platform trial. Tumor shrinkage (>20% reduction in volume) was seen in 18% of 88 tumors. There was also a reduction in the growth rate of some tumors post-treatment, especially seen in non-vestibular

schwannomas and meningiomas.

To optimize the accuracy and consistency of volumetric measure of optic pathway gliomas (OPG) between institutions and MRI manufacturers, a multi-center study using Quantitative Image Analysis in NF1-OPG was presented by **Robert Avery, DO**, from Children's Hospital of Philadelphia. The goal of this analysis will be to use automated volumetric MRI analysis to identify patients at low-risk of vision loss OPGs from patients at high risk of vision loss to guide clinical care and therapeutic clinical trials.

**Amy Armstrong, MD**, from Washington University provided a review of the phase 2 trial using cabozantinib for the treatment of NF1-associated progressive, clinically significant or inoperable plexiform neurofibroma in children. Of 21 patients, two (9.5%) showed a partial response of cabozantinib, and eight patients with progressive plexiforms before the study had stability of their plexiforms while on the trial. The researchers indicate that this may be a viable option for patients in cases where MEK inhibitors are not effective or tolerated.

A retrospective study looking at children on a selumetinib clinical trial for inoperable plexiform neurofibroma was provided by **Andrea Gross, MD** of the National Cancer Institute, (NCI). Of 49 evaluated children in the study, 33 (67%) had scoliosis and 38% of those had worsening of spine curvature while on treatment. Of seven subjects who had a spinal fusion during treatment, all had a large paraspinal plexiform with a majority having stable or partial response of the large adjacent plexiform neurofibroma during selumetinib treatment. The study did not support that treatment with selumetinib prevents the progression of scoliosis, even in patients with plexiforms that were responsive to selumetinib. However, given the limited numbers and methodology of the study, more investigation will be required to confirm these findings.

**Pam Wolters, PhD**, from National Institutes

of Health discussed patient-reported outcome (PRO) measures of the phase II SPRINT trial to document the long-term clinical benefit of selumetinib in children with NF1 and inoperable plexiform neurofibromas. In a previous study, of 50 children on selumetinib for one year, 68% had partial response of their plexiform and a majority of these reported improvement in PRO measures including pain intensity, pain interference, and quality of life. The current study evaluates whether the PRO gains continued after the first year. The study found significant improvements in tumor pain intensity, pain interference, and quality of life that persisted over four years. Looking at qualitative data in 21 patients, a vast majority of children and their parents reported positive changes, especially with improved function, improved appearance, and decreased pain.

**Longitudinal analysis of whole-body MRI (WBMRI)** in NF1 was provided by **Eva Dombi, MD**, from the National Cancer Institute (NCI). Seventy-five patients enrolled in the NCI NF1 Natural History study were included in the analysis. At baseline, 71 of patients (95%) had plexiform neurofibroma involvement in at least one body region. Over time, an increase in tumor involvement was seen in 29 patients (39%), and 15 patients (20%) had neurofibroma burden regression. Patients with an increase in tumor involvement tended to be younger compared to those without an increase. Twenty-two patients developed new areas of tumor in previously unaffected body regions which were either distinct nodular lesions or nodular areas along major nerves, but the development of new bulky plexiform neurofibromas was not seen. It is important to note that the NCI study group was not representative of the general NF1 population.

To read more about the NF Conference, go to [nfconference.org](https://nfconference.org)

## TRAVEL GRANTS: Professional Development Opportunities

The Children's Tumor Foundation Europe is offering travel grants to a selection of multidisciplinary NF centers throughout Europe to further the professional development of clinicians and allied healthcare professionals who see NF patients. While these grants are not restricted to applicants based in Europe, because of the short duration of these visits, it is expected that many of the grantees will be based in Europe. Applicants based in other continents, especially those who will happen to be in Europe for other reasons, are of course welcome to apply.

Participating clinics offer a pre-programmed 1-to 3-day visit, as well as à la carte training. Please click the link at each location to review each center's program or à la carte offerings. Please note that language restrictions apply, but many centers offer training in several languages. Each center has noted language restrictions in its program offerings.

If you have questions, please reach out to the contact at the NF center to which you are interested in applying. For general questions, please reach out to CTF Europe Scientific Officer Marco Nievo at [mnievo@ctf.org](mailto:mnievo@ctf.org).



### To Apply

Applicants are invited to submit a CV along with an explanation of their motivation for applying and a description of the program or à la carte training they wish to receive. Please email these items to the site contact, which is included along with specific information about each clinic at [ctfeurope.org/research](http://ctfeurope.org/research). Please submit at least three months in advance of the time frame in which you hope to attend.

### Grant Amounts and Reimbursement

Once selected by the clinic and the program visit has been planned, the grantee will be contacted by CTF with a reimbursement procedure. CTF Europe will reimburse up to 500 Euro for travel in economy class, up to 150 Euros per night for lodging, and up to 50 Euros per day for food.

To learn more about these educational opportunities, go to [ctfeurope.org/research](http://ctfeurope.org/research)

## NEUROFIBROMATOSIS EUROPEAN MEETING

The 20th European Neurofibromatosis Meeting will be held in person in Manchester, United Kingdom for two days, October 10-11, 2022.

There will be an innovative and thought-provoking speaker agenda, including a keynote lecture from Gareth Evans, MD, Professor in Medical Genetics and Cancer Epidemiology. Go to the [convenzis.co.uk](http://convenzis.co.uk) website for more information, or to register.

NF News is the official publication of the Children's Tumor Foundation. All issues are available on our website at [www.ctf.org](http://www.ctf.org). Please direct any questions or feedback to [info@ctf.org](mailto:info@ctf.org).

NF News Editor, Vanessa Younger

NF News Design Director, Susanne Preinfalk

The Children's Tumor Foundation is the world's leading nonprofit dedicated to funding and driving innovative research that will result in effective treatments for the millions of people worldwide living with NF, a group of genetic disorders that causes tumors to grow on nerves throughout the body. One in every 3,000 people is born with some type of neurofibromatosis or schwannomatosis, which may lead to blindness, deafness, bone abnormalities, disfigurement, learning disabilities, disabling pain, or cancer. NF affects all populations equally, and while there is no cure yet, the Children's Tumor Foundation mission of driving research, expanding knowledge, and advancing care for the NF community fosters our vision of one day ending NF. For more information, please visit: [ctf.org](http://ctf.org).

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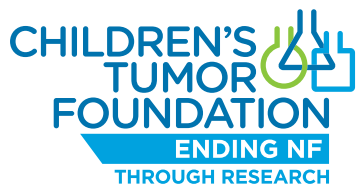
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