

2024 - 2025

YEAR IN REVIEW

NYU DYSAUTONOMIA CENTER



The era of genetic therapy for FD has begun

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Letter from the Director

Dear Families, Friends, and Supporters,



For 16 years, I dreamed of the day when genetic therapy for those born with Familial Dysautonomia (FD) would become a reality. Last June, that dream came true when the first FD patient received an antisense oligonucleotide (ASO)—a potentially groundbreaking genetic treatment—at NYU. The ASO treatment requires spinal injections, and not all patients may be eligible. To expand treatment options, three additional genetic therapies are in development: a kinetin derivative that may become an oral treatment for FD, a gene insertion system using a viral vector—delivered via eye injection—to prevent progressive vision loss, and a gene-editing technique using CRISPR.

Offering multiple treatment options will help make genetic therapy accessible to patients of all ages. This remarkable progress is the result of decades of collaboration with exceptional scientists, driven by the hope that these therapies will halt disease progression and mark a turning point in the fight against FD.

Understanding the mechanisms that drive FD is essential for developing new therapies. One particularly exciting new discovery is that inflammation occurs in the FD retina before nerve cell degeneration begins. This finding opens the door to potential treatments targeting inflammation, which could be key to preserving vision in the future. FD is not a one-size-fits-all disease—each patient is unique and faces different medical challenges. Our goal is to use a combination therapy approach to tailor treatments to each patient’s individual needs. Clinical care remains our top priority, and autonomic crises continue to be a major challenge for some FD patients. To improve that, we are conducting a new FDA-sponsored clinical trial testing sublingual dexmedetomidine as a home-based treatment for autonomic crises. Early results have been promising, and we hope this fast-acting, under-the-tongue medication will provide an effective way to manage these episodes outside the hospital.

Through a new collaboration with the HSN4 Foundation, we have launched a patient registry and database for individuals with a related genetic disorder: Congenital Insensitivity to Pain with Anhidrosis (CIPA). Children with CIPA share many features with those who have FD. Studying these diseases side by side lays the foundation for future discoveries that may benefit both patient groups.

This has been a transformational year for our Center. In this Year in Review report, you will find details about these exciting developments. None of these achievements would have been possible without the unwavering support of the Familial Dysautonomia Foundation, Inc., and our incredible community of families, donors, and researchers. A special thanks to Adrian Krainer and the n-Lorem Foundation for making genetic therapy a possibility. Together, we have made great strides in shaping the future of FD care and treatment.

With gratitude,

A handwritten signature in blue ink, appearing to be 'H. Kaufmann', written in a cursive style.

Horacio Kaufmann, MD, FAAN

Gene Therapy for Familial Dysautonomia: The dawn of an era

On June 20, 2024, the field of familial dysautonomia (FD) research reached a groundbreaking milestone.

A young patient with FD received the first dose of an antisense oligonucleotide (ASO), a drug designed to correct the genetic defect underlying FD. This marks the beginning of a new era of genetic therapy for this devastating condition.

The first patient to receive this experimental treatment arrived at NYU early in the morning, marking an emotional moment for the team that had worked for decades to reach this point. The treatment was administered via a spinal injection, allowing the drug to distribute throughout the nervous system, including the brain and dorsal root ganglia, where sensory nerve cell bodies reside. With a skilled team in place in a state-of-the-art NYU operating room, the procedure was completed smoothly in under an hour with light sedation. The patient was wheeled back to their room nearly awake. As we gathered around the bedside, we felt a profound sense of achievement, and hope—hope that this could become a disease-modifying therapy for patients with FD.

The patient will be closely monitored, and if the treatment proves successful, it will be expanded to more individuals.

Evaluating Treatment Efficacy

FD patients are born with severe sensory deficits that persist throughout life and may be difficult to reverse. However, vision and balance are intact at birth but deteriorate progressively, making them key targets for genetic treatment.

The drug we are testing, an antisense oligonucleotide (ASO), is a small RNA molecule that corrects the FD splicing defect, thereby increasing the production of functional ELP1—the protein deficient in FD.



Dr. Alejandra Gonzalez-Duarte and her team at NYU Langone Health administering the first dose of gene therapy.

Outcome Measures

To assess the impact of this therapy, which will be administered every four months for two years as part of the clinical trial, we are utilizing a range of clinical and functional measures.

- **Gait analysis** using a specialized computerized assessment called "Mobility Lab."
- **Proprioception assessments** to evaluate knee joint position awareness.
- **Patient-reported questionnaires** to capture subjective experiences.
- **Visual function tests** to monitor neurological effects.
- **Retinal thickness measurements** via optical coherence tomography (OCT).
- **CSF and blood ELP1 levels** to track target engagement and biological response.

The Path to Genetic Therapy



Dr. Riley and Dr. Day

The journey to this achievement began in 1949 when **Drs. Conrad Riley and Richard Day**, two New York pediatricians, first described familial dysautonomia in five children from the Jewish Orthodox community in Brooklyn and hypothesized a genetic basis for the disorder. Recognizing the urgent need for research, a group of concerned parents established the FD Foundation in 1951.

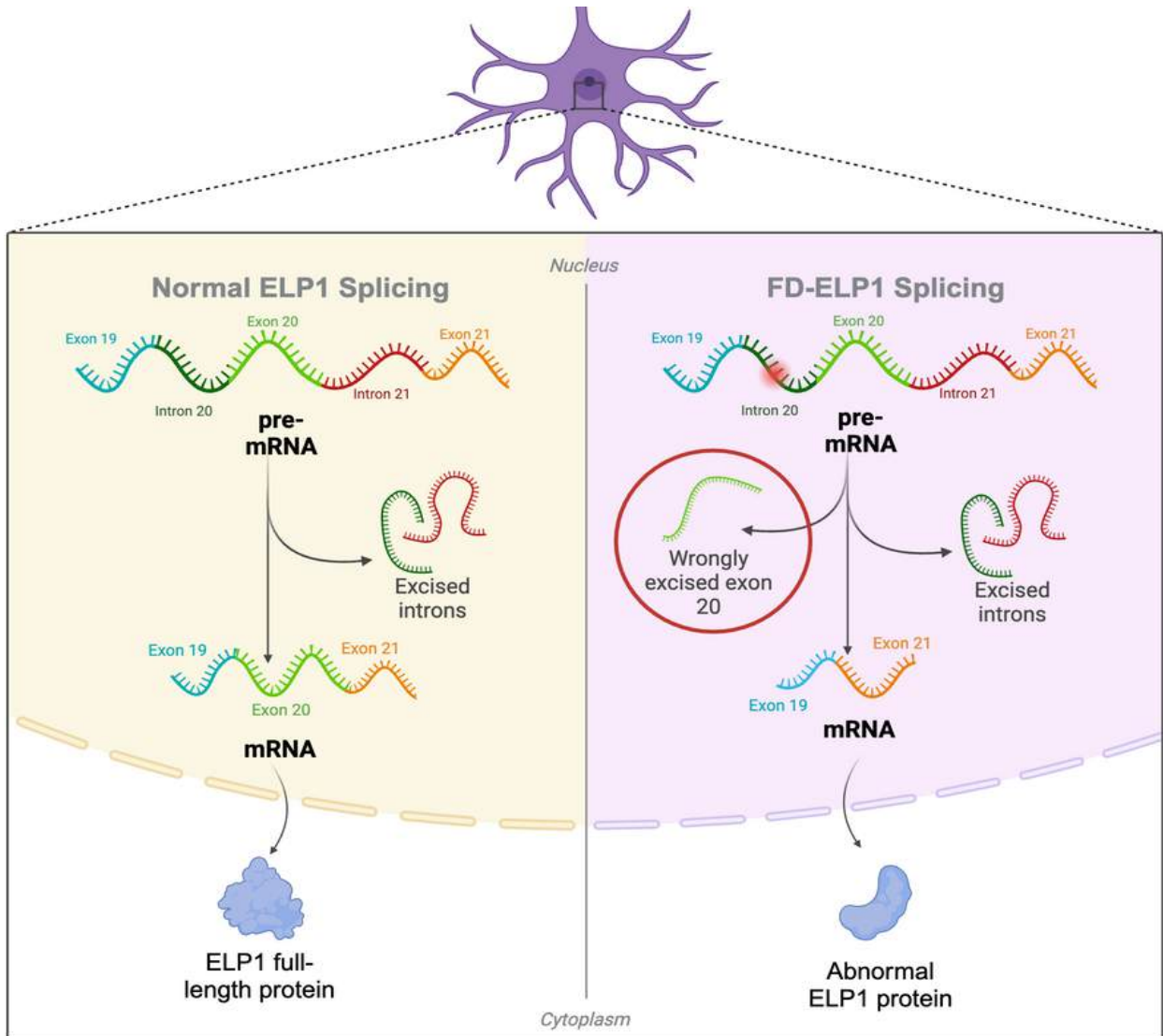
A breakthrough came in 1969 when **Dr. Felicia Axelrod** initiated the FD registry at the NYU Dysautonomia Center, centralizing patient care and research.

With a large collection of patient blood samples from NYU and Hadassah Hospital in Israel, **Dr. Sue Slaughaupt** at Massachusetts General Hospital identified the causative mutation in the ELP1 gene (formerly IKBKAP) in 2001. This mutation disrupts RNA splicing, leading to reduced levels of functional ELP1 protein, which is essential for neuronal development. The defective splicing process results in the exclusion of exon 20 from the mature mRNA, preventing sufficient ELP1 protein production.



Dr. Felicia Axelrod and Dr. Susan Slaughaupt

The FD Splicing Defect



Breakthroughs in Splicing Correction

Efforts to correct this splicing defect have been ongoing for decades. In 2007, the first breakthrough came with Dr. Slaughenput's discovery that a small molecule, kinetin, could partially restore proper splicing. However, limitations in efficacy and safety led researchers to seek alternative approaches.

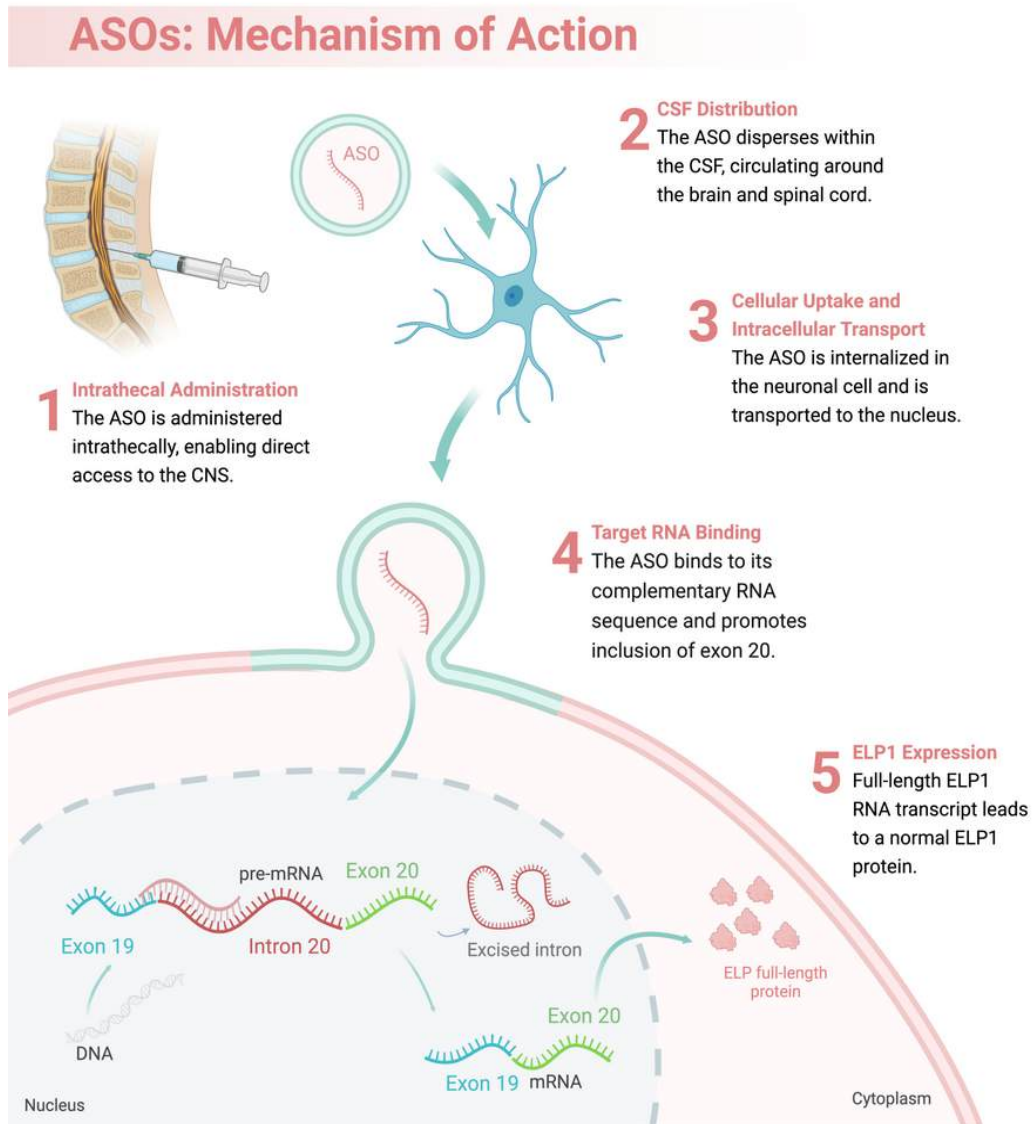
In 2018, **Dr. Adrian Krainer** at Cold Spring Harbor Laboratory demonstrated that ASOs could successfully correct the splicing defect in a mouse model of FD. His expertise in ASO technology had already led to the FDA approval of Spinraza®, a transformative treatment for spinal muscular atrophy, in 2016.



Dr. Adrian Krainer

What is an ASO and How Does It Work?

An ASO is a short, synthetic strand of RNA designed to bind to a specific RNA sequence. It works like a puzzle piece, fitting precisely onto its target sequence in the RNA. In FD, the ASO binds to the ELP1 pre-mRNA at the site of the splicing defect, preventing the faulty splicing signal from excluding exon 20. This correction ensures exon 20 is included in the final mRNA, allowing cells to produce functional ELP1 protein. By guiding the splicing machinery to correctly process the RNA, the ASO effectively addresses the genetic error at its source, offering a precise and targeted therapeutic approach.



The Role of the n-Lorem Foundation

In 2020, n-Lorem, a non-profit organization founded by Dr. Stanley Crooke, former CEO of Ionis Pharmaceuticals (developer of Spinraza®), committed to providing ASO therapies for ultra-rare diseases at no cost for a patient's lifetime.



n-Lorem leveraged the FDA's newly established regulatory pathway for drugs targeting ultra-rare diseases. This pathway allowed for fewer studies and a streamlined approval process. If an application was accepted, the FDA allowed treatment for a single patient. Under this initiative, n-Lorem conducted all the necessary toxicology and pharmacology studies in animals to secure FDA regulatory approval for ASO therapy in FD.



Julie Douville, PhD
Vice President, ASO
Discovery and Development



Laurence Mignon, PhD
Executive Director, Clinical
Development



Megan Knutsen, MS
Director, Clinical Operations
and Project Management



Sarah Glass, PhD
Chief Operating Officer

A Pathway to Treatment

FDA regulatory approval for FD ASO therapy faced challenges. Initially, the FDA rejected the application, as it did not classify FD as an ultra-rare disease. However, after submitting additional data and making a compelling case, the program was ultimately accepted after two rounds of discussions. An Investigational New Drug (IND) application was submitted in October 2023.

Following extensive regulatory review at NYU, we successfully administered the first ASO dose in June 2024, with subsequent doses in August 2024, October 2024, and February 2025. The treatment is planned to continue every four months thereafter.

Looking Ahead

This landmark achievement is the culmination of decades of research, collaboration, and dedication from both the scientific and patient communities. As we gather more data on the efficacy and safety of ASO therapy in FD, we remain hopeful that this approach can be expanded to more patients soon. The success of this initiative represents a beacon of hope for the future of genetic therapies in neurological diseases.

Stay tuned for further updates as we continue to advance this pioneering treatment.

Other Genetic Therapies in Development

Developing multiple disease-modifying therapies for FD is essential, as it allows for personalized treatment strategies tailored to each patient's individual needs. The primary goal of genetic therapies is to increase ELP1 protein levels, potentially slowing disease progression and reducing its severity.

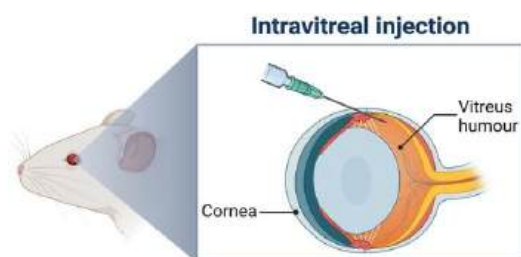
An important consideration is the method of administration. Some treatments require injections into the spine or eye, while others can be taken orally or through a G-tube. Ensuring a range of delivery options will help make these therapies accessible to all patients.

Intravitreal Gene Insertion to Prevent Vision Loss

A promising gene therapy approach for FD-related vision loss involves delivering a functional ELP1 gene directly to the retina using an adenovirus as a carrier. This research, pioneered by Dr. Lefcort and Dr. Chekuri, has already shown success in preclinical models, preventing the death of retinal cells in an FD mice. These findings bring hope that the therapy could one day prevent progressive vision loss in people with FD.



Dr. Frances Lefcort



Currently, clinical trials in an FD mouse model are underway to determine the optimal dose. Before it can move to human trials, further testing in animal models is required to ensure both its effectiveness and safety.

Oral Kinetin Derivatives

Kinetin, a plant-derived cytokinin, has shown promise in improving motor coordination and proprioception in FD mouse models. However, the high doses previously needed to achieve these effects came with significant side effects, such as nausea. In recent years, researchers led by Susan Slaugerhaupt at MGH have optimized new kinetin derivatives that are more potent than traditional kinetin, allowing for lower, safer doses that could be used in human treatments.

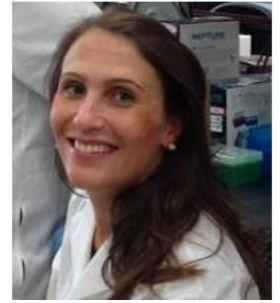
The leading kinetin derivatives currently in development is BPN680, which has shown improvements in survival, gait abnormalities, and retinal degeneration in FD mouse models.

This compound represents an exciting advance because it could be taken orally or through the g-tube. Safety studies are under way as part of the NIH blueprint grant to clear the path to be tested in humans.

Gene editing

CRISPR-based therapies are gene-editing treatments that use CRISPR molecules to modify DNA in the body. **Dr. Elisabetta Morini** and Dr. Alves at MGH are developing a base editor (BE) designed to specifically and permanently correct the FD mutation. BEs are genome-editing tools capable of introducing precise point mutations at targeted genomic locations.

Dr. Alves's group has led preclinical efforts to optimize novel BE technologies for treating spinal muscular atrophy (SMA). They are now expanding on these studies to develop optimized BE strategies for precisely and efficiently correcting the *ELP1 T6C mutation*. Gene editing offers a promising approach to permanently correct genetic mutations, providing a long-term solution for diseases like FD.



Dr. Elisabetta Morini

CRISPR-based therapies are gene-editing treatments that use CRISPR molecules to modify DNA in the body



Measuring ELP1 Levels in Blood: A Biomarker for Tracking Genetic Therapy in FD

Genes serve as the body's instruction manual, directing the production of proteins essential for all biological functions. In patients with Familial Dysautonomia (FD), a mutation in **the *ELP1* gene** disrupts the synthesis of elongator acetyltransferase complex subunit 1 (ELP1), a protein critical for developing and maintaining a healthy nervous system—enabling normal sensation and movement. The FD mutation leads to lower **ELP1 protein** levels, preventing the nervous system from developing properly. As a result, individuals with FD experience difficulties with sensation and motor control—hallmark symptoms of the disease. Additionally, low ELP1 levels after birth contribute to progressive vision and balance impairments.

Studies in FD mouse models have shown that certain compounds can partially correct the genetic defect. We know this because, after treatment, postmortem brain analysis revealed higher levels of normal ELP1 messenger RNA, which should, in turn, increase ELP1 protein production. However, actual ELP1 protein levels were not measured due to a lack of an appropriate method.

The goal of genetic therapy—whether using an antisense oligonucleotide (ASO), a small molecule, or gene insertion via a viral vector—is to correct the genetic defect and increase ELP1 levels in the brain and other tissues. While the precise sources of ELP1 in the blood are not fully defined, they may reflect levels in the brain and peripheral nerves, making blood ELP1 a potential biomarker for evaluating drug effectiveness. In addition to clinical measures such as vision tests, gait analysis, and sensory assessments, measuring ELP1 levels in blood may provide critical evidence of target engagement—proof that a drug is having its intended biological effect.

Developing a Blood Test for ELP1

To facilitate the assessment of genetic therapies in FD, our team has been working on a method to measure ELP1 protein levels in the blood.

In collaboration with **Syneos**, a commercial laboratory, we developed a blood test capable of accurately measuring ELP1 levels from a small blood sample. Using this test, we analyzed ELP1 protein levels in 124 individuals, including 58 FD patients and 67 carriers of the FD genetic mutation (parents). To assess the test's reliability, we collected two samples from 43 participants and additional samples from 22 of them one year later.

Key Findings

The results showed that FD patients had significantly lower ELP1 protein levels than carriers. On average:

- FD patients had 244 pg/ml of ELP1 protein
- Carriers had nearly ten times that amount, averaging 2,210 pg/ml

Every FD patient had a significantly lower blood ELP1 level than their parents. Furthermore, when the same person's blood was tested twice—even a year apart—the ELP1 levels remained nearly identical, confirming the test's reliability.

We also examined the threshold ELP1 level that distinguishes FD patients from carriers. Our findings revealed that no carriers had an ELP1 level below 800 pg/mL, indicating that anyone with a level under this threshold had FD. While some FD patients exhibited higher ELP1 levels, their levels were always lower than those of their parents.

Every FD patient had a significantly lower blood ELP1 level than their parents.



Implications for Genetic Therapy and Diagnosis

Tracking ELP1 protein levels in clinical trials for FD patients could be very useful. By monitoring blood ELP1 levels over time, doctors and researchers can better assess treatment effectiveness and make more informed decisions about patient care—potentially leading to improved management and therapies for FD.

Additionally, measuring ELP1 levels in the blood may help determine whether newly identified mutations in the ELP1 gene are pathogenic.

News and Breakthroughs

A Public Benefit Corporation Focus on FD Drug Development

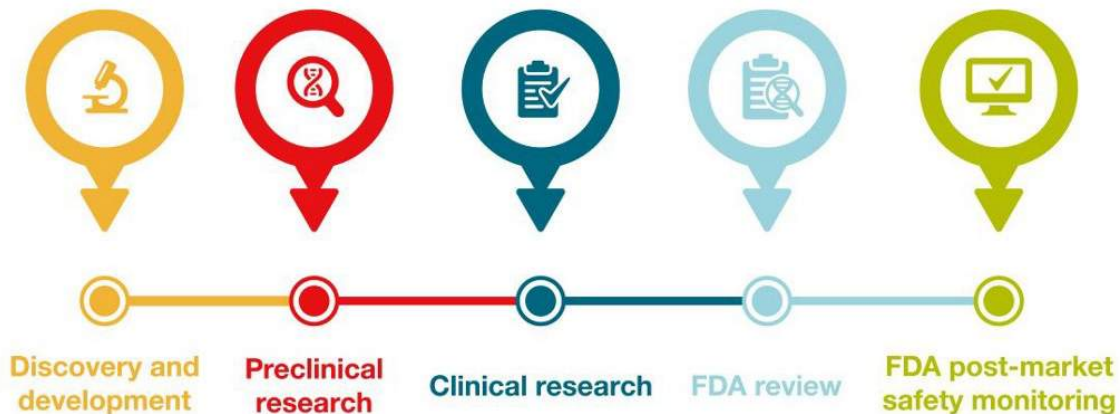
Last year saw the formation of a company whose sole focus is on developing therapeutics for FD. It is called **Tikun Therapeutics** (tikuntherapeutics.com) and is a wholly owned subsidiary of the FD Foundation. It is established as a for-profit, public benefit corporation.

Currently the two major research projects being pursued by Tikun include **Dr. Susan Slaughaupt's** small splicing molecule and **Dr. Frances Lefcort's** gene therapy vector which is now being further developed in **Dr. Anil Chekuri's** lab. **Adam Sachs** is Tikun's CEO.

In 2024, Tikun received both **Rare Disease and Orphan Disease Designations from the FDA** for both therapeutics, opening the door to future funding opportunities to support the translation of these therapeutics to the clinic.



The five stages of drug development



Clinical and Translational Research

New Findings in the FD Retina

This past year has revealed novel findings about the FD retina.



Optical coherence tomography (OCT) scan showing a normal retina.

In one major study—made possible by a generous gift from a special FD family and led by Dr. Frances Lefcort in collaboration with a group in Spain led by **Dr. Nicolas Cuenca** at the University of Alicante, along with **Dr. Carlos Mendoza-Santiesteban**, **Dr. Horacio Kaufmann**, and **Dr. Alejandra Gonzalez-Duarte**—we discovered that, in addition to the loss of retinal ganglion cells, **an inflammatory process occurs in the FD retina**. This inflammation is marked by the activation and overgrowth of another cell type, called glial cells. We also found that the same process exists in our FD mouse model retina.

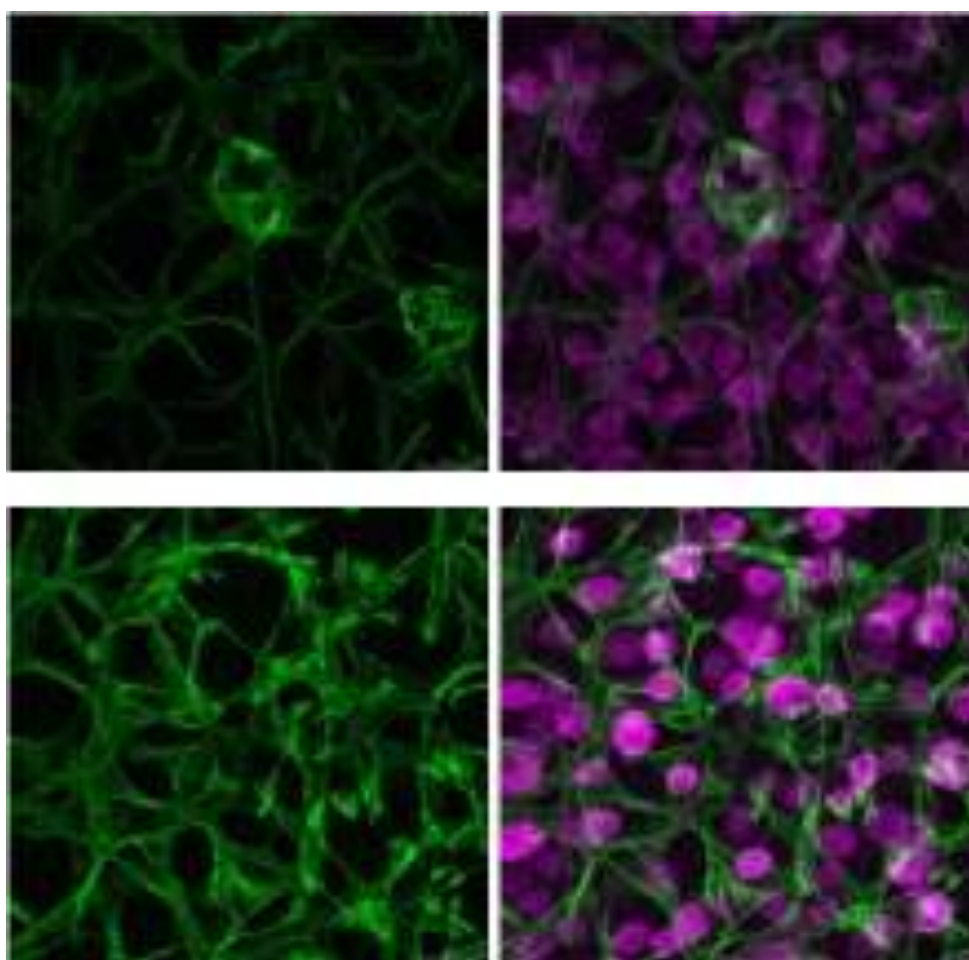
This glial response precedes neuronal degeneration in mice. For years, we have known—thanks to the elegant work of Dr. Carlos Mendoza-Santiesteban, Dr. Horacio Kaufmann, and Dr. Felicia Axelrod—that people with FD progressively lose vision due to the slow degeneration of retinal neurons, particularly retinal ganglion cells. When these neurons die, visual signals cannot reach the brain. However, our new findings show that retinal neurons are not the only cell type affected in the FD retina; glial cells and the retinal vasculature are also disrupted in FD. This is particularly significant because it is well known that retinal neurons, glial cells, and vasculature form what is called a neurovascular unit. These three cell types communicate extensively, and when the neurovascular unit is unhealthy or inflamed, the neurons suffer.

The good news is **that this discovery provides additional therapeutic targets**. Other optic neuropathies also involve vascular or glial cell dysfunction, so we can now take advantage of existing research to develop strategies aimed at reducing glial and vascular responses in the FD retina. By doing so, we may slow down or even prevent the death of retinal ganglion cells.

This work was led by Dr. Frances Lefcort's PhD student, **Dr. Anastasia Schulz**, at Montana State University and was made possible by a special FD family and an interdisciplinary team of physicians and scientists at NYU, the University of Miami, and the University of Alicante in Spain. It was published in *Glia* in 2024 (Schulz et al., 2024).

The good news is that this discovery provides additional therapeutic targets.

In a second study published in 2024 (Costello et al., 2024), in collaboration with Dr. Valerie Copie's lab at Montana State University, it was shown that the metabolism of the FD mouse retina is severely deficient. Several critical metabolites were reduced, including taurine, and the most affected pathways were those related to energy production for neurons. Metabolites involved in mitochondrial function, ATP production, and phospholipid metabolism were diminished in the FD mouse retina. These findings, coupled with our previous studies on FD metabolism published in 2023, indicate that **therapeutics aimed at restoring cellular energy production should be considered for FD.**



Comparison of the retina in a control mouse (top 2 panels), vs that in an FD mouse (bottom 2 panels). Glial cells are stained green and retinal ganglion cell nuclei are stained purple. It is apparent that there are many more glial cells in the FD retina than in the control retina.

Clinical and Translational Research

Your pluripotent stem cells/neurons as a platform for FD therapy

For years, the **Zeltner Lab** has been using special stem cells, called induced **pluripotent stem cells (iPSCs)**, to study Familial Dysautonomia (FD). These stem cells come from patients with FD, and we can use them to make the nerve cells that do not function properly in FD. This allows scientists to better understand how the disease affects the body. They are also helping researchers discover potential new treatments.



Dr. Nadja Zeltner from the Zeltner Lab

In 2024, the Zeltner Lab made two major discoveries. In one study published in the journal *Cell Stem Cell* [1], the team found that a specific type of nerve cell—**parasympathetic neurons**, which help the body relax—**do not work properly in people with FD**. This dysfunction contributes to the overall nerve problems seen in the disease.

In another study published in the journal *Science Translational Medicine* [2], the team identified a new drug compound called genipin. When tested on neurons grown from FD stem cells, **genipin prevented developmental defects and kept the nerve cells from dying**. This suggests it could be a potential new treatment to slow down the progression of FD.

Parasympathetic neurons, which help the body relax, appear defective in FD

Even more exciting, when genipin was given to pregnant mice carrying FD-affected pups, it was safe for both the mothers and their developing babies—and it prevented FD symptoms in the pups. Genipin also helped nerve fibers regrow after injury, showing potential for repairing nerve damage. Importantly, it works through a different pathway than existing treatments for FD, meaning it could be used alongside other therapies to support nerve health.

Together, these findings suggest that genipin could be a promising treatment for preventing nerve damage and potentially even helping nerves repair themselves in FD.

References:

- 1 Wu, H. F. et al. Parasympathetic neurons derived from human pluripotent stem cells model human diseases and development. *Cell Stem Cell* 31, 734-753 e738 (2024). <https://doi.org/10.1016/j.stem.2024.03.011>
- 2 Saito-Diaz, K. et al. Genipin rescues developmental and degenerative defects in familial dysautonomia models and accelerates axon regeneration. *Sci Transl Med* 16, eadq2418 (2024). <https://doi.org/10.1126/scitranslmed.adq2418>

Expanding Our Understanding in Hereditary Sensory and Autonomic Neuropathies

Reduced Sensitivity to Pain: FD and CIPA

Reduced sensitivity to pain is a hallmark of **Familial Dysautonomia (FD)** and other genetic disorders known as **Hereditary Sensory and Autonomic Neuropathies (HSAN)**. One of the most severe conditions in this group is **Congenital Insensitivity to Pain with Anhidrosis (CIPA)**, also known as **HSAN type IV**.

At the Dysautonomia Center, we care for and study 20 individuals with CIPA, aiming to better understand the condition and explore potential treatment strategies. The progress made in FD research has provided a framework for approaching related disorders like CIPA.

The HSAN4 Foundation: A Parent-Led Initiative



Recognizing the urgent need for research and medical guidance, dedicated parents founded the HSAN4 Foundation to advocate for their children and support scientific advancements (hsaniv.org). The foundation is now partnering with the FD Center to establish a patient registry and database —critical steps toward better understanding CIPA and developing future treatments. Their commitment is driving research forward and improving patient care.

What Have We Learned About CIPA?

Dr. Margarita Grobocopatel, a visiting medical scholar at NYU, conducted a thorough review of all the Center's cases and the published reports containing genetic data. Her findings confirm that CIPA results in a more severe sensory neuropathy than FD and other HSAN types.

Key observations include:

- **Demographics** – Unlike FD, which primarily affects individuals of Ashkenazi Jewish descent, CIPA affects patients of varied ancestry.
- **Sensory Loss** – Insensitivity to pain was observed in all patients, resulting in frequent fractures, wounds, and burns, particularly on the hands and legs.

- **Autonomic Dysfunction** – All individuals had markedly reduced or absent sweating, blood pressure instability—a hallmark of FD—was not a major issue in CIPA.
- **Self-Mutilation** – Behaviors such as biting the tongue, lips, fingers, and arms afflicted 18 patients.
- **Developmental Delay and Behavioral Issues** – Mild developmental delay was present in 17 individuals, with behavioral issues affecting 12 patients.
- **Orthopedic Complications** – Severe orthopedic issues, including Charcot joints, osteomyelitis, and hip dislocations, often led to wheelchair dependence.

These insights help refine our approach to caring for individuals with CIPA and highlight differences and similarities with FD.

Future Directions

While genetic therapy for CIPA remains a long-term goal, **FD research has demonstrated a path forward**—from genetic discoveries to the development of the first targeted treatment. This journey serves as an inspiration for advancing therapies for other rare diseases, including CIPA.

A major challenge in developing treatments for CIPA is its genetic variability, which makes targeted therapy more complex. However, with the support of the **HSAN4 Foundation** and the dedication of families, our team at the **Dysautonomia Center** remains committed to advancing research, improving care, and deepening our understanding of CIPA to enhance the lives of those affected.

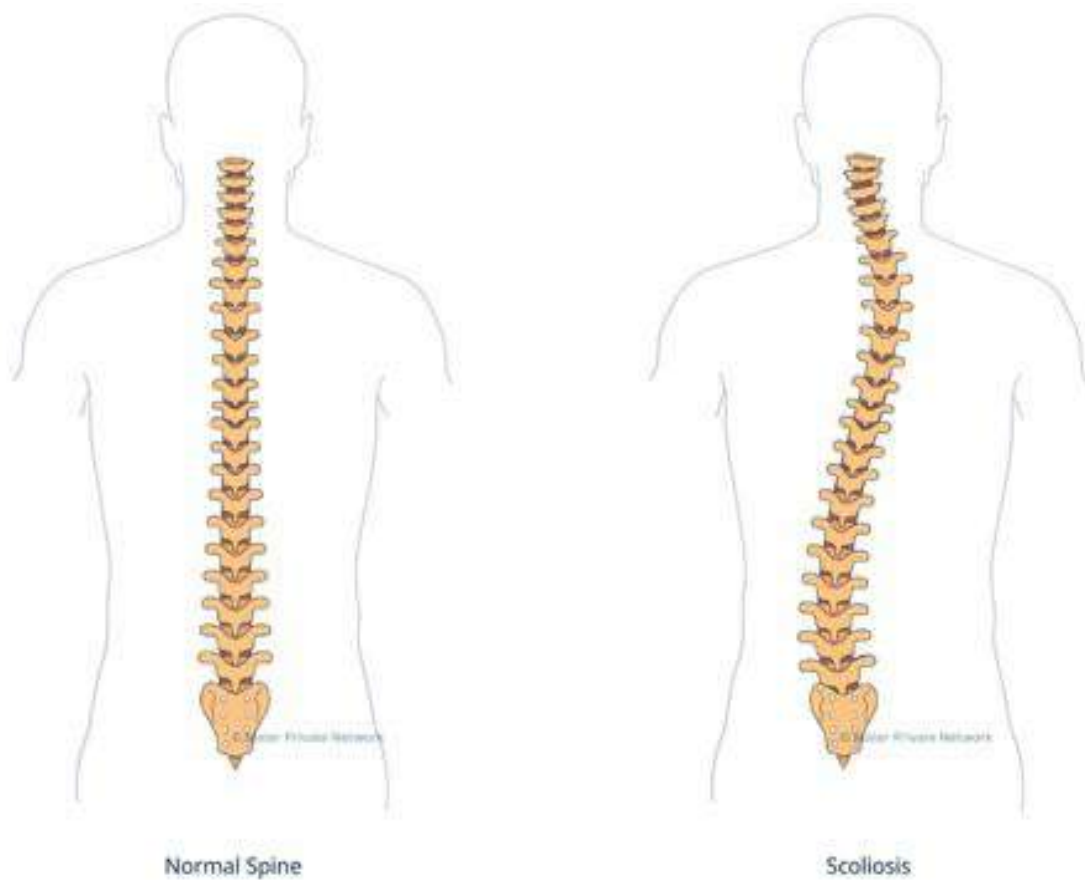


Nicole Carter
Founder of the HSAN IV Foundation

Scoliosis, Back Surgery, and Breathing in FD:

What We Found

Scoliosis, a condition where the spine curves abnormally, is common in Familial Dysautonomia (FD). Scoliosis typically begins around four years of age, with half of the patients developing some form of spinal curvature by age 10, and almost all patients affected as they grow older. This curvature can impact posture, movement, and breathing by compressing the lungs and limiting their ability to expand fully. Spinal fusion surgery is often recommended to correct the curve and stabilize the spine. Surgery effectively improves spinal alignment and may dramatically improve appearance and quality of life. Its potential long-term impact on breathing remains an important consideration.



Evaluating the Impact of Spinal Fusion Surgery

To evaluate the long-term impact of spinal fusion surgery on breathing in FD patients, we utilized the extensive Familial Dysautonomia (FD) database at the NYU Dysautonomia Center. This registry, which includes detailed medical records of 686 patients, is the most comprehensive resource for studying the impact of FD on various bodily functions. We selected 216 patients from the database: 137 who had undergone spinal fusion surgery and 79 who had not. The patients in both groups were similar in age and had undergone at least five, but often more, pulmonary function tests over 10 years. Of the total group, 121 were women and 95 were men. Our goal was to determine whether spinal fusion surgery improved lung capacity over time.

Findings on Lung Function Decline

Before surgery, lung function was similar in both groups. One year after surgery, there were no noticeable changes in lung function. However, by five years, patients who had undergone spinal fusion began to show a significant decline in lung function, as measured by Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV₁). By 10 years, both FVC and FEV₁ had declined significantly in the surgery group, while lung function in patients who had not undergone surgery remained stable.

FVC measures how much air a person can exhale forcefully after taking the deepest breath possible, reflecting the overall capacity of the lungs to expand and contract. FEV₁, on the other hand, measures how much air a person can exhale in the first second of a forced breath, providing insight into the strength and efficiency of the airways. These findings suggest that, over time, spinal fusion surgery may contribute to a decline in lung function.

Weighing the Risks and Benefits

While spinal fusion surgery can correct spinal curvature, it may lead to long-term breathing challenges. These results highlight the importance of carefully considering the potential impact on lung function when deciding on spinal fusion surgery for patients with FD, a condition already characterized by complex nervous and musculoskeletal involvement. However, it is important to note that the observed decline in lung function may not necessarily be due to the surgery itself. Patients who underwent surgery may have had more severe scoliosis or other underlying conditions that contributed to their deteriorating lung capacity.

Beyond Spinal Alignment: Other Considerations

Additionally, spinal surgery has potential benefits beyond spinal alignment. Improved posture can enhance self-image, mood, and social interactions, contributing to overall well-being. These factors should also be considered when weighing the risks and benefits of spinal fusion surgery in FD patients.

_____ Clinical Care and Prevention _____

Encouraging Results with SGLT2 Inhibitors in Patients with Renal Impairment

Familial Dysautonomia (FD) often leads to renal impairment and proteinuria. Beyond ensuring adequate hydration and optimizing blood pressure control, there are currently no specific treatments available for managing kidney dysfunction in FD patients.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of medications that reduce glucose reabsorption in the kidneys, leading to increased urinary glucose excretion. Initially developed for diabetes management, these agents have demonstrated renoprotective effects, in other words they slowed the worsening of kidney function, in both diabetic and non-diabetic patients with kidney disease.

At the NYU Dysautonomia Center, we have initiated treatment with SGLT2 inhibitors in seven FD patients with proteinuria to evaluate their potential renoprotective benefits.

The preliminary results are encouraging. All seven patients had a reduction in proteinuria following treatment initiation. This outcome aligns with growing evidence supporting the renoprotective effects of SGLT2 inhibitors in non-diabetic populations. Beyond reducing proteinuria, these agents may play a role in preserving kidney function and mitigating the long-term progression of renal disease in FD patients.

Given the small sample size, further studies are necessary to validate these findings. However, our initial experience suggests that SGLT2 inhibitors may offer a novel therapeutic strategy for managing renal impairment in FD patients. Ongoing monitoring will help refine treatment protocols and expand our understanding of their long-term benefits in the FD population.

***These agents may play a role in preserving kidney function and mitigating the long-term progression of renal disease in FD patients,
Dr. Alejandra Gonzalez Duarte***



Dr Alejandra Gonzalez-Duarte

These promising results underscore the importance of exploring targeted interventions to improve outcomes in FD.

Clinical Care and Prevention

Osteonecrosis of the Jaw:

Protecting Jaw and Bone Health in Familial Dysautonomia

Osteoporosis is the weakening of the bones leading to an increased risk of fractures and it is very common in patients with FD.

To help strengthen bones and prevent fractures, doctors have used a type of medications called bisphosphonates for many years. Bisphosphonates have been beneficial, but like all treatments, they come with risks. One rare but serious complication is osteonecrosis of the jaw (ONJ), a condition where the jawbone loses its blood supply and does not heal properly. The prevalence of ONJ in the general population is very low, estimated to be less than 0.001%. However, the risk varies depending on underlying health conditions and treatments. It is estimated that ONJ affects 0.001% to 0.01% of people taking oral bisphosphonates for osteoporosis, and 1% to 15% in cancer patients receiving high-dose intravenous bisphosphonates. Recent findings suggest that people with FD may have a higher-than-expected risk.

For most people, the benefits of bisphosphonates far outweigh the risks. However, in FD, we are still learning how often ONJ occurs and how best to prevent and manage it. The first case of ONJ we took care of in someone with FD prompted us to take a closer look. Are individuals with FD more vulnerable? What steps can we take to prevent it? And how do we treat it if it happens?



At the Dysautonomia Center, we identified five cases of ONJ in patients with FD, representing a **prevalence of 0.70% in the FD population**—low but higher than in the general population. The age of onset of ONJ ranged from 11 to 38 years old. Only one of these individuals, a 38-year-old male, had taken bisphosphonates, alendronate for five years and zoledronic acid infusions once a year for three years.

ONJ typically occurs when an area of the jawbone is exposed and does not heal within eight weeks. The condition is more common in patients receiving high- dose intravenous bisphosphonates and those undergoing long-term treatment.

A challenge with ONJ is that it often has no early symptoms. This makes it difficult to diagnose until the condition has progressed. By the time it is identified, treatment can be more challenging. This highlights the importance of regular dental check-ups and preventive care.

Steps for Prevention

Because individuals with FD may be more susceptible to ONJ, extra precautions are essential:

- **Daily oral hygiene** – Brushing and flossing regularly can help keep the mouth healthy and reduce infection risk.
- **Routine dental visits** – Regular check-ups and professional cleanings allow early detection of potential problems.
- **Monitoring for dental infections or sores** – Notifying a clinician about loose teeth, or slow- healing sores can help with early diagnosis.
- **Regular jaw x-rays** – Imaging can help detect changes in the jawbone before symptoms appear.

A Collaborative Approach to Decision-Making

Deciding whether to use bisphosphonates should be a team effort. Patients, families, doctors, and dentists should work together to weigh the benefits and risks. Key factors to consider include:

- **Kidney function** – Bisphosphonates may not be suitable for those with kidney disease.
- **Dental health** – Individuals with frequent oral infections or those needing major dental work may have a higher risk of complications.
- **Fracture risk** – If the risk of fractures is low, alternative options may be considered.

If bisphosphonates are determined to be the right choice, following preventive measures—such as maintaining good oral hygiene and scheduling regular dental visits—can help reduce the risk of ONJ.

Clinical Care and Prevention

Mental Health in Familial Dysautonomia

Lily Armstrong, our licensed professional counselor at the FD Center, has been providing mental health support for individuals with FD since 2015. In 2017, she relocated to Portland, Oregon, and now conducts all sessions virtually via phone or computer.

Lily is dedicated to holistic mental health care, addressing each person's unique story, diagnosis, and sense of self. She approaches anxiety, depression, and other emotional challenges as opportunities for growth and self-awareness. Through mindfulness practices and compassionate advocacy, she helps clients foster a stronger mind-body connection and build self-esteem.



Lily Armstrong

One of Lily's earliest clients was Stevie Schwartzberg, a remarkable individual whose life was cut short. To honor his memory, his family established a memorial fund in his name, ensuring the continuation of therapy sessions for those in need.

P.E.A.C.E.

Living with a chronic illness can profoundly affect mental well-being, often amplifying anxiety. Anxiety functions like a smoke alarm—sometimes signaling an immediate concern, other times drawing attention to something meaningful. Visualization can be a powerful tool to manage these feelings: recalling a moment of contentment, such as sitting in a hammock gazing at trees, can create a sense of calm even in stressful moments.

Lily's goal is to help each client find their personal source of calm using the acronym P.E.A.C.E.:

- **P – Presence:** Therapy provides a safe space to acknowledge experiences, fostering awareness of their impact on the mind and body.
- **E – Exploration:** Challenges become opportunities for growth. By reflecting on past experiences and sharing them with trusted individuals, we gain valuable insights.
- **A – Allowing:** Therapy nurtures internal safety, creating space for difficult emotions without overwhelm. Facing emotions, rather than avoiding them, leads to healing.
- **C – Curiosity:** Approaching our thoughts and feelings with curiosity rather than fear allows for productive self-discovery and creative problem-solving.
- **E – Expansion:** Developing resilience through engagement, advocacy, and empowerment enables individuals to live meaningfully—creatively, actively, and gratefully.

Lily looks forward to connecting with you. As a passionate advocate for mental health, she is available to answer questions about how chronic illness impacts emotional well-being. If she can be of service, please reach out: lily.armstrong@nyulangone.org.

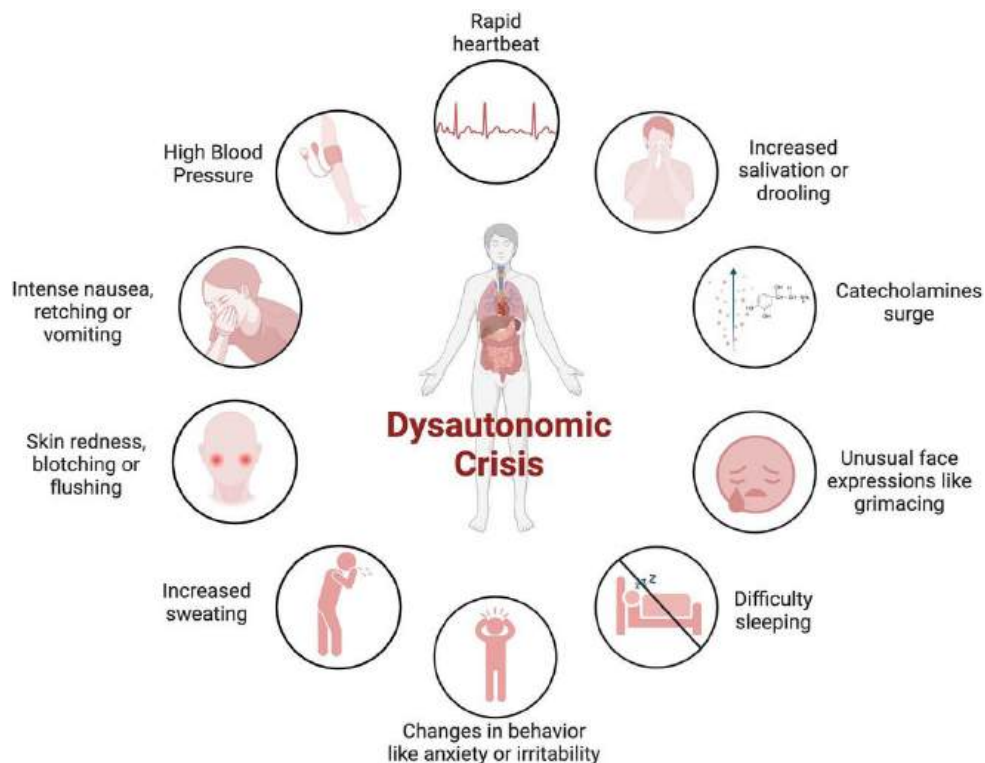
Clinical Care and Prevention

Why We Need an Autonomic Crisis Scale – and How to Use It

One of the most debilitating symptoms of Familial Dysautonomia (FD) is the sudden onset of autonomic crises. These episodes, triggered by emotions, stress, or illness, result from a surge of catecholamines—chemicals released by nerve terminals and endocrine gland—into the bloodstream. During an autonomic crisis, the body goes into overdrive, causing severe symptoms such as a rapid heartbeat, high blood pressure, intense nausea, retching or vomiting, skin flushing, and excessive sweating. These episodes can last from minutes to several days, with severity varying both between patients and within the same patient over time. This unpredictability makes FD particularly difficult to manage and treat.

Autonomic crises are the most common emergency reported to the Dysautonomia Center. However, the term "crisis" can mean different things to different patients and families. Moreover, because no single sign or symptom defines a crisis, assessing severity and determining the effectiveness of treatments has been challenging.

To improve crisis management, we needed a standardized and reliable method to measure severity. We developed the Autonomic Crisis Scale (ACS) to provide a consistent way for doctors and patients to assess symptom intensity. The scale offers a scoring system, where higher numbers indicate more severe symptoms. It was designed to be user-friendly, accessible via smartphones or laptops, and integrated into the NYU database in real-time.



Developing the Autonomic Crisis Scale

To validate the ACS, we conducted a preliminary study on 43 autonomic crises in four FD patients (two males and two females) with an average age of 32 years. We recorded vital signs and symptoms during each crisis and identified six symptoms consistently present: increased blood pressure, elevated heart rate, skin flushing or blotching, excessive sweating, nausea/retching/vomiting, and restlessness or agitation.

We then assigned severity scores to each symptom. For instance, an increase in heart rate to 150 beats per minute was rated as more severe than an increase to 120 beats per minute and retching or vomiting scored higher than mild nausea. Blood pressure and heart rate increases were graded on a scale from 0 to 4, while other symptoms were rated from 0 to 2, yielding a maximum possible score of 16.

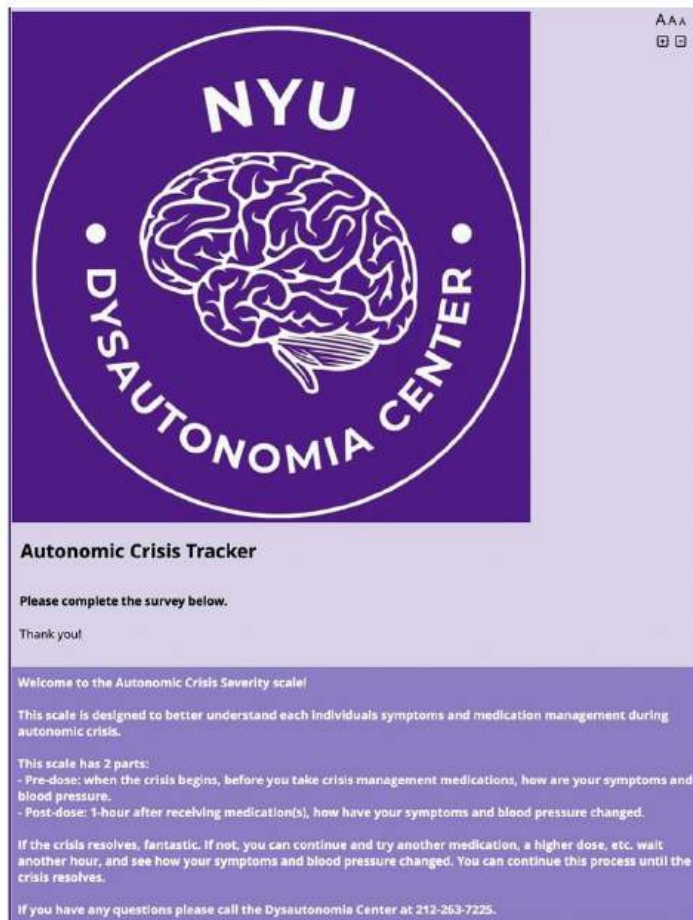
By analyzing these scores, we established a threshold for distinguishing active crises from resolved episodes. The median total score during a crisis was 5, which dropped to 1 when patients reported the crisis had ended. A score greater than 2.5 effectively differentiated ongoing crises from resolved ones.

Implementing the Scale for Patients

To facilitate patient use, we integrated the ACS into a secure database, allowing patients and caregivers to record crisis symptoms in real-time. The tool also enables users to log medications taken and potential crisis triggers. Once a crisis resolves, the recorded data can be downloaded as a PDF, helping patients track symptom patterns over time. Identifying individual triggers is essential for tailoring preventive strategies and treatments to each patient's needs.

The Future of Crisis Management with ACS

The Autonomic Crisis Scale is now freely available to all FD patients. We hope it will improve communication between patients and doctors, enhance the evaluation of crisis severity, and allow more accurate assessment of treatment effectiveness. By collecting data from multiple patients over time, the NYU Dysautonomia Center can gain deeper insights into autonomic crises and refine treatment approaches. This tool is already helping us make more informed decisions and improve patient care.



Link for Autonomic Crisis Tracker: <https://redcap.link/ACS>

Clinical Care and Prevention

A Year in Care:

Supporting FD Patients at NYU Dysautonomia Center

At the NYU Dysautonomia Center, patient care extends far beyond traditional medical visits.

Every week, the team manages a relentless schedule of consultations, prescriptions, emergency calls, and logistical coordination to ensure that patients with FD receive the specialized attention they need. The scale of this effort is impressive—amounting to over 11,000 distinct patient-related activities annually, translating into more than 4,400 hours of dedicated care. In the first line of almost all clinical calls are Kaia Dalamo or Andreama Barnett, our extraordinary nurse practitioners.



Kaia Dalamo and Andreama Barnett

Throughout the year, the center remains a vital lifeline for its FD patients, handling thousands of interactions, from routine follow-ups to critical interventions. The data speaks volumes about the intensity and complexity of the care provided:

- **50 follow-up calls per week**—addressing everything from routine infections to life-threatening autonomic crises.
- **200 MyChart messages per month**, used for scheduling, prescription requests, and patient inquiries.
- **Annual visits lasting up to four hours**, ensuring in-depth patient evaluations and planning for the year ahead.
- **1920 insurance approvals and care coordination tasks yearly**, facilitating critical treatments and interventions.
- **Over 360 emergency calls handled outside regular hours**, offering crucial support on weekends and after hours.

Beyond these numbers lies a dedicated team ensuring that every FD patient receives the attention they require, whether in the hospital, at home, or via telehealth.

The Work Behind the Care

Each activity requires a significant investment of time and expertise. For example:

- **Follow-up consultations take an estimated 1,200 hours annually**, involving everything from discussing treatment plans to managing acute medical needs.

- **Coordinating 24-hour blood pressure monitoring** requires not only scheduling but also reviewing and interpreting data, totaling 288 hours per year.
- **Prior authorizations and anesthesia recommendations**—essential for enabling treatment access—consume 960 hours annually.
- **Writing comprehensive FD annual reports** for each patient accounts for 208 hours of physician time every year.

These figures highlight the unseen efforts that sustain a robust patient care system.

The Human Side of the Numbers

While statistics provide a clear picture of the workload, they don't capture the profound impact of this work on patients and their families. Each phone call represents a concerned caregiver seeking guidance. Every MyChart message reflects a need for reassurance. Each prescription request ensures a patient has essential medications. The center operates not just as a medical facility, but as a trusted partner in the lives of those with FD.

Looking Ahead

The NYU Dysautonomia Center remains steadfast in its mission to provide the best care for FD patients. With an aging patient base and an evolving medical landscape, the need for comprehensive, personalized, and accessible care is greater than ever. By streamlining workflows and integrating new medical technologies, the center is continually refining its approach to ensure that every FD patient receives the highest standard of care. As we look forward, we remain committed to advancing patient care, improving outcomes, and ensuring that every individual with FD receives the support they need to lead the best life possible.



Photo by Chanie Profesorske

DYSAUTONOMIA CENTER

New Faces



Britney A. Paredes Lopez

Clinical Research Coordinator

Britney came to the Center from the NYU Center of Biorepository Research and Development in December 2024. Coming from a world of test tubes and bio-samples, Britney was excited for the opportunity to work with people. Although her role as a research coordinator is extremely demanding, Britney approaches each challenge with determination, perseverance, and a smile, she does not back-down from a challenge and is always willing to lend a hand.



Grace Nkrumah

Clinical Research Coordinator

Grace joined our team in January 2025, assisting Mecky and Britney to manage all research trials at the Center. Before joining NYU, Grace worked as a research coordinator at the University of Rochester Center for Health and Technology. Her experience in clinical trial management has helped her to excel at the Center. Grace brings confidence, innovation and enthusiasm to each task, she approaches all obstacles head-on while maintaining a supportive and collaborative environment. Grace hopes to attend medical school and pursue a career as a neurologist.

International Medical Scholars



**Daniel Rebolledo
García, MD**
MEXICO



**Juan Carlos Lopez
Hernández, MD**
MEXICO



**Jesús Romero-Mera,
MD**
MEXICO



**Margarita
Grobocopatel
Marra, MD**
ARGENTINA



Joel Gutierrez-Gil, MD
CUBA



Mostafa Elsheikh, MD
EGYPT



Anabella Cecilia Gomez, MD
ARGENTINA

Research Interns



Daniel Morales. Danny began interning with the Center in 2023. Since then, he has helped maintain and update the Natural History of Familial Dysautonomia research database. Danny is currently a senior at Hofstra University studying pre-medical studies.



Sofia Aisiks. Sofia has been interning with the Center since 2024. Her work at the Center has largely been focused on analyzing and interpreting the results of the autonomic crisis scale and understanding thermoregulation. Sofia graduated from Amherst College in 2019 and plans to begin medical school in the Fall.

Summer 2024 Interns



Jessie Eisner
New York



Emily Szor
London



Lila Zahmoul
London



Leon Villagran
New York

Our interns spent the summer upgrading the Center's social media platforms. They curated informative posts to raise awareness about the conditions that we treat and bring attention to our ongoing clinical trials. They also helped with data entry and data analysis.

DYSAUTONOMIA CENTER

Staff

Horacio Kaufmann, MD
Professor, Director

Alejandra González Duarte, MD, PhD
Associate Professor, Co-Director

Patricio Millar-Verneti, MD
Instructor, Neurology

Mecky Kuijpers, BA
Junior Scientist

Kaia Dalamo, NP, DNP
Specialist Nurse Practitioner

Andreana Barnett, NP
Specialist Nurse Practitioner

Britney A. Paredes Lopez, BS
Clinical Research Coordinator

Grace Nkrumah, BS
Clinical Research Coordinator

Lee-Ann Lugg, BS
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Nadia Zeltner, PhD
Sumantra Chatterjee, MD
Patrick Hof, MD
Shruti Ravindramurthy, MD
Chethan Ramprasad, MD

Support for the Program

Familial Dysautonomia Foundation, Inc.
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The Montreal Chapter of Dysautonomia
n-Lorem Foundation
J Aron Charitable Foundation Inc.
The Kopelman Foundation
Anonymous

The Clare and Philip Wexler Research Fund
The Slomo and Cindy Silvan Foundation Inc.
Henry E. Niles Foundation
Joe Namath Foundation
The Schwartzberg Family

FD at NYU

The NYU Dysautonomia Center has existed for over half a century and is dedicated to FD patients 24/7

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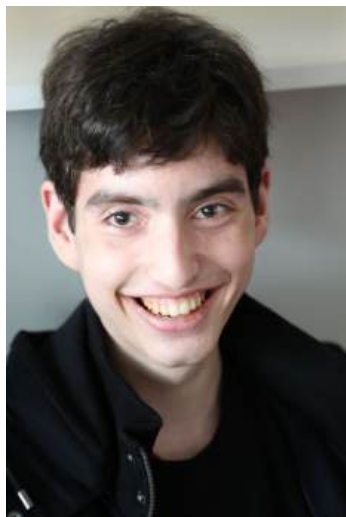
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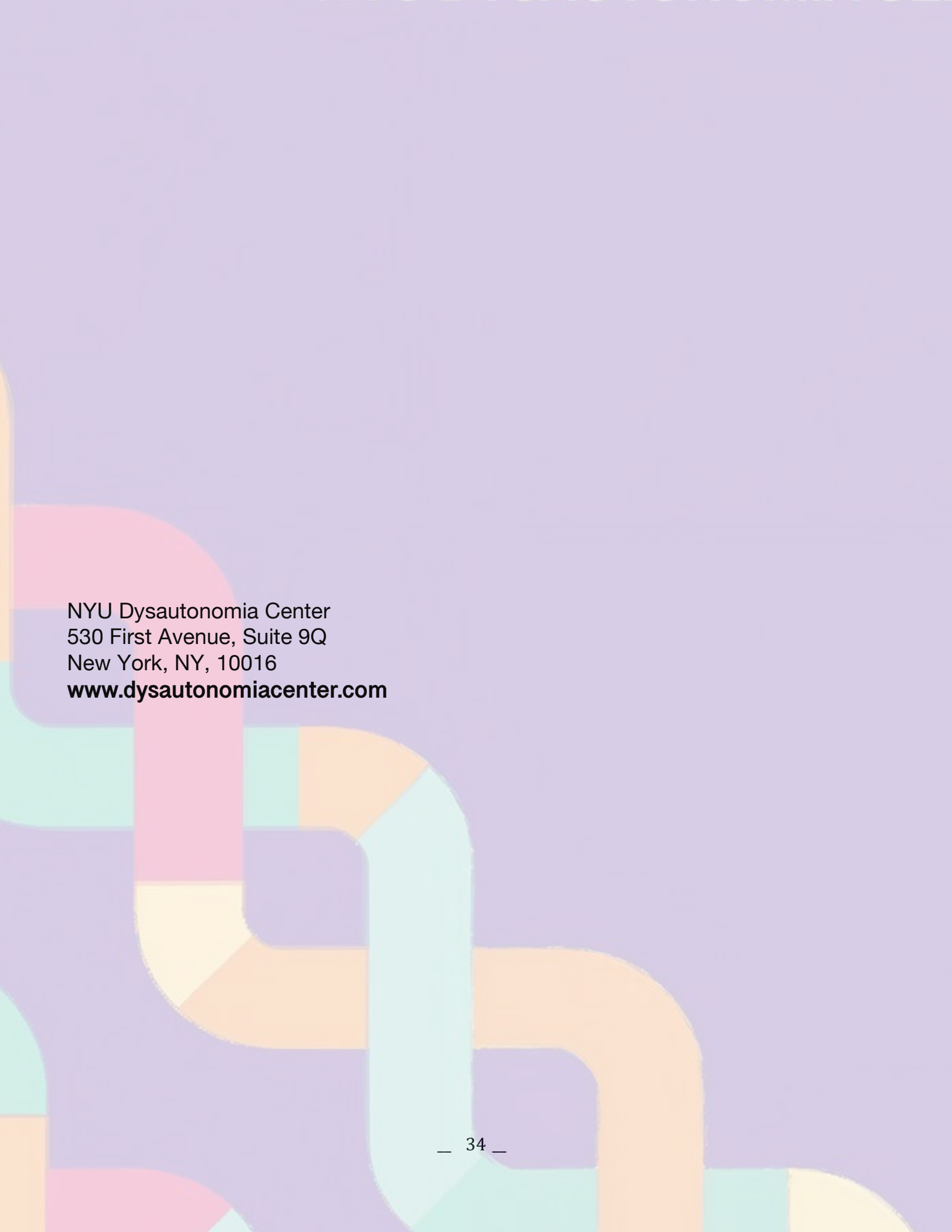
<https://familialdysautonomia.org>



<https://nyulangone.org/locations/dysautonomia-center>



Photos by Rick Guidotti



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