

Voice of the Patient Report for Charcot-Marie-Tooth Disease and Inherited Neuropathies

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Authors and contributors have nothing to disclose.

Funding for the EL-PFDD Meeting was provided by:

Accelaron Pharma, Athena Diagnostics, Charcot-Marie-Tooth Association (CMTA), Ceres, Cresco Labs, Cydan, Everylife Foundation, Flex Pharma, Ionis, Muscular Dystrophy Association (MDA), Pharnext, Southern Vermont Wellness / Champlain Valley Dispensary.

Version Date: August 19, 2019

This document has not been revised and/or modified in any way after August 19, 2019.

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Externally-led Patient-Focused Drug Development Meeting



VOICE OF THE PATIENT REPORT

Charcot-Marie-Tooth & Inherited Neuropathies

**Submitted as patient experience data for consideration
pursuant to section 569C of the Federal Food, Drug, and Cosmetic Act to:**

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

Hosted by: The Hereditary Neuropathy Foundation

A MESSAGE OF THANKS AND HOPE

As a community, people living with Charcot-Marie-Tooth (CMT) disease and other inherited neuropathies (IN) rarely get the proper diagnosis, treatments, and support they need, at the moments they need them. All too often we feel unseen, unheard, and poorly understood. As such, our lives are significantly challenged.

On September 28, 2018 hundreds of CMT/IN Patients, Caregivers, Government Officials, Healthcare Providers, Industry, Patient Advocates and Payors came together for an Externally-led Patient-Focused Drug Development (PFDD) meeting for CMT/IN to have our voices heard, and to prepare for a brighter future. We heard from our community through stirring testimonies, community polling, and open discussions, together addressing the critical issues that patients and their families are dealing with throughout their lifetimes. Our hope was to improve inclusion and empathy, reduce stigma, and address the unmet medical needs of our community today.

We want to thank the US Food and Drug Administration (FDA) for honoring the Hereditary Neuropathy Foundation (HNF) request to hold this very important meeting, and for all the industry and advocacy sponsors who made this possible. Special thanks go to our honorable FDA speaker, Lucas Kempf, MD, PLLC, Acting Associate Director, Rare Disease Program at FDA, Office of New Drugs, CDER, FDA, for his time and support of this meeting, and to all the senior FDA leaders who attended the meeting. A very special thanks for the ever-present expertise and meeting planning guidance received from Meghana Chalasani, Decision Support and Analysis Team, FDA.

We were very privileged to be joined by a group of thought-leading scientific and medical experts in the field of CMT and inherited neuropathies. Many thanks to Michael Shy, MD, Stephan Züchner, MD/PhD, and Florian Thomas, MD/PhD for their contributions to this meeting, and for being great supporters of the CMT/IN community.

We would like to thank the Charcot-Marie-Tooth Association and the Muscular Dystrophy Association for their sponsorship of the meeting and for their support in the development of this Voice of the Patient report on behalf of the entire CMT/IN community.

This meeting simply would not have happened if not for the amazing collaboration with James Valentine, JD/MHS, who served not only as an excellent moderator, but also as a critical advisor as we prepared for the meeting.

This Voice of the Patient Report marks the beginning of a brighter future for people living with all types CMT/IN throughout the world. We especially want to recognize the panelists who generously gave their time and who were so brave in sharing the intimate stories of their lives and experiences living with CMT/IN. We are grateful to all the patients and their caregivers, and to all the people who selflessly participated live and on the webcast in this landmark event. Thank you all for sharing your hopes, expectations and desires for future treatments. Your voices will impact the future of CMT/IN and without your contributions, this meeting would not have been possible!

Allison T. Moore
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EXECUTIVE SUMMARY

Charcot-Marie-Tooth disease (CMT) is one of the most common inherited nerve disorders, affecting an estimated 1 in 2,500 people in the United States. CMT is the most common of all the 7000 rare disease reported in the US. Along with other inherited neuropathies, the disease causes problems with the sensory and motor nerves. Over time, this causes muscles in the feet, legs, and hands, as well as other parts of the body, to lose strength. Often, the muscle loss happens unevenly, which causes deformity as muscles waste away (atrophy) at different rates. It can also have serious impacts on vision, hearing, breathing, speech and swallowing.

CMT and other inherited neuropathies (CMT/IN) are chronic, painful, life-long, disabling diseases that can present in childhood or later in life and have a severe impact on quality of life. They are considered “family diseases” meaning that patient care has a significant impact on family life and often multiple members of a family are affected.

The Hereditary Neuropathy Foundation applied for and was granted the opportunity to host an Externally-Led Patient-Focused Drug Development meeting, a parallel effort to [FDA’s PFDD initiative](#) to systematically obtain patients’ perspectives on the burden of disease and impact of current treatments or lack thereof in Hyattsville, Maryland on September 28, 2018. Through this meeting, CMT/IN patients, families, and caregivers were able to share their unique insights on the impact of CMT/IN to their day-to-day lives. Perspectives on currently available treatment options and strategies for disease management, as well as expectations for the future treatments, were also shared.

The objective of the meeting was to increase FDA’s understanding of how patients, families and caregivers experience and manage CMT/IN, and the factors that are considered when treatments are chosen. This will, in turn, help the FDA understand the appropriate benefit-risk balance for new treatment options, the severity of these conditions, and the urgency of unmet medical needs.

The voice of the CMT/IN patient was heard through courageous patient/caregiver testimonies, polling of the broad audience, open discussions with the meeting attendees, and pre-meeting surveys. The PFDD meeting was attended in-person by 155 people, and via a livestream webcast by 543 registrants.

Throughout the course of these activities, the voice of the CMT/IN patient was heard strongly and consistently, and the following key messages emerged:

- **CMT/IN are complicated and diverse family diseases**
 - Caused by hundreds of inherited genetic mutations
 - Span multiple generations, causing overwhelming impacts on family life and finances
 - Appear with widely diverse symptoms and manifestations, even within families
 - Present drug development challenges because of disease variability and subpopulations
- **There is a disturbing lack of awareness of the devastating impacts of CMT/IN**
 - Not only with society in general, but also within the healthcare provider community
 - Patients feel their disease is “unseen,” which causes them to despair and retreat
 - Patients suffer through physical and emotional indignities every day
 - To date, there are no approved therapeutics

- **CMT/IN patients continuously deal with very difficult issues in their daily lives**
 - Progressive loss of mobility
 - Balance issues / falling
 - Lack of coordination with hands and arms
 - Inability to participate in or perform daily activities
 - Inability to work or go to school
 - Chronic Pain
 - Fatigue
- **Social and emotional issues are very common and can be very distressing in CMT/IN patients**
 - Anxiety and depression
 - Relationship apprehension
 - Concern over starting a family
 - Stress over managing within a family when multiple generations are impacted
- **Pediatric and young adult CMT/IN patients have particular difficulty with social and emotional challenges and these have lasting effects throughout their adult lives**
 - Social withdrawal
 - Loss of friends
 - Inability to keep up with peers in school and sports
 - Public humiliation
 - Bullying
 - Fear of future
- **Severe, life-altering and life-threatening impacts based on autonomic neuropathy were highlighted as a largely unrecognized area of unmet need**
 - Breathing
 - Swallowing
 - Choking
 - Vision
 - Hearing
 - Incontinence of the bladder and bowels
- **The current state of managing CMT/IN is largely focused around adaptive devices and complementary methods**
 - The standard braces are unacceptable
 - Physical and occupational therapy are heavily relied upon
 - Nutrition and diet are crucial to better health
 - Many patients use complementary methods such as exercise, swimming, acupuncture, meditation, and massage
 - Patients are very creative in finding adaptations to help with their daily lives and are happy to share their ideas with others

- **New treatments should focus on the following unmet needs**
 - Ability to walk unaided
 - Ability to balance/stand
 - Improved hand function
 - Respiratory weakness and other autonomic neuropathy effects
 - Fatigue
 - Pain (the use of medical marijuana was strongly supported)
- **Patients are most likely to use a new medication based on benefits shown for symptoms of importance, and on their ability to access the drugs (insurance coverage)**
- **Patients and families are willing to participate in clinical trials, and many are open to doing what is needed (both at home and with clinical measurements) as part of a study**
 - Life in a CMT/IN family is very challenging, so simplification of clinical study participation is beneficial

This PFDD meeting was a critical step forward for the Charcot-Marie-Tooth and other Inherited Neuropathies community. The insights collected and reported on in detail in this “Voice of the Patient” report reflect important perspectives of people living with these diseases and will inform the pharmaceutical companies to develop the critical medicines that are desperately needed by this community. These insights will now be used to help develop a benefit-risk framework that the FDA may utilize in their regulatory decision making. Some preliminary recommendations for this benefit-risk framework can be found in this report.

“What I was impressed with from the beginning is that this is a very organized community. I'd like to recognize the fact that your board has been so forward -thinking about how they've been approaching positioning this community for drug development and therapeutic development in general. It sounds like you've been very diligent about developing a very good understanding of the natural history of the illness. You have characterized the variability and then done all the hard basic science research of characterizing the genetics that help understand all that variability, so that when it comes time for therapeutics to come into your community, it's going to be very targeted and very easy to do. It's those sort of things that will come out of your analysis of the survey work that you did today that will really make a difference for helping drug developers, or device developers or biologics or gene therapy developers understand what they should be measuring and how to address this population, meet you where you are for what you want in the future. So, at least from the FDA, I appreciate this meeting. I think it was very successful. You should all be very proud of the work you did today.”

- Lucas Kempf, MD, PLLC, Acting Associate Director, Rare Disease Program at FDA, Office of New Drugs, CDER, FDA

CMT/IN EXTERNALLY-LED PFDD MEETING DESIGN

The goal of the meeting was to increase the FDA's understanding of how patients, families and caregivers manage CMT/IN, and the most important factors that are considered when a treatment is chosen. This in turn, will inform the FDA regarding the benefit-risk balance of treatment options, the severity of the condition, and the urgency of unmet medical needs.

"I'm here today representing the US Food and Drug Administration, and I'm joined here by several of my colleagues...We understand that CMT is a complex and serious condition with physical, emotional and social impacts and that there is an unmet medical need for patients. Having this kind of dialog today is extremely valuable for us because hearing what patients care about can really deepen our understanding and help us lead the way in figuring out how to best facilitate medical product development for CMT...I know that we will all leave here today both inspired and humbled by your strength, determination, and resilience, in the face of the many challenges of living with CMT."

- Meghana Chalasani, FDA Decision Support and Analysis Team

At this meeting, groups of panelists (representing pediatric and adult patients living with all types and stages of CMT/IN) shared impactful testimonies to communicate the real and specific ways by which their lives are impacted by CMT. Each round of panelists was followed by a polling session and a period of facilitated discussion with participants who attended live in Hyattsville, MD, as well as participants from across the US and Internationally who attended via a live streaming webcast.

In addition to the patient voices heard throughout the meeting, two very moving videos were shared. One video conveyed what it is like for a family to live with CMT1A. The Warren family story helped us gain a better understanding of the daily challenge of growing up with CMT and trying to support a family while dealing with this difficult condition. Here is the link to the view the video, "Faces of CMT"

www.hnf-cure.org/Faces-of-CMT/

"If you have CMT, you have to work that much harder. I have a regimen in the morning that can take two to three hours, and what I've decided to do is just be determined about doing that every day and not letting it stop me."

- Phil

"It's imperative on us to raise awareness and to find a cure for this because if we can help one in 2500 people live their lives pain free, without the deformities, and the surgeries, and the medical costs, and the insurance, and the social impact, and the depression, and the anxiety. It's just imperative that we find a solution, now."

- Brooke

The second video, "Voice of the CMT Patient" was a compilation of responses from patients who were gathered using True Reply Voice Activation Technology from the Hereditary Neuropathy Foundation's Global Registry for Inherited Neuropathies (GRIN) patient registry and in partnership with Inspire, asked the CMT community two questions:

1) What is the one symptom of your CMT that has the biggest impact on your life?

2) How does this symptom affect your daily life?

Hundreds of patients responded to this survey, and the video shares many of their voices. Here are some of the many impactful words the community spoke about dealing with CMT/IN:

“Muscle atrophy” “Weakness” “Fatigue” “Balance”
“Numbness” “My feet” “Foot deformity” “Stumbling”
“Muscle loss” “Numb and sore feet” “Sensory deprivation”
“Not being able to use my hands” “I can't walk without braces”
“Not knowing when I'm going to fall”

“It's my daughter's life, and it takes a toll on her life”

“My inability to walk and stand up properly for long periods of time”

“The one symptom is the fact that I am losing the use of my hands. I've lost so much of the use of my feet, but I find that the loss of the use of my hands is the most devastating.”

“The biggest symptom of CMT has had on my life has been basically the loss of my independence”

“I can't sleep or work or drive. There's no comfortable position for me that doesn't feel like I'm on fire. Honestly, it's like being tortured, and to add to the misery, I'm treated like a drug addict.”

“That pain is a horrible thing to deal with, and just the fact that CMT has robbed me of so many opportunities to enjoy life, is very depressing. When your feet hurt, you don't really want to do anything, except stay home and hide. That's one of the things that I regret about having this disease, you know, missing out.”

“It makes it hard to do things around the house, and to take care of my kids when I feel so exhausted that I just want to lie down all the time, period.”

“It is becoming harder and harder to look after my personal hygiene, to make meals for myself.”

“I'm weak. It affects my balance. I look weird. I have to wear braces to accommodate my muscle loss, and I know that it will only get worse.”

"It's disabling. I'm unable to perform household chores. It's very difficult to even get showered and take care of myself. Some days I'm so tired, I cannot even get up out of my chair or bed."

"It makes everything difficult for daily tasks like getting dressed, cooking, reaching, grabbing things, doing laundry, folding, even petting my dog or holding my husband's hand."

"With regards to my loss of independence, I basically have to rely on my caregiver, which is my loving wife, to assist me with the typical daily needs and activities. Whether it's going out of the house, whether it's getting dressed, whether it's dinners or feedings. It's quite, if you will, depressing not to do the things that you could at one time, and now you find yourself in a situation where you can no longer accomplish the simplest of things."

Watch the full video, "Voice of the CMT Patient" www.youtube.com/watch?v=y0fjioG2NIM

The voice of the patient was supplemented by detailed presentations:

- What is CMT? - Michael Shy, MD, Director, Division of Neuromuscular Medicine, University of Iowa; Director, Inherited Neuropathies Consortium
- Genetics of CMT - Stephan Züchner, MD, PhD, Professor of Human Genetics and Neurology, University of Miami Miller School of Medicine; Chairman, Dr. John T. Macdonald Foundation Department of Human Genetics; Co-Director, Hussman Institute for Human Genomics
- Pipeline Overview Therapies in Development - Florian Thomas, MD, MA, PhD, MS, Founding Chair and Professor, Department of Neurology, Hackensack University Medical Center and Hackensack Meridian School of Medicine at Seton Hall University; Director, HNF Center of Excellence

Key insights from these presentations have been pulled into the disease background section of this report, and the full presentations are available on the HNF website. www.cmt-pfdd.org

BACKGROUND ON INHERITED NEUROPATHIES (IN) AND CHARCOT-MARIE-TOOTH (CMT)

What are IN and CMT?

Inherited Neuropathies (IN) are a group of inherited disorders affecting the peripheral nervous system. The hereditary neuropathies are divided into four major subcategories: hereditary motor and sensory neuropathy, hereditary sensory neuropathy, hereditary motor neuropathy, and hereditary sensory and autonomic neuropathy. The most common type is Charcot-Marie-Tooth disease.

Charcot-Marie-Tooth disease (CMT), named after three doctors who first identified it in 1860, is one of the most common inherited nerve disorders. The most reliable evaluation of CMT prevalence is one affected person in 2500.

CMT is also commonly called hereditary sensory and motor neuropathy. This means that the disease runs in families and causes problems with the sensory and motor nerves, the nerves that run from the

arms and legs to the spinal cord and brain. When the parts of the nerves—the axons and the myelin—become damaged, messages that run along the nerves move more slowly or have a weak signal. Over time, this causes muscles in the feet, legs, and hands to lose strength. Often, the muscle loss happens unevenly, which causes deformity as muscles waste away (atrophy) at different rates.



Researchers recognize five main types of Charcot-Marie-Tooth disease and many sub-types. CMT can be separated into different types based on where the problem starts, which can either be in the myelin insulation around the peripheral nerves (e.g., CMT1) or in the nerve fiber or axon (CMT Type 2). Research is still underway to define the different types fully. CMT type 1 is the most common form of the disease. The Inherited Neuropathies Consortium published a report in 2015 showing the frequency of different CMT subtypes that ranged from 62% of patients with a genetic diagnosis for the most frequent subtype (CMT1A) up to 0.1% for CMT1D.

What causes Charcot-Marie-Tooth disease?

Researchers know that faulty genes cause CMT disease. Although more than 100 of these genes have been identified, ongoing research continues to discover additional genes involved in CMT. CMT has been divided into two groups; primary demyelinating (Type 1) and primary axonal (Type 2). [1] Among the CMT Type 1 group, there are x-linked, autosomal dominant and autosomal recessive types. The four most prevalent genes are PMP22 (CMT1A/HNPP), GJB1 (CMT1X), MFN2 (CMT2A), and MPZ (CMT1B). There are rarer forms of CMT that are autosomal recessive demyelinating motor and sensory neuropathies that include several genes categorized as CMT4. GDAP1 (CMT4A), MTMR13 (CMT4B1), MTMR2 (CMT4B2), SH3TC2 (CMT4C), NDG1 (CMT4D), EGR2 (CMT4E), PRX (CMT4F), FDG4 (CMT4H), and FIG4 (CMT4J). There are instances where the gene mutation causing CMT is a new mutation within a family, which occurs spontaneously and was not passed by a parent(s).

What are the symptoms of Charcot-Marie-Tooth disease?

Symptoms differ from person to person and even between members of the same family. Here is a list of some common symptoms:

Early symptoms of CMT:

- Clumsiness
- Slight difficulty in walking because of trouble picking up the feet
- Weak leg muscles
- Fatigue
- Absence of reflexes

Common symptoms of CMT:

- Foot deformity (very high arched foot/feet)
- Difficulty lifting foot at the ankle (foot drop)
- Curled toes (known as hammer toes)
- Loss of lower leg muscle, which leads to skinny calves
- Numbness or burning sensation in the feet or hands
- “Slapping” when walking (feet hit the floor hard when walking)
- Weakness of the hips, legs, or feet
- Leg and hand cramps
- Loss of balance, tripping, and falling
- Difficulty grasping and holding objects and opening jars and bottles
- Pain (both nerve pain and arthritic pain)

Later symptoms of CMT:

- Similar symptoms in the arms and hands
- Curvature of the spine (scoliosis)

Other reported/known symptoms of CMT:

- Speech and swallowing difficulties
- Breathing difficulties, especially when lying flat
- Hearing loss
- Vision loss
- Vocal cord paralysis

A recent prospective study commissioned by the HNF in collaboration with Acceleron Pharma through HNF's Global Registry for Inherited Neuropathies (GRIN) and presented at the meeting provided patient and caregiver insight into the most important symptoms with impact on quality of life. These insights were used to develop the questions for the polling survey that was part of this PFDD meeting. The full study can be viewed here: <http://acceleronpharma.com/wp-content/uploads/2017/07/PNS-2017-CMT-Patient-Survey-Final.pdf>

Factors	Very Much	Moderate	Slightly	Not at all
Problems with balance	67	20	11	2
Ankle weakness (foot drop)	64	24	8	4
Fatigue	52	28	13	6
Abnormal sensation in lower leg/foot	44	30	18	8
Foot contractures/deformities	37	26	20	18
Pain in lower leg/foot	35	30	17	18
People's lack of understanding	35	28	22	15
Hand muscle weakness	31	33	27	9
Change in appearance/body image	27	27	29	16
Awkward social interactions	26	26	28	20
Muscle cramps or spasms in lower leg/foot	24	28	13	6
Anxiety/fear	24	27	30	20
Pain in back	24	27	27	22
Depression	20	24	30	26
Sleeping issues	19	23	24	34
Abnormal sensation in hand/forearm	16	23	31	31
Hand contractures/deformities	14	18	24	44
Forearm muscle weakness	13	25	38	25
Pain in hand/forearm	13	22	29	36

How is Charcot-Marie-Tooth disease diagnosed?

Not all doctors are familiar with CMT. As CMT affects approximately one in 2500 people, and the average primary care provider follows approximately 1500 patients, they may only ever see one CMT patient in their practice. Therefore, diagnosing CMT disease can be challenging. To help in the diagnosis, a primary care doctor or neurologist may perform the following examinations and tests:

- Medical and family history
- Physical examination to look for symptoms of CMT and other health problems
- Nerve conduction velocity (NCV) test during which electrodes are placed on the skin over the nerves on legs and arms to measure how quickly the nerves carry electrical signals (this test can be uncomfortable)

- Electromyography (EMG) during which a needle electrode is inserted through the skin on legs and arms to measure the electrical signals received by muscles (this test can be uncomfortable and, for some people, painful)
- Genetic screening (blood or saliva test) for possible genetic mutations causing CMT (not always conclusive)

How is CMT/IN currently treated and managed?

There are currently no targeted drug therapeutics approved with the treatment of CMT/IN. These diseases are currently managed using a combination of the following interventions:

- Surgeries
- Bracing and adaptive devices (ankle-foot orthoses [AFOs], knee-ankle-foot orthoses [KAFOs], crutches, canes, scooters, wheelchairs)
- Pain medications
- Muscle relaxants
- Antidepressants / anti-anxiety medications
- Psychotherapy / behavioral therapy
- Physical therapy / occupational therapy
- Diet / nutritional modifications
- Complementary therapies (e.g., exercise, acupuncture, meditation, massage)

What research is currently being conducted to develop new therapies for CMT/IN?

The Inherited Neuropathy Consortium (INC) has greatly progressed the understanding of the natural history, biology, and genetics of these diseases.

The INC has been instrumental in developing new clinical and patient-reported outcomes and quality of life instruments, which are important in the clinical development of new medicines.

- Variety of research projects with ultimate goal of learning more about CMT
- 9800 participants in protocols; 250 Manuscripts; 5000 patients
- Natural History studies: understanding how different types of CMT progress over time
- Outcome Instruments: longitudinal measure for adults and kids
- Developing Quality of Life Instruments: development of QoL for children and adults
- Genetic Research: identifying novel genetic causes and modifier genes
- Identifying Biomarkers: MRI and skin biopsies
- Biobanking: fibroblasts for iPSC

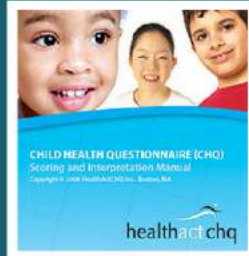
Clinical Disability Outcome Measures for CMT -



0 - 4 Years

CMT Infant Scale

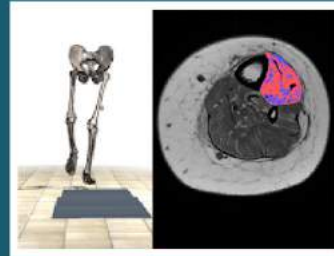
Mandarakas M,
Sanmaneechai O et al.



3 - 20 Years

CMT Pediatric Scale

Burns J et al. Annals of
Neurology 2012



18+ Years

CMT Neuropathy Score

Shy M et al. Neurology 2005

#HNF4CMT

Patient Reported Disability Outcome Measure for CMT (CMT-HI for adults)



CMT-HI Scale

- Measure therapeutic benefit in CMT Clinical Trials
- Measure overall patient health in a clinical setting

#HNF4CMT

Considering the complexity of the genetics on CMT/IN, an additional resource called The Genesis Project has been created to help collect and analyze genome sequencing data in a standardized fashion, allowing scientists from different countries to access the data and work together to find genetic causes.

Genome sequencing and data sharing for scientists - The Genesis Project Foundation

- Revolutionizes the ability to identify genetic causing and biology of CMT/IN
- Enhancing collaboration connecting clinicians and researchers worldwide to accelerate therapy development
- Identifying the complexity of symptoms associated with the various types of CMT
- Identifying diagnosis and novel genes when DNA testing is not confirmed.

While there are currently no approved drug treatments specifically targeted at the underlying cause of CMT/IN, there are many new potential treatments in clinical development, including the following:

- PXT3003: a three-drug cocktail (Pleotherapy) intended to reduce the amount of PMP22 protein made in patients with CMT1A. A pivotal, Phase 3 study has been completed and positive topline results have been reported.
- ACE-083: a locally-acting muscle therapeutic that has an ongoing Phase 2 clinical study of people with CMT1 and CMTX.
- Gene therapy: a newer technology that is now being studied in a variety of diseases, including Giant Axonal Neuropathy. This involves an intrathecal injection of a viral vector containing a non-mutated gene.

There are many other possible therapeutic targets being investigated in preclinical studies, that may progress to human clinical studies in the coming years.

Non-pharmacologic approaches are also being researched, including balance focal mechanic vibration for balance improvement, and a study of the outcomes of surgical procedures.

MEETING PARTICIPANT DEMOGRAPHICS

The CMT PFDD meeting was attended in-person by 155 people in Hyattsville, Maryland. In addition, there were 543 unique registrants for the livestream webcast. The polling was made available to all participants, and approximately one-third engaged in the polling exercises.

The polling revealed that almost all of the participants were US-based. The majority of the participants were CMT/IN patients and caregivers. Others in attendance came primarily from industry, advocacy organizations, and government. Gender representation was balanced, with slightly more females than males. There was a good representation across all the different age groups.

The poll results showed that the majority of the patients have had genetic testing. About half of the participants have been diagnosed with CMT1A (PMP22 duplication). After CMT1A, the most common diagnoses were CMT2A and other types of CMT. While for a large percentage of participants, it took less than one year to receive a diagnosis, collectively, for many it took much longer. Many reported it took over ten years to receive a diagnosis.

SESSION 1: THE VOICE OF THE CMT PATIENT - PEDIATRIC AND YOUNG ADULT PERSPECTIVES

The voice of the pediatric and young adult CMT patient was heard by listening to stirring testimonies directly from young patients, by polling the attendees on specific questions, and by in-depth discussion with the audience members. The perspectives described here came from young patients, adult patients, and caregivers, but are all given from the perspective of what is like to live with CMT as a child and young adult. The objective of the session was to determine the symptoms and daily challenges that matter most and have the greatest impact on the daily lives of pediatric and young adult patients living with CMT/IN, as well as how these may vary over time. The session also sought to uncover what things are the most concerning and worrying to patients in this age group.

PATIENT TESTIMONIES

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Reagan-

"At a very young age, I felt normal. In pre-K my life changed. When I wrote, I would get tired easily. I couldn't run as fast. I also noticed that I tripped often and always got tagged on the playground. I couldn't get a good grip while climbing because my hands and legs were too weak and gave out. Suddenly climbing was impossible. I thought that there was something wrong with me. And for the first time in my life, I felt weird and embarrassed..."

...CMT hurts both physically and emotionally. During school I can't keep up...

...CMT is exhausting and takes away my ability to just be a kid. I had another surgery when I was eight years old to fix my hip again. Surgeries are expensive and exhausting. Recovery is challenging for the whole family."

Drew-

"Keeping up with my friends was hard enough. But the AFOs [Ankle Foot Orthotics] made it impossible to participate in the sports and activities I wanted to try..."

...So far, I've had three major surgeries that include lots of tendon transfers, and bone reconstruction of both feet. After one of the operations, I suffered through four months of CRPS. Or complex regional pain syndrome. My new foot felt like it was on fire for weeks following my surgery. Every touch or bump sent sharp pains up my leg and physical therapy felt like torture..."

...CMT also caused me to develop scoliosis. For the past four years, I've had to wear a back brace 16 hours a day. The brace was uncomfortable and made it difficult to move around or sleep. But it looks like it helped, and I might be able to get by without having back surgery. My sister was not so lucky. She had to have spinal surgery and has metal rods in her back to keep her spine straight."

Jakeb-

"Kids see my leg braces and wheelchair instead of the person I am..."

...I find that I have less and less friends as my disease progresses. I have all these emotions and I don't know how to deal with them. I am mad that I can't keep up with other kids, and I am sad that I'm getting weaker and weaker..."

...My whole life has changed. I am 12 and a half years old, but I move like a senior citizen. I feel bad that my family has to watch me go through this pain and lose my abilities to do things I really like."

Cassidy-

"I've had trouble ambulating since my diagnosis, so I wear bilateral AFOs. Additionally, I have a tremendous amount of trouble with activities that involve the use of fine motor functions, which affects the way I write, type, use a zipper, and grab things. I have tremors in my hands that can be particularly hard to deal with and they're often exacerbated by exhaustion..."

...I have actually lost the ability to ride a bike, walk on the sand, climb a staircase unassisted, move my toes, and cut my food..."

...The symptoms that matter the most to me are the lack of fine motor skills and the strength in my hands. What worries me most is the very real possibility of losing my ability to play the drums as my CMT gets worse."

Sean-

"I can't even begin to relay the impact this disease has had on my life. This disease has disrupted my life, my family, ever since I was two years old..."

...In elementary school, when I functioned normally, I had a ton of friends. As soon as middle school came around, I had reconstructive foot surgeries for my high arches and toe fusions because of my hammer toes. I lost most of my friends...

...My daily pain consists of shooting, stabbing, numbing pains in my feet, toes, back, neck, and hands. This pain is all because of CMT causing my muscles to deteriorate in my legs, hands, and forearms, creating hand contractures. The pain is becoming so bad that I had to stop physically going to high school last year because I could no longer walk the halls and navigate the stairs...

...Why should I waste my time doing well in school when I could be having the little fun I can get? I feel like I'm going to end up in a wheelchair and government housing, living off social security checks anyway? Who is going to want to marry me? I'll never have children to pass this disease onto."

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

The pediatric and young adult patients reported the top three symptoms with the most impact on the daily life of pediatric and young adult patients are as follows:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

Social or emotional consequences that are the most significant to pediatric and young adults:

- 1) Ability to participate in or perform daily activities (such as work, school, sports, driving, hobbies, etc.)
- 2) Emotional impacts (such as fear, embarrassment, self-esteem, depression, anxiety, etc.)
- 3) Ability to get around (such as stairs, walking, getting up from sitting without using your hands)

Progression of the following symptoms worries pediatric and young adult patients the most:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

Group Facilitated Discussion:

The following is a sampling of insightful comments that were made by the broader attendees, both in the meeting room and listening to the live webcast on-line.

Discussion Question 1:

Of the symptoms and impacts of CMT/IN, which have the greatest impact on your daily life and why?

"...our 13 year- old son has CMT2A...as he's getting older, his middle school, high school, he's become socially withdrawn. I think that the mobility issue and the fear of not being able to be independent or falling in front of his peers, or asking for assistance is what holds him back the most....you just fall all of a sudden and there's no way to see it coming...But as his hands have weakened and he's lost so much muscle tone in his hands, I think that is the greater impact for him...I don't think he remembers not being able to walk without falling or not being able to walk without the braces, but the hands really took a toll from him physically, but of course mentally. You know. Only 13 and you need help doing everything."

- Grace

"My daughter has giant axonal neuropathy and she's a freshman in high school. Just like the panelists, she's experienced the loss of elementary friends as her disease has progressed. She does have a one-on-one aide at school who is always helicoptering, so even if the teenagers do want to come and talk with her, they're resistant because the aide is always nearby. This has been such a huge impact on Hannah's life the past three years."

- Lori

"If your school does not have [a diversity assembly], it's something you have the right to go in, speak to the principal about. The school needs to have a diversity assembly. They help tremendously. It gives the children the ability to ask all the questions that they're so afraid of."

"I was about 100 pounds bigger than what I am at one point. I put on a lot of weight because I was really depressed about what was going on...Now my respiratory is getting worse, which is really scary, the respiratory thing and the choking spells...And the fatigue is just brutal, and the pain."

- Alex

"So, I think really just the mobility issue of not being able to keep up with other kids in high schools and probably middle school is, I think would be the most detrimental thing to me that I found in my high school experience." - Ayo

"My son Zachary is 20 years old and he has Charcot-Marie-Tooth Type 6. It took us 14 years to get diagnosed and it has been quite a journey. We actually moved our family from South Florida to upstate New York to help Zach with getting the services that he needed through his school district. Zachary is legally blind with a vision of 20/400 and suffers from optic atrophy as well as the hand weakness, the hand tremors. He's had bilateral foot surgery, walks with leg braces. Suffers from balance, and I can see more anxiety now starting to creep in...He can't cut food, and so therefore that's some things that are embarrassing, because every time I'll pick him up ... and he can't drive, and he's a real car guy, so that's something that really bothers him that he'll never be able to drive. He works out a couple times a week, and so we're very proactive in keeping his health and keeping that muscle that he has, but the hands are definitely coupled with the visual impairments. The zipper, it's one thing to pull the zipper, but not even be able to see and feel where the zipper starts..."

- Debbie

"Looking back, feeling weak, not good at physical things. Not knowing what was wrong and feeling different."

- Webcast Participant

"And as a student, I remember vividly having to go to gym and go through the state test, and the things that really set you apart from everybody else that was on the floor. Really just made everything else that went on with your friends that much more difficult to deal with."

- Matt

"I have Type 1A. I found out I had CMT when I was 17, my parents knew when I was 18 months old, but they didn't tell me. I grew up with very mild symptoms, but I knew that I had something wrong with me. I think the hardest part about being a kid not really knowing what's going on, was that public humiliation. There was so much humiliation, whether it was the falling, or the kids running after you making fun of the way that you run, or not being able to keep up with your friends, or that darn Presidential Physical Fitness test that we had to take...I think it's the lack of compassion from the public. Knowing what's going on when maybe there's not an obvious leg brace or an obvious wheelchair or an obvious walker, an obvious aid. And they see you're just a funny, awkward, clumsy, klutzy, dorky little girl. And that little girl still lives in me. She's deep down in here but she's still here. And I'm really looking forward to the day when we can get rid of that."

- Susan

"Whether you're in a playground or trying to play a sport, you're not part of any team. Your best friend on the playground isn't hanging with you, she's running because she wants to run, too. So, you constantly kind of feel betrayed even by your closest friends. So, you just have this constant inability to be part of something as a young

child...constantly telling teachers, P.E. coaches, principals that there is something wrong, that she's not being lazy. That this isn't made up...And just trying to really educate people and re-educate people. "

- Brooke

"...people don't really realize you have CMT, and they do stuff that makes you feel really bad and you have to explain to them constantly, "I have this, I have that. I can't do this, I can't do that. So, the hardest part is the fact that they don't pay attention and they forget, because a lot of times with me, I kind of sometimes at the end of the day I just go into my room and start crying, like why did this happen to me today? And the next day I get really nervous, will it happen again? Just a constant reminder that they're forgetting."

- Reagan

"People use names at my school that I just think are totally not acceptable, but there's nothing that you can really do except for tell the teacher or the principal. And if they don't talk to them, then you're stuck in this giant gap. And I know that I said in my speech that there's a lot of bullying going on, but I finally have a chance to talk. I can't deal with this anymore."

- Jakeb

"My mother tried to get help, however medical professionals said that there was nothing wrong and to stop looking otherwise... So, there's still a lot of confusion out there and frustration finding the right care."

"The fear of walking and following profoundly changed my ability to be my normal self. This spiraled into depression that took years to come out of. "

"Because I didn't have anybody showing me what CMT is and how to prevent it from getting worse, I started to use drugs to make friends and to stop the pain."

- Three Webcast Participants

Discussion Question 2:

Can you share any examples of the impact of CMT early in life, from zero to four years of age?

"I have Type 1A that was diagnosed when I wasn't crawling or doing all the other things that the toddlers were doing. I was the weird kid, I got made fun of a lot. And way worse than the pain of waking up in the middle of the night with all of your muscles cramped up, and just screaming and not understanding as a little kid... the thing that affected me when I was young and still affects me...when I was young, doctors prompted my parents to have me not play with baby dolls because it would give me the wrong idea about having a family...I want to be like other people, I want to have a family too."

- Lelia

“We had a lot of trouble finding out why Cassidy was having trouble walking during that time period that you had mentioned, zero to four years...He jumped off the couch at one point and he broke his leg and we thought that was really strange...And we started taking him to doctors, we took him to an orthopedic surgeon at Columbia and they said "No, he's fine. He'll grow out of it...Even with really good physicians sometimes it's hard to diagnose this problem.”

- Jeffrey

SESSION 2: THE VOICE OF THE CMT PATIENT - ADULT PERSPECTIVES

The voice of the adult CMT patient was heard by listening to inspiring testimonies directly from adult patients, by polling the attendees on specific questions, and by in-depth discussion with the audience members. While the perspectives described here came from both adult patients and caregivers, they were all given from the perspective of what is like to live with CMT as an adult. The objective of the session was to determine the symptoms and daily challenges that matter most to adult patients living with CMT and inherited neuropathies, as well as how these may vary over time. The session also sought to uncover what things are concerning and worrying patients the most in this age group.

PATIENT TESTIMONIES

The full testimonies from each patient can be found in Appendix 1. Here are some of the most impactful comments made by each.

Michelle-

"I was sent to a neurologist who did a nerve biopsy and diagnosed me at age 12 with what was then called Dejerine-Sottas. I was given a Xeroxed page about it and was told was that I might experience breathing problems someday. "But if that happens, just go to the hospital and get some oxygen," ...

...that was the worst possible advice they could have given me...When I began blacking out during my classes, I checked myself into the hospital to get some oxygen as ordered. 3 days later I suffocated from CO₂ in my bloodstream, despite being on oxygen the entire time. Doctors resuscitated me and did an emergency intubation without sedation...

...The ventilator finally allowed me to blow off the excess CO₂, but by then my phrenic nerve had deteriorated to the point where I could no longer breathe on my own at all. The nerves in my arms also deteriorated a great deal while I was unconscious in the ICU. In the hospital I was depressed, suicidal, and unable to speak because of the type of trach tube that they had used."

Lainie-

"It was lonely and scary to be a teenager with CMT and I became depressed. Even though I saw several therapists at the time, CMT was not thought of as a contributing factor to my teenage angst. I was an expert at keeping CMT and its effects hidden from everyone, especially from myself. At age 16, I cried out for help by swallowing a bunch of sleeping pills that I'd found in my dad's medicine cabinet. I didn't want to die, I wanted to be seen. I felt as invisible as the invisible physical challenges I kept hidden..."

...After many years of counseling, I learned coping tools for dealing with the fear and uncertainty that CMT brings. Worries like will I ever need a wheelchair, and what if my hands get like my mom's. How will I remain independent? In my late twenties, when the scrapes and bruises from falling down on sidewalks became an everyday thing, I was in a

much better place to accept my need for leg braces. When buttoning shirts and opening clasps on my necklaces became harder, I found adaptations."

Estela-

"CMT is the imaginary friend that no one ever wants. Although it may seem absent to many on the outside, it is a constant and uninvited guest, showing up at the most inconvenient times. It will pull you out of dance class because you can no longer stand on your tippy toes and proceed to kick you off the softball team when you can no longer run or close your mitt around a fly ball..."

...It will grease the classroom door knobs making them impossible to turn open and then cross off fashion design from your career wish list because sewing and CMT do not get along... when you've arrived home safely with your newborn daughter, it will take away half the strength in your arms for the first few weeks of her life and hand her off to others as you're just too weak to hold her..

...It will force you to sit down, when all you want to do is stand up and play catch with your son and then let you miss the look on his face when he skis for the first time...It will cancel plans with friends because the bruises from your leg braces have not yet healed and then let your phone calls go to voicemail because today your voice just feels too fatigued to catch up."

Bernadette-

"I had depression and sometimes took my anger and frustrations out on the ones I loved the most. And I often isolated myself from my family and my friends..."

...I had thoughts of suicide and had to seek counseling in high school. CMT has had a huge impact on my life since I can remember...

...I also discovered with researching CMT that it can affect the way we hear, especially in loud environments. That explains why I always had to say, "What?" I could never understand what others were saying unless I read their lips and listened as hard as I possibly could...

...I knew that one day, CMT would start affecting my hands and the ability to work normal and function properly. My fine motor skills are completely gone now. I experience pain, especially in the bitter cold, or in the hot heat. Bone deformity and ligament tightness had caused my hands to start feeling like my feet. I have bone deformity and atrophy in both my legs and my hands...

...What worries me the most about the future of living with CMT is the ability to continue to take care of myself and be independent."

Lorenzo-

“The braces have improved my quality of life by reducing the number of embarrassing episodes of falling and tripping. While I have great levels of academic excellence and continue to practice scholarship, CMT has slowed my ability to type and to get professional work done in an expedient manner. In addition, getting dressed, buttoning down my shirts, tying my shoes, clipping my finger nails, putting cream in my hair, zipping up my pants and jackets have become a daunting task...

...CMT has definitely affected my mental health in a small way. Particularly, my self-image and physical confidence...

...I have become determined to not let CMT condition give me a negative self-concept. CMT does put limits on my physical abilities, but it will not limit my self-confidence and the building of positive social relationships. I learn to accentuate the social skills and how to build meaningful relationships because, having CMT, I realize we need help from other people.”

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

Adult CMT/IN patients also reported that the top three symptoms with the most impact on the daily quality of life of adult patients are as follows:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

The following aspects of daily life are most challenging to adults:

- 1) Exercising
- 2) Hobbies (such as gardening, sewing, painting, sports)
- 3) Using your hands (such as handwriting, typing, cutting food and handling utensils)
- 4) Working or going to school

The following mental health concerns are most felt by adults living with CMT/IN:

- 1) Feeling nervous and anxious, or on edge
- 2) Feeling down, depressed, or hopeless
- 3) Interacting socially, such as friends or family

Group Facilitated Discussion:

The following is a sampling of insightful comments that were made by the broader attendees, both in the meeting room and listening to the live webcast on-line.

Discussion Question 1:

Of the symptoms and impacts of CMT/IN , which are the most burdensome and why? Starting with less prevalent ones – sensory hearing loss or vision loss.

“So, at age four years old, is when we first figured out that he had a type of vision loss... And then finally we discovered when someone looked into his eyes, because usually little kids, they don't look in their eyes and give them eye exams. That we noticed the peeling, or the narrowing of the optic nerve. It wasn't until many years later when he finally got diagnosed for the CMT 6, that the two kind of came together well, it is a nerve, so it kind of makes sense.”

- Debbie

“So, the hearing loss really interferes with your performance on your job. I still do work a full-time job. It interferes when you're out to dinner with people, because that background noise is awful. You're in a restaurant and the waitress is asking you what you want, and you have no clue what she's saying. So, every day is just a journey with this. Every day you wake up with another, "Is this CMT related? What is this? What's going on with my body?"

- Linda

Discussion Question 2:

Considering the most burdensome symptoms and impacts of CMT/IN, please now discuss those that include vocal cord strain and weakness, difficulty with swallowing, and breathing difficulties

“My husband has CMT 1A. Also, very rarely, he has diaphragm paralysis and is hugely impacted respiratory. That was a game changer for us, really. It came on later after we were married. CMT's hard to deal with. I think the respiratory part of it brings it to another level. It becomes a fatal disease. He was hospitalized for respiratory failure. His CO₂ levels were up to 75, that's pre-organ failure. And we had a doctor that had prescribed him oxygen, which is not right ... So again, we have doctors that don't know what they're doing, and we have now CMT is now a fatal disease for some people.”

- Brooke

“In 1990, my mom's CMT became worse. She was the first one in our family to have CMT. Hers progressed to the point that she was bedbound. So, we created a bed in the living room, and she then started to have respiratory problems. At the time we weren't aware of any respiratory component of CMT, so her physicians tried to assist her by putting her

on CPAP, giving her inhalers and oxygen. I know now that, two of the three caused her breathing problem to increase and worsen...

...She'd died from respiratory arrest at age 63. And it didn't need to happen. It just didn't need to happen. So, as I said we weren't aware of any CMT component...

... with my history in medical, I know to ask more questions, I know to ask for what I want, and I know that I don't have to accept every answer that the physician may give me. I don't think that they're bad physicians. I think they're uninformed physicians. So, when they gave my sister CPAP oxygen again, I said, "No, we're repeating the same thing 30 years later...And at that point we were able to get her directed to the right people with the right information, and she is currently now on BiPAP with no oxygen...

...Studies that show that CMT has Autonomic Neuropathy associated with it. What does that mean? Autonomic is muscles, in our bodies that affect things that we don't have to think about, breathing, swallowing, smooth muscles and glands. These are all being affected by CMT and not just one flavor of CMT, but many of the different CMTs...

... So, what I would like to see is that, we more accurately diagnose patients with autonomic neuropathy and develop accurate and effective treatment modalities for these patients."

- Diana

"I have CMT2C. And what I dislike most about it, is having breathing problems and having scoliosis and these two influence each other. When I was a teenager, I got a severe scoliosis and it's still getting worse every year. Some of my breathing muscles are paralyzed... when I go by wheelchair, I couldn't have a conversation at the same time, because I am searching for air."

- Anna

Discussion Question 3:

How is your hand involvement impacting your daily quality of life?

"Ultimately because of fatigue and especially hand issues, pain, but inability to do fine manipulation and do the keyboarding, et cetera. I ultimately had to leave my work, and I loved my work just like I loved being in the military...And that's I think still one of the major concerns for me because we express ourselves in many ways through our hands, and we do work, and a lot of stuff that legs are important, but the hands ultimately I think, are more so."

- Richard

"I have CMT1A. With regards to the motor and fine movement, for me it mostly affected my ability to play video games. I can't hold traditional controllers very well all the

time...It's a huge combination of things. The clawing aspect of my hands, it forces me to grip the controller really tightly and then I can't reach certain buttons. And then at the same time, just the dexterity of hitting all those different small buttons, I can't just do that."

- Ayo

One viewer, who's had over 20 surgeries, has had to give up driving, which is something that was mentioned earlier. Big part of her story. It's caused her to have to move back home with her aging parents. And she says, " My dad currently drives me 100 miles a day, both ways, to and from work. Due to fatigue, my mom is doing everything for me at home. I'm jumping through hoops to keep my life normal."

- Webcast Participant

Discussion Question 4:

What other symptoms and impacts, such as issues with ankle weakness, balance, mobility, are the most burdensome to your daily life and why?

"I have CMT1A. I think the thing that messes with me the most is not feeling my feet sometimes [at least once a day], trying to get into my outfit. And balance, for the most part. I swim mostly as therapy and to bring to joy to children, like me."

- Helena the Mermaid

"I'm trying to prepare for retirement, old age, all of this, but the people who are really having a problem with this are my sons. My oldest son has CMT and lives in Israel...And I had that discussion with my son. We met in a restaurant and I said, "I can tell ... are you mad at me because you think you got the CMT from me?" That was a critical moment and it takes a lot of courage, I think. He said yes. And then we had to communicate...So I worry about the aging and I worry about the CMT, and to tell you the truth, I haven't read anything on aging and CMT. And I think that's a major lack."

- Unnamed Speaker

Discussion Question #5:

What worries you the most about your future of living with CMT/IN?

"I mean, right when you said that, for me, it is the pulmonary ...we live in Michigan and we were in a year's worth of hospitals and not one doctor mentioned CMT related to pulmonary issues.

- Lainie

"For me, I think about the issues of having a lasting, meaningful relationship in my life. I know a number of people have touched on this in some way or another. But it's been a long struggle...and I hate the fact that I'm always thinking about where I was in my ability to do whatever, five years, ten years ago, and then God, what am I going to be like those increments of time down the road? ... It's perplexing, and it's frustrating, and at times very depressing."

- Richard

"You have to find a way to work together to deal with the anger, to deal with the disappointment, to deal with the dreams that have to change. But sometimes what's happening in a relationship is that in fact, the disease is being allowed to pull you apart. And it just can't do that."

- Ellen

SESSION 3: PATIENT PERSPECTIVES ON TREATMENTS FOR CMT

To understand the perspectives of patients of all age groups regarding current and desired future treatments, a panel of CMT patients/caregivers shared their thoughts and experiences. This was augmented by a poll of the broader audience on specific questions, and by in-depth discussion with the audience members. The discussions focused not only on pharmaceutical interventions, but also on the range of devices, physical exercises, occupational therapies, nutritional/dietary tactics, lifestyle modifications, and mental health approaches the community utilizes to help treat or manage the daily impacts of their diseases. The objective of the session was to gain a better understanding of the pros and cons of current treatments, and then to develop patient-focused insights on what the community values most in the development of new therapies.

PATIENT/CAREGIVER TESTIMONIES

Joy-

“The state of bracing for people with neuromuscular disease is quite honestly disgusting to me. While amputees now have state-of-the-art blades for running and skiing and wearing pretty shoes, we are offered a custom molded brace that’s ugly, bulky, limits mobility, and does nothing but prevent the ankle from rolling. And off-the-shelf, one-size-fits-all carbon fiber brace which offers little individualized correction, or the \$15,000 option that I was lucky enough to have my dad help me pay for, custom molded, carbon fiber Helios braces that correctly align my ankle, knee, and hip, and have some spring in them which provides so much needed pep in my step and energy return. I prayed these would be the answer to living a normal life, and they do help me walk and stand unaided with better balance. But they added new challenges...

...Finding the right shoes to accommodate the bulky brace, they didn't work well on hills or beaches, and they still make me feel disabled. It has finally been acknowledged that the phrenic nerve which conducts signals for breathing to the diaphragm can also be affected, and not just in rare types. Diana, Lanie, and I have lost our moms to CMT-related respiratory failure. I'd do almost anything for a treatment to help me regain the strength in my diaphragm muscle. I'm terrified of the flu and pneumonia, and I'd love to be able to lay flat for a massage or in a dentist chair without having to sit up every ten minutes to catch my breath. I'm sick and tired of being hassled by TSA over my leg braces and BiPAP when I travel. Wouldn't it be awesome to ditch them both?”

Stephanie-

“But of all my symptoms, the respiratory weakness and its severe fatigue that goes along with it, make the most impact on my daily life. I have to sleep more than the average person. I often have to leave work and important family and social gatherings early or miss them altogether due to extreme fatigue. And I'm not able to fly, or travel, as much as I want with my husband. Because of the respiratory insufficiency and vocal cord paralysis that goes along with my rare form, it can be life threatening...

...I am in need of treatments to extend my life expectancy, to keep me off of a ventilator full-time in the future, to reduce fatigue so I can work more hours, spend more time doing advocacy work, participate in social activities and family gatherings, and to strengthen my muscles to make ADL's easier. I need treatments that will improve my respiratory function, so I do not live in fear during cold and flu season, because of my higher risk of airway obstruction and respiratory failure."

Kristin-

"I've been in the hospital three times this past year. Each time being a little more serious and requiring a little more intervention. The very last time, I spent the week in the ICU and on a ventilator, something I really never want to experience again. Nor do I want my son to ever have to see me like that again. I depend on a BiPAP at night; it gives my lungs a break from working so hard. So far, it's kept me out of the hospital and breathing a bit easier. Unfortunately, because diaphragm paralysis is not something widely known about, there's been no standard of care developed for those affected. There's no standard treatment..."

...I had progressed so much during pregnancy, I was relying heavily on my wheelchair. When Parker was born, using a wheelchair no longer seemed like a good option while I could still walk. I wanted to enjoy my time with him. I started taking him for short walks, further and further each time, until I had regained some of the strength I had lost. As time passed, I walked with crutches more and more, and used my chair less and less. I continued to do the exercises that I know will help, I tried to eat more balanced, and continued to remain as active as possible.

I follow-up with my neurologist to help me manage my pain with the use of daily medication...Without the medication, I'm bed-bound and unable to move...Now, with the new restrictions and mandates that are continually placed on pain medications, I fear the day my neurologist says you will no longer be allowed to prescribe it. I know I would be forced to use my wheelchair more and lose the ability to enjoy my life with my son. If I become bed-ridden, that terrifies me."

Lori-

"GAN is ultra-rare with about 75 known cases worldwide. At the time of Hannah's diagnosis, there was one investigator in the world studying GAN. There were no treatments, no best practices, and no translational research underway. After picking ourselves off the ground, we decided to fight. On July 21st, 2016, Hannah received the first in-human intrathecal gene therapy gene transfer, funded grassroots by an army of supporters..."

.... The injection was her only chance at having any quality of life. Her tomorrow looked grim. She was fragile. She weighed 58 pounds. She would go to the nurse's office at school, sometimes twice a day, to nap. She would rarely make it to the restroom in time, both at home and at the long hallways at school. She couldn't feed herself...The natural

history of GAN reveals a dramatic change in these children in just a six-month period...We feel incredibly blessed. From a quality of life standpoint for Hannah, my husband and I, Matt, and Hannah's caregivers, I feel continence of bladder and bowel and the ability to stand to transition to the toilet are critical...

... However, we notice Hannah has been having choking episodes while eating. If she doesn't swallow twice per mouthful, food that's drenched in saliva at the back of her tongue will slide down her throat as she's focused on the new mouthful of food...These are indicators that we must move quickly to get a trial underway targeting the autonomic nervous system...If we're able to launch an autonomic gene transfer IND for the treatment of GAN, we expect this intervention to help with body temperature control, sleep apnea, swallowing, weak speech, likely from a weak diaphragm, constipation, bladder control, respiration, and abnormal heart rate which appears late in the disease process."

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

The top three treatment benefits that would be most meaningful to patients are as follows:

- 1) Ability to walk unaided / reduced falls
- 2) Ability to balance / stand
- 3) Improved hand function (such as grip strength, fine motor skills)

The most commonly used medications or therapies are as follows:

- 1) Bracing or adaptive devices (such as AFOs [ankle-foot orthosis], crutches / cane, scooter, wheelchair)
- 2) Physical therapy / occupational therapy
- 3) Complementary therapies (such as acupuncture, meditation, massage, exercise)

The following are most important in making a decision about taking a medication:

- 1) How much the medication showed benefit for a specific symptom
- 2) Your access to treatment (such as insurance coverage)

The following measurements would discourage clinical trial participation:

- 1) None – for 46% of respondents, no measurements would discourage them from participating
- 2) Nerve biopsy
- 3) Electrodiagnostic testing (such as NCV, EMG)
- 4) Walking unaided for a specified distance, as quickly as possible

The overwhelming majority of the respondents would be willing to do all the following things at home as part of a clinical study. Only three respondents responded that they would not be willing to do anything at home.

- 1) Wear one or more devices to monitor activity (such as ankle sensor, armband)
- 2) Answer a brief questionnaire by calling a toll-free number
- 3) Maintain a specified exercise and/or diet regimen
- 4) Fill out a daily electronic diary/questionnaire

- 5) Submit a videotape on a regular basis (such as weekly, monthly)

The overwhelming majority of the respondents would be willing to undertake the following procedures/activities in a clinical study. Only one respondent responded that they would not be willing to undertake any of these procedures/activities.

- 1) Providing blood samples
- 2) Lying inside an imaging machine for long periods of time (such as MRI)
- 3) Providing tissue samples (such as skin, nerve, muscle biopsy)
- 4) Receiving injections into muscle on a periodic basis of an investigational/experimental drug therapy (such as diaphragm, peroneal, hands)

Group Facilitated Discussion:

The following is a sampling of insightful comments that were made by the broader attendees, both in the meeting room and listening to the live webcast on-line.

Discussion Question 1:

Please share your treatment experiences – both those that have worked well and those that have not worked so well

“I'm very excited about this. I put these rings on my wallet, on here, and it's so exciting because I can now open it up...And then the other thing it, when you get your credit card, I found out a way to be able to pull something out like this, so I don't have to use my teeth. And I just have systems that I'm constantly coming up with. So, these are very exciting. I put them on my boots. The independence is incredible.”

- Shari

“I'll be the first guy in the room to mention medical marijuana...So, fortunately I was in Seattle at the time, and medical marijuana started to become a lot more accepted. So, I started on that and was able to reduce the amount of Fentanyl that I was taking on a bi ... every other day ... by 60%. And I'm on the same amount of pain medicine for the last seven years using marijuana...the medical marijuana not only relieves the pain, but it also kind of changes your mindset. It comforts you, it relieves the anxiety...”

...There are different methods, obviously, of either ingesting it through an edible or smoking or vaping or all these other things that they're coming up with. So, the respiratory thing is something of a concern with smoking it. But I've found that edibles are actually ... makes a bigger impact on the pain, and less impact on my mind.

... If anybody's going to try it, I would definitely recommend the edible route first, and give yourself ample amount of time before you try something again because sometimes when you eat it, it takes an hour, hour and a half to kick in and feel it. So, it's something that you need to slowly get into under a doctor's supervision, and they'll tell you all the different information that you need to know.”

- John

“And I just want to encourage whoever's in the audience, or whoever's on the FDA who doesn't believe that marijuana is an answer to a lot of this pain, you really need to look at things a little bit closer because the news skews the way people views things and the views are very skewed on opiates right now.”

- Unknown Speaker

"Since we're on the topic of medical marijuana ... I just recently kind of came out of the whole being hesitant to talk about it. I think the stigma is finally being lifted, especially in the medical community, and it is being finally recognized as a valuable treatment for pain...

...Working full- time and taking care of your family and your home, there are days where 3 or 4 o'clock rolls around and I just want to collapse into my bed. And the only thing that prevents that is the use of medical marijuana. And it alleviates any anxiety that I have as well as my muscle fatigue, and from that point forward, I am able to complete my day successfully as a high functioning adult...

...And I'm also able to exercise. And I think that really makes a difference whether you have the ability and the energy to exercise on a regular basis and not because for me exercise is vital to my health... So, if I'm able to have the additional energy, I'm able to get on a treadmill, which can improve my cardiac, you know, my cardiovascular health. It also, I believe, fundamentally that movement is medicine and that if you are able to keep your body moving, you are slowing the progression. And if you're able to add some kind of resistance training, some kind of weight, to your exercise program, even if it's not significant, if it's more than your body weight or your body weight alone, it makes a difference to slowing the progression and sometimes even reversing it...So, the use of medical marijuana for me is incredibly important, and I urge all of you ... if you do have some hesitation, to do some more research, and to really look into it."

- Estela

"My mom has also tried all kinds of pain medications. Some of the other options on here as well, like weekly massages, acupuncture, which she actually found acupuncture helped a little bit. But, so one of her concerns with medical cannabis was ... you know, my mom's never done anything illegal in her life so... she was just really afraid to try it. She said she doesn't want to feel high. And so, I think that ... to Estela's point ... educating ourselves on it, and you know, she's been able to use just the pure CBD oil, which we eased into it because we were very nervous that maybe she would feel high or fall down and hurt herself. But she felt nothing like that...I asked her at the end of the first day, I'm like, "How do you feel?" And she had to just think and almost look around and was like, "I don't have any pain." I'm in tears because I've never heard my mom say that."

- Kara

"I find that I don't really have a single treatment that solves everything. It's really a treatment program for me. I do take medications, Elavil and Gabapentin, but very low doses. That seems to work for me. Exercise helps with pain management. Physical therapy has worked for me... I use a treadmill. I have two different sets of handles on it so that I can both maintain my balance and switch my hand grips because my hands tire quickly and easily...I guess that the sum total which works for me. All sorts of adaptations around the house. I have a cane that I don't see very many people use, but it converts to a seat because standing for one place for very long ... just standing in a grocery store line is really agony...But I've also found that being aware of other issues, health issues that I could have that are unrelated to CMT, it's important to differentiate those, and then treat

and deal with those because it really is a total body concept. Finding vitamin deficiencies and correcting those; finding hormonal deficiencies and correcting those. That it's all everything together that really sort of keeps me in the ballgame."

- Bob

"One viewer recommends alpha lipoic acid, which is an over the counter supplement she's successfully used to relieve neuropathy pain."

"Plastic AFOs are not effective and prone to break very easily. Unfortunately, insurance coverage lacks for cost of carbon fiber AFOs, so not only finding something that works but something that's going to last is definitely a challenge."

- Two Webcast Participants

"Both patients and caregivers need to take time for themselves, whether it's exercise or mindfulness or whatever is going to help you help yourself, don't forget to take care of yourself because it's so easy to get swept up dealing with the everyday frustrations, or dealing with being a caregiver, but don't forget to take care of yourself...For me, it's getting on my bike."

- Matt

"One thing that has come to my mind, as we've had this discussion, is the importance of finding your tribe, I guess you could say, and considering treatment options...We found a Facebook group that Stephanie started a year ago when my daughter was diagnosed. I would have no idea what to look for, as the many, many doctors we saw had never heard of this particular type. And it was helpful in speaking to her just to find a neurologist who had actually seen her type, and it has been so helpful."

- Crystal

"I use an elliptical, I use Yoga. I go on YouTube and I get some Tai Chi going on, and I mean, that YouTube is like an amazing thing...I was also using the AlterG, I just wish I had more coverage with insurance to use it. I found that to be phenomenal, because I was really able to see the progress. I didn't use my braces, but I had the support of the machine, and I wish I could afford to have that in my house, because I was really ... I was working the gait, which the braces cut off, so that was amazing..."

...The other thing is that to never give up on finding a doctor, they're out there, that listen to you and work with you...I have a variety of them, I have a medical doctor, I have a doctor of osteopath, I'm working on a variety of things, and finally is diet. I'm doing no flour, no sugar, the inflammation, and really listening to how my body reacts to different foods and really trying to understand what's working, what's not working. It's a total picture, and that's my deal."

- Shari

"The one thing that I've done that I feel like has slowed the progression is Pilates. Not just mat Pilates, if you're familiar with Pilates. Unlike Yoga, it doesn't require any balance, and you're always holding onto something. It's something that after 20 years, I'm really good at.....Pilates is very expensive, but where I live, with Blue Cross, it covered, you know when you get my physical therapist. Physical therapist can be Pilates teachers, and so, I would have a doctor write a script..."

...I can do stairs. I take the stairs, I don't avoid the stairs. It's hard. My feet don't have any movement, but I make a point of doing the stairs, like, use it or lose it. When you can, you should..."My doctor told me never to exercise, that I can make CMT worse." I'm like, okay, please don't sue me, but please start exercising, because that's the only thing you can do...My mom, who passed away, yes, it was from respiratory issues, but it was also because she never exercised."

- Lainie

"I did want to talk about acupuncture, because someone mentioned that, and it's really dry needling, is what Jacob receives. He receives that once a week, during physical therapy... I tell you what, he went from falling multiple times a day, to maybe, maybe five in a month. His balance is much better than it ever has been. Of course, he's still losing strength. His grip strength seems to decrease every single month, but he's able to not fall as much, and he does seem to be stronger. I would encourage you to look into dry needling, because it has really helped him."

- Carlee

"What helps me most is going swimming. If I go swimming twice a week, I don't have any pain in my back, and if I stop going swimming, after a couple of weeks, I get headaches and pain in my back. I've done it all my life, and I think that's what's keeping me alive."

- Anna

"I have an indoor therapy pool. It's probably the best thing that's ever happened to me in my entire life... I want everybody to know that being in the water has definitely saved my life...Being in water, the hydrostatic therapy and pressure is so good for us, even just being in water and just sitting in water, is healing for anybody. I highly, highly recommend anybody getting in warm water, especially for circulation and pain."

- Bernadette

"I started taking off-label phentermine, which is a diet drug, and unfortunately, it has not helped me lose any weight, because it really is just giving me the energy to get past that 3:00 p.m. hitting the wall. It would be wonderful if it could be prescribed for that, not just off-label, so that my insurance would actually cover it, because it's made a huge difference in my life."

- Lelia

We've got one CMT patient who's a big fan of rowing machines, a concept two rowing machine, so you don't need to have any balance. He's put in over 2.5 million miles, in the past two and a half years, so, obviously it's working for him.

- Webcast Participant

...I would like to see either treatments that incorporate better into your daily life routine. I can't do physical therapy exercises on my own, half the time. If there were exercises that I could do at a gym or just a better exercise routine that I could carry on without the supervision of a physical therapist, that would be great. For drugs, if it was a finite amount of time that you had to take the drug, because I personally don't want to be on drugs for the rest of my life."

- Ayo

PRELIMINARY BENEFIT-RISK FRAMEWORK PROPOSAL FOR CMT

In 2013, the FDA published a draft implementation plan for a structured approach to benefit-risk assessment in regulatory decision-making for new drugs in development. This framework calls for assessing five decision factors, including: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When the framework is completed for a specific product, it summarizes each decision factor and explains the FDA's rationale for its regulatory decision. The benefit-risk framework is important for both regulatory and treatment decisions.

The PFDD process is designed to bring in patient's voices to help construct a benefit-risk framework for use in the evaluation of new treatments. People living with a disease have a unique perspective on the unmet medical needs of their condition, and the benefit-risk tradeoffs that may be acceptable across the heterogeneity and progression of the disease. Their input should be the foundation of therapeutic development and regulatory decision-making, so that treatments are developed that are clinically meaningful and that address aspects of disease that are most critical to people living with it. Moreover, by reflecting the perspective of people with a disease, drug developers may be better able to design clinical trials that have a higher chance of success.

The input provided by people with CMT/IN and their representatives at the CMT Externally-led PFDD Meeting is summarized in the table on the next page. This is a sample framework that is intended to provide an understanding of the benefit-risk aspects for two of these decision factors: Analysis of Condition and Current Treatment Options.

This sample framework is likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a drug under review.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Charcot-Marie-Tooth disease is also commonly called hereditary sensory and motor neuropathy. Disease onset can occur in childhood or over time, nerve damage causes muscles in the feet, legs and hands to lose strength. Often the muscle loss happens unevenly, causing deformities. There are five main types of CMT and many subtypes that result from mutations in >100 genes. CMT/IN are inherited, progressive, heterogeneous diseases that cause serious disability, loss of function, and difficulty performing activities of daily living. The loss of muscle strength in the feet, legs and hands leads to difficulties with mobility, balance and hand coordination. In some cases, respiratory issues may cause a shortened lifespan. Other autonomic neuropathic impacts (hearing, vision, swallowing) are now also being recognized.	These diseases place a large burden on families and are the cause of great physical and emotional pain. It results in life-long impacts on individuals' ability to go to school and work. Fatigue, anxiety and depression are common. Children are particularly impacted by social emotional concerns, which can have lasting impacts throughout their lives.
Current Treatment Options	There is a high unmet need in the overall management of CMT/IN. The current state of adaptive bracing is disappointing and there is a high unmet need for more functional bracing. Patients have become very creative in finding nutritional and additional complementary methods (e.g., swimming, acupuncture) that may help in the disease management, but with disease progression, daily activities of life become more and more challenging. There are no drugs approved for the treatment of CMT/IN. Symptoms of the diseases are currently managed with bracing and adaptive devices, physical and occupational therapy, surgery, and complementary therapies such as exercise, acupuncture, meditation, and massage. Prescription pain medications, muscle relaxants, and antidepressants are commonly used.	New treatments should focus on improving the ability to walk unaided, improving the ability to balance/stand, improving hand function, improving respiratory function, and improving the management of pain and fatigue. The use of medical marijuana is supported.

CONCLUSIONS

On Friday, September 28, 2018 HNF hosted an Externally-led Patient Focused Drug Development (PFDD) Meeting. In attendance were patients, caregivers, government officials, healthcare providers, industry representatives, patient advocate and others. The PFDD meeting was an opportunity for patients and families to inform the FDA, drug developers and other key stakeholders on the true burdens of living with CMT and how patients view the benefits and risks of treatments for CMT. This groundbreaking meeting included facilitated panel discussions designed to provide the FDA with perspectives from people with hereditary neuropathies, advocates and caregivers.

The meeting was highly successful in bringing the voice of patients and caregivers to the FDA and other stakeholders who are important in bringing desperately-needed new medications to the market to treat the high unmet needs of patients with CMT/IN.

Robert Moore, patient advocate, caregiver, and advisor to the Hereditary Neuropathy Foundation, concluded the meeting with a call to action for all CMT/IN patients and families to continue to get involved to move progress forward and bring new medicines to the patients who need them. He described a new movement, called **#CMTItsNotOK**

Robert summarized this call to action with the following motivating declarations:

CMT It's Not OK - that the doctors that we go to don't know what CMT is

CMT It's Not OK - that it can take up to five years or more to get a definitive diagnosis

***CMT It's Not OK - that once you get that diagnosis,
they send you home and say there's nothing that you can do***

***CMT It's Not OK - that insurance does not cover the devices and treatments
that we need to deal with this disease***

***CMT It's Not OK - that the rare forms of CMT disease may not get the attention
or research funding needed to find the same cures that we're developing for CMT1A
and the other types of the disease***

***CMT It's Not OK - that the burden of genetic diagnosis up to this point
pretty much has fallen on the patient***

***And last, but certainly not least, CMT It's Not OK - that up until this point there
have been no treatments or cures for this disease!***

**We thank the hundreds of individuals that helped to make this meeting a
success and who participated in-person and on the webcast**

Your Voices were HEARD!

APPENDIX 1 – FULL PATIENT AND CAREGIVER TESTIMONIES

Session 1 – The Voice of the Pediatric / Young Adult CMT Patient:

Reagan

My name is Reagan, and I am nine and a half years old. And I have CMT1A. My father also has CMT 1A. He is severely affected and has a paralyzed diaphragm, meaning that CMT severely impacts his breathing. He was rushed to the hospital by ambulance for respiratory failure when I was only eight. He is my hero. At a very young age, I felt normal. In pre-K my life changed. When I wrote, I would get tired easily. I couldn't run as fast. I also noticed that I tripped often and always got tagged on the playground. I couldn't get a good grip while climbing because my hands and legs were too weak and gave out. Suddenly climbing was impossible. I thought that there was something wrong with me. And for the first time in my life, I felt weird and embarrassed. I thought I was a brave little girl. I didn't know these challenges were just the beginning of my journey with CMT.

Why is my body falling apart? You know how if your iPad breaks you can go to the Apple store and get it fixed? Well for me there's no store that can fix my CMT. When I sit, my knees feel weird bent. When I walk, my knees weird straight. If I stand up from sitting, my legs often will fail. My ankle joints and wrist just drop down. They have no strength. I can't pull my toes up. And my leg muscles are so tight that I can't really bend to get something on the ground without my knees popping forward and destabilizing me. It is difficult to keep up with my peers. I lose my balance so unexpectedly that I can't even break my fall. I fall probably at least once a day. I hurt all over when I fall. I bang up my whole body, and I am sore for days.

CMT hurts both physically and emotionally. During school I can't keep up. The teacher is on the next problem before I finish the first one. It's annoying because my handwriting is sloppy as my hands give out. My dad and I can't even open soda cans by ourselves. We have trouble with buttons and hooks on our clothes. At the age of five, I had my first surgery to correct hip dysplasia. It was so hard and so painful. I started kindergarten still in a wheelchair after wasting my whole summer recovering. I was nervous what people would think of me. After extensive rehab, I started walking again. I was confused because I still had weakness. At the age of seven, my parents told me that I had CMT. I knew immediately what this meant because I had seen my dad struggle for years.

CMT is exhausting and takes away my ability to just be a kid. I had another surgery when I was eight years old to fix my hip again. Surgeries are expensive and exhausting. Recovery is challenging for the whole family. Since 2014, my dad and I have had six surgeries combined. My mom has to be a full-time caregiver and can't work. I have settled into understanding what is happening to me. It is hard at first because I didn't understand why I couldn't change it. People in my class still leave me out and hurt my feelings. Because I can't keep up and always trip. This is what happens when you are different from other people. Thank you for your attention. Together I hope we can do something for people with CMT.

Drew

Hi. My name is Drew. I'm 16 years old, and I'm a junior in high school. I was diagnosed with CMT1A when I was four years old. My twin sister does not have CMT. But my dad, my little sister, and brother all do. Some relatives on my dad's side of the family also have CMT. When I was little, doctors recommended that I wear ankle foot orthotics [AFOs] because I would get tired when walking and had trouble lifting my feet. I tried using AFOs, but they made it really hard to go up and down stairs. And I couldn't run in them. Keeping up with my friends was hard enough. But the AFOs made it impossible to participate in the sports and activities I wanted to try. Doctors told me the only real solution for me was to have surgery. So far, I've had three major surgeries that include lots of tendon transfers, and bone reconstruction of both feet. After one of the operations, I suffered through four months of CRPS. Or complex regional pain syndrome. My new foot felt like it was on fire for weeks following my surgery. Every touch or bump sent sharp pains up my leg and physical therapy felt like torture. Most of my surgeries were during seventh and eighth grade. I missed a lot of school and had to be tutored at home for most of the year. All the pain and medication made it hard to concentrate. And it was really difficult to catch up once I got back to school. CMT's a lot to handle. Especially when you're in middle school. Surgeries straightened my feet and toes, but I still have problems with my feet turning in and my ankles turning over. It's easier to turn my ankle or trip. Once playing a tennis match at school, I fell and banged up my knee and elbow in front of a lot of people. Times like these are aggravating, because it's so hard for me to do some things that are easy for other kids.

CMT also caused me to develop scoliosis. For the past four years, I've had to wear a back brace 16 hours a day. The brace was uncomfortable and made it difficult to move around or sleep. But it looks like it helped, and I might be able to get by without having back surgery. My sister was not so lucky. She had to have spinal surgery and has metal rods in her back to keep her spine straight. It makes it hard for her to do regular things like get her shoes on or sit up for long periods of time. My little brother has his first foot surgery about a year ago. And my dad has had six surgeries to fix his feet and hip. Dealing with so many surgeries has been difficult for me and my family. My mom and dad have to take a lot of time off of work to help us. Dealing with the surgeries and recoveries is really stressful and exhausting for everyone.

As difficult as it's been for me, I know it can get worse. I've seen how bad CMT can get as you get older. My grandfather lost use of his hands and feet because of CMT. And was forced to use a wheelchair and needed full time help. I hope drug trials for CMT are successful. It'd be great if there was something that could make me stronger or even just keep me from getting weaker. I'm tired of having to explain why I walk or run differently. And why I had to have surgery. And I don't want to worry about how bad my CMT's going to get when I get older. Thank you for listening to how CMT has affected me and my family.

Jakeb

Hello everyone. My name is Jakeb and I am the Colorado State ambassador for the MDA. I am also 12 years old. I have a very rare form of CMT called 4J. I am one of 22 in the world with this type. It was only two years ago that I was diagnosed, but it feels like a lifetime. I have a Facebook page called Jakeb's Journey where you can read all about my journey to a diagnosis and how I was a competitive hip-hop dancer, before this disease took that away from me.

What I really want to talk about is how CMT4J affects my life today. Before I had CMT, I had lots of friends and of course, the ladies loved me. Wink, wink. But now, it's hard. I use leg braces to help me walk, they put a spring in my step and lift my feet up so I'm not falling all the time. They really help me, but I also have to use a wheelchair for long distances like at school or even the store.

Kids see my leg braces and wheelchair instead of the person I am. They call me names like Ankle Breaker and Forrest Gump. I find that I have less and less friends as my disease progresses. I have all these emotions and I don't know how to deal with them. I am mad that I can't keep up with other kids, and I am sad that I'm getting weaker and weaker.

In two years, my whole life has changed, and I've had to change the way I do everything. I need a shower chair because I can't stand in the shower without falling. I can't wear shirts or pants with buttons because my hands are too weak to use the buttons. My mom helped me, by the way, with these clothes. I love drawing and being creative, but my hands cramp up after a while when holding a pen or pencil.

My whole life has changed. I am 12 and a half years old, but I move like a senior citizen. I feel bad that my family has to watch me go through this pain and lose my abilities to do things I really like. What I need is a cure and with my type of CMT, I'm racing against the clock. This disease is progressing faster and faster. I am scared of what my future will look like, or if I'll even have a future if a cure is not found. I want to feel like a normal kid again, and with your help, be a part of history and beat this disease. Thank you for listening.

Cassidy

Hi, my name is Cassidy. I'm 19 and study at Virginia Commonwealth University. I was diagnosed with CMT type 2A in November of 2004. CMT has affected me profoundly throughout my life. I've had trouble ambulating since my diagnosis, so I wear bilateral AFOs.

Additionally, I have a tremendous amount of trouble with activities that involve the use of fine motor functions, which affects the way I write, type, use a zipper, and grab things. I have tremors in my hands that can be particularly hard to deal with and they're often exacerbated by exhaustion.

Immediately following my diagnosis, I was enrolled in physical and occupational therapy. Although this helped to keep certain symptoms at bay and I had wonderful therapists working with me, in the end, the therapy was not enough to keep my symptoms from progressing. I have actually lost the ability to ride a bike, walk on the sand, climb a staircase unassisted, move my toes, and cut my food.

The symptoms that matter the most to me are the lack of fine motor skills and the strength in my hands. I'm a music student at Virginia Commonwealth University who loves to play the drums. Playing the

drums can be especially hard for someone who has poor wrist strength, so I've had to adapt how a neurotypical person would normally play the drums. I use a hand brace that holds my wrist in place and that keeps me from dropping my sticks. However, even with the hand brace, playing the drums can be straining and difficult.

Acclimating to college proved to be pretty challenging at first. My dorm building suffered infrequent but frustrating elevator outages and although my room was only on the second floor, elevator outages every month or so can be wildly inconvenient for anyone, but especially someone who has no choice but to use the elevator.

Additionally, there's a few buildings at my school that lack some basic handicap accessibility. But other than that, my experience at college so far has been like anybody else's.

When I was 14, I got a tendon transfer at the University of Utah with the expectation that it would yield a stronger grip on drumsticks, cutlery, zippers, and everything else that requires an ability to pinch. Although it provided me with increased dexterity in my thumbs, my fingers were still lacking the strength to be able to manipulate small objects with ease. Because of the lack of success from the surgery, I use a hand brace to support my left hand when I play the drums.

What worries me most is the very real possibility of losing my ability to play the drums as my CMT gets worse. I'm hopeful that more treatments can help me keep playing. I'm grateful and thank you all for the opportunity to share my story with you. Thank you.

Sean

Hi, my name is Sean. I'm 16 years old and have CMT1A, just like my dad. We are the first generations to be diagnosed in our family. My dad could not be here today as he is still recovering from a below-the-knee amputation he had on his right leg last November because of CMT. My dad was diagnosed at age 42 and I was officially diagnosed at age 7.

When I was asked to provide testimony today, I was happy and scared. Scared that I would become emotional, but happy that people are hearing those of us affected by CMT and are working towards a cure to stop the progression of this disease. I can't even begin to relay the impact this disease has had on my life. This disease has disrupted my life, my family, ever since I was two years old.

My family has not been on a family vacation in over 10 years because my dad has not been well enough to travel, because of ongoing wound treatments, chronic pain, muscle weakness, constant surgeries, and fatigue. Plus, this disease absorbs all our one-household income on things like medications, therapies, and doctor visit copays, home modifications, accessible vehicles, et cetera. I've gone to so many places as a youth disability advocate and met so many people, all without my dad by my side because of this disease.

At one time, I could play sports. I wanted to play basketball so badly. I love basketball. Even when I could play sports, my dad couldn't practice with me that much, as he was dealing with non-healing wounds in his foot and legs due to this disease.

In elementary school, when I functioned normally, I had a ton of friends. As soon as middle school came around, I had reconstructive foot surgeries for my high arches and toe fusions because of my hammer toes. I lost most of my friends. I was called Scooter Boy or Concentration Camp Boy because I was so skinny. Because people don't understand why I'm so skinny, why I walk differently, why I can't play sports, no matter how many times I tell them.

My daily pain consists of shooting, stabbing, numbing pains in my feet, toes, back, neck, and hands. This pain is all because of CMT causing my muscles to deteriorate in my legs, hands, and forearms, creating hand contractures. The pain is becoming so bad that I had to stop physically going to high school last year because I could no longer walk the halls and navigate the stairs. Sure, there's an elevator, but what good does it do when you have to walk across a whole entire antique building that spans a city block to get into it? I refuse to use a scooter or a power wheelchair until I just can't walk anymore. I do this, so I can retain as much muscle as possible as long as I possibly can. Being home with my dad for all these eight months while we're both in pain, recovering, and being isolated from the outside world on some days made us the best of friends. On other days, made us the worst of enemies.

It's hard to look at my dad with all his loss and pain, wondering if that's going to be me someday, where my someday will be here sooner rather than later as the age of onset and severity of this disease is so highly variable from one family member to the next, and I have CMT worse than my dad. My dad feels guilty he gave me this disease and although I know he didn't know and it's not his fault, I do blame him sometimes.

My mom is constantly telling me to do well in school, so I go to college and live a good life. In my mind, I yell back, what does it matter? Why should I waste my time doing well in school when I could be having the little fun I can get? I feel like I'm going to end up in a wheelchair and government housing, living off social security checks anyway? Who is going to want to marry me? I'll never have children to pass this disease onto.

Many adults I know with this disease, marriages end up in divorce. My parents fight so much sometimes, I wish they would get divorced. I see my mom being a caregiver and how it's killing her, and I see how my dad's fighting for my life. I can't choose a side and we're tired all the time.

Session 2 – The Voice of the Adult CMT Patient:

Michelle

Good morning. I'm Michelle, from Staten Island New York. When I was born 44 years ago, I was a "floppy baby", and I didn't hit my developmental milestones on time. Doctors ran the nerve conduction test on me when I was 2 years old, decided, erroneously, that I had non-specific myopathy, and prescribed a walker and orthopedic shoes. At age 10, I suddenly developed scoliosis, and it progressed so rapidly that I was quickly referred to a surgeon. The surgeon wanted a more definitive diagnosis before he would operate. As he put it, "Why should I bother if she's going to die in a few years anyway?" So, I was sent to a neurologist who did a nerve biopsy and diagnosed me at age 12 with what was then called Dejerine-Sottas. I was given a Xeroxed page about it and was told was that I might experience breathing problems someday. "But if that happens, just go to the hospital and get some oxygen," I was told.

The neurologists didn't know it, but that was the worst possible advice they could have given me. About 6 years later, when starting at Barnard College, I did develop breathing problems. I didn't know to watch out for the subtle symptoms of weakened breathing muscles and carbon dioxide buildup. When I began blacking out during my classes, I checked myself into the hospital to get some oxygen as ordered. 3 days later I suffocated from CO₂ in my bloodstream, despite being on oxygen the entire time.

Doctors resuscitated me and did an emergency intubation without sedation. The ventilator finally allowed me to blow off the excess CO₂, but by then my phrenic nerve had deteriorated to the point where I could no longer breathe on my own at all. The nerves in my arms also deteriorated a great deal while I was unconscious in the ICU.

In the hospital I was, depressed, suicidal, and unable to speak because of the type of trach tube that they had used. After 5 months of this, I was fortunate that they transferred me to a hospital where pulmonary complications of neuromuscular diseases were better understood. When I was finally released, my insurance company raised our premiums to three times the size of our mortgage.

I taught myself web design and programming so that I could put up a forum, looking for others with the same diagnosis. Eventually we found each other, and then found that we were now considered to have a rare type of Charcot-Marie-Tooth. But all the research and fundraising seemed to be aimed at the people with milder versions of the disease, and we wondered when the researchers would ever get around to us. It's a terrifying thing, to have a rare disease that doctors don't understand, and realize that no one is working on your type.

In an attempt to understand my own disease, I started taking online classes in genetics. They illuminated so much for me that I decided to go back to school to finish the degree that got derailed so many years ago due to CMT. It took a few years of wrangling with vocational rehabilitation, but three weeks ago I started classes at Columbia University with the goal of becoming either a genetic counselor or genetic researcher.

I never wasted a moment of time asking why me? Why did I have to get this disease? That part is easy; I have a duplication of exon 4 of the PMP22 gene, and a point mutation of LITAF. The real question is, how does it work? Together, I hope we'll find out. CMT, we got this.

Lainie

Hi, my name is Lainie. I'm 48 years old and from Michigan. And I have type 1A CMT. For the first two decades of my life, I rarely if ever talked or even thought of having Charcot-Marie-Tooth disorder. It was just this weird sounding disease I had the bad luck of inheriting from my mom and the reason for my fear of relay races and embarrassing low scores on those awful required presidential fitness tests in elementary school. I didn't think or talk about Charcot-Marie Tooth in middle school either, which is when I first started hating my body and comparing it to others, nor did I think about it during or after the three months spent recovering from the triple orthosis surgery I had to have on both my feet the summer before my freshman year of high school.

A surgery that involved pins being permanently placed inside each foot plate to fuse the bones together to prevent them from over pronating and breaking. During that recovery and many years after, I made up stories and lies about having CMT. When people asked what had happened to my feet, or why I was walking funny, I would say I was in a ski accident or trampoline jumping incident. My lies always involved activities I wished I was able to do. I experienced serious anxiety and eventual depression during those high school years. I was constantly worried about everything, from having to climb the bleachers to someday needing leg braces to walk, which of course I eventually needed.

It was lonely and scary to be a teenager with CMT and I became depressed. Even though I saw several therapists at the time, CMT was not thought of as a contributing factor to my teenage angst. I was an expert at keeping CMT and its effects hidden from everyone, especially from myself. At age 16, I cried out for help by swallowing a bunch of sleeping pills that I'd found in my dad's medicine cabinet. I didn't want to die, I wanted to be seen. I felt as invisible as the invisible physical challenges I kept hidden.

My mom who had CMT did the best she could. She did not live her life defined by her disabilities even when she could barely get out of a chair or pull up her own pants. She would say, "It could be worse." And downplay both the emotional and physical impact CMT had on her day to day life. But, of course, I and everyone else could see her unspoken struggles. After many years of counseling, I learned coping tools for dealing with the fear and uncertainty that CMT brings. Worries like will I ever need a wheelchair, and what if my hands get like my mom's. How will I remain independent? In my late twenties, when the scrapes and bruises from falling down on sidewalks became an everyday thing, I was in a much better place to accept my need for leg braces. When buttoning shirts and opening clasps on my necklaces became harder, I found adaptations. My daughter Zoe who's here with me this weekend also has CMT 1A. Unlike my childhood, we talked openly about living with CMT and she even wrote one of her college application essays about the challenges of being a teenager with invisible physical disabilities.

I was always told that CMT is not a fatal disease and yet my mom just died in January from flu-related complications due to extreme pulmonary weakness caused by CMT. I'm here with you today because of my beautiful, strong and amazing daughter Zoe. I would of course love for there to be a treatment or cure for CMT in my lifetime, but I will do everything I can to help ensure there's a cure for CMT in hers.

Please support our efforts so CMT doesn't take anyone else's mom or grandma away. Thank you for listening.

Estela

Good morning. And thank you for this opportunity to speak with you all today. My name is Estela and I am 38 years young. My sister Melissa and I were both diagnosed with Charcot-Marie-Tooth Type 2 before the age of 4. My frequent falls, trips and flappy gait sparked early concern in my parents, Miguel and Anita. Luckily their questions were soon answered after a painful nerve conduction testing at LAJ in New York.

No one in my family had ever heard of CMT. And there was no family history to be found. By the time my parents had a name for this disease, they had also picked out a name for my newborn sister. And like a cruel *deja vu*, they relived the heartbreak two years later when my sister started showing the same dropped feet as me. Because we were both diagnosed so young, we have very little memory of life before CMT. It is woven into who we are. From the smallest details all the way into our life's biggest decisions.

CMT is the imaginary friend that no one ever wants. Although it may seem absent to many on the outside, it is a constant and uninvited guest, showing up at the most inconvenient times. It will pull you out of dance class because you can no longer stand on your tippy toes and proceed to kick you off the softball team when you can no longer run or close your mitt around a fly ball. It will stand outside your junior high school, just so it can trip you down a flight of stairs and sit right at your hospital bedside while your surgeon is pulling six-inch steel pins from your fused ankles.

It will laugh long with the school bully as he does impersonations of your awkward gait and then tell you to walk right past the kick line tryouts and onto your bus back home. It will grease the classroom door knobs making them impossible to turn open and then cross off fashion design from your career wish list because sewing and CMT do not get along.

It will glue debit cards into ATM machines and numb your feet with ice as you sleep, and when you've arrived home safely with your newborn daughter, it will take away half the strength in your arms for the first few weeks of her life and hand her off to others as you're just too weak to hold her. It will let her hair run wild because closing hair clips and pulling on rubber bands feel more like battles than motherhood. It will force you to sit down, when all you want to do is stand up and play catch with your son and then let you miss the look on his face when he skis for the first time.

It will cancel plans with friends because the bruises from your leg braces have not yet healed and then let your phone calls go to voicemail because today your voice just feels too fatigued to catch up. It will get you into heated arguments with strangers in parking lots because you do not fit their visual criteria for a handicapped parking spot and force you to watch from your front window as your children make snowmen in the front yard because cold weather and atrophy equal pain.

It will turn first dates into research projects, just so you can ensure that that awesome rooftop restaurant also comes with an elevator. It will do all of these things, while remaining unnoticed by those around you and then it will have the audacity to ask you smile through it all. And so, we do. We smile through the pain, the frustration, the disappointment. We carve career paths around the roadblocks and we raise children with messy hair, but big hearts.

We share our stories with you today not for anyone to feel sorry for us, but to raise the urgent awareness needed for CMT treatments and research. I have fallen 53 times so far this year alone, but I have gotten up 54. To my fellow CMT community, keep going. Keep supporting each other and speaking up. You have the power to impact this world for the better. To the FDA, Thank you for listening. May today's insight translate into oversight for tomorrow's treatments. We call on you to improve policies, research, therapies and the support these families deserve. Thank you.

Bernadette

Good morning. It's an honor to be here in front of you all. My name is Bernadette and I'm 39 years old and reside in Jackson Hill, PA. I was born with Charcot-Marie-Tooth disorder Type 1A. It was passed on from my late father John to me and my older brother. Living with this rare disease, I was always in pain as a child, especially in my hips. I was constantly and would frequently complain about walking far distances. I was tired and fatigued every day. I quickly discovered most people never even heard of CMT, especially before the internet, so it was very uncomfortable to talk about growing up.

I barely knew exactly what CMT was, let alone try to explain it to my peers. Some kids even thought I was faking the pain. I even felt feelings of anger, isolation, fear and anxiety, and this completely affected my school experience and friendships. Although I had many friends, and many who stuck up for me, I did get teased and made fun of throughout my school years, which took a toll on my confidence and self-esteem. "Gimp" was one nickname engraved in my mind.

I had depression and sometimes took my anger and frustrations out on the ones I loved the most. And I often isolated myself from my family and my friends. I lived in fear as a child from the thought of having surgery that my parents waited until I was sixteen years old to have a much-needed hip surgery for my hip dysplasia. It used to keep me up at night thinking one day, I needed to get this big surgery. The pain was so unbearable my hips, I remember thinking, if I don't get this done soon, I don't know how much longer I can bear this pain.

I had thoughts of suicide and had to seek counseling in high school. CMT has had a huge impact on my life since I can remember. Before I did anything with friends, I had to do my leg exercises and all my stretches. It was like a chore. I just wanted to be with my friends and keep up, but I never could. Working out was something I always loved, and I remember when gripping the weights, it was hard for me and I often started to lose my balance. I loved it but still never got as strong as I wanted. I also discovered with researching CMT that it can affect the way we hear, especially in loud environments. That explains why I always had to say, "What?" I could never understand what others were saying unless I read their lips and listened as hard as I possibly could.

Watching TV, people would ask me if I'm deaf and frankly sometimes, it feels like it. 28 operations under my belt due to CMT. Dozens of physical therapists and occupational therapists worked with me throughout the years and some still do and all of them have been a part of my growing up. I hated seeing my father in pain all the time. He was a master hair stylist and owner of our family salon and was robbed in his forties when not being able to cut hair anymore.

CMT for my family was referred to as the family secret. No one wanted to accept life with a rare chronic progressive disease. I knew that one day, CMT would start affecting my hands and the ability to work normal and function properly. My fine motor skills are completely gone now. I experience pain,

especially in the bitter cold, or in the hot heat. Bone deformity and ligament tightness had caused my hands to start feeling like my feet. I have bone deformity and atrophy in both my legs and my hands. Due to poor circulation, pain in my toes and ugly looking nails, I had my toenails removed during one of my ligament transfer surgeries.

What worries me the most about the future of living with CMT is the ability to continue to take care of myself and be independent. I hope to one day be able to walk again. And run and utilize my body the way that I used to be. Thank you for hearing my story.

Lorenzo

Good morning. Thank you for being here to hear my story. I am the face of CMT. My name is Dr. Lorenzo. I grew up in Philadelphia. I'm 54 years old. I grew up in foster care systems, so I found out about CMT at the age of five living in foster care.

CMT has impacted my life in a slow progressive manner. I first began noticing physical signs and symptoms as a child about five during play. I realized running and keeping up with my peers was difficult. Swimming was one of the many activities that I did well, and it gave me some leverage and self-confidence over my peers. Later in my teen years, cycling provided me with some stamina and strength against gradual weakness against certain peripheral muscles like my calves, ankles, hands, wrists and forearms. As I reached my thirties and forties, I began noticed increased weakness in my wrist, hands, ankles and feet.

I used to be able to lift thirty to thirty-five pounds with one hand. Now that is very difficult. Standing in line for a public activities, concerts or sports events has become frustrating and physical strain along with running which is very difficult now that I have to wear ankle braces. The braces have improved my quality of life by reducing the number of embarrassing episodes of falling and tripping. While I have great levels of academic excellence and continue to practice scholarship, CMT has slowed my ability to type and to get professional work done in an expedient manner.

In addition, getting dressed, buttoning down my shirts, tying my shoes, clipping my finger nails, putting cream in my hair, zipping up my pants and jackets have become a daunting task. The other thing CMT has impacted is, and that is aggravating is when I'm eating foods like hot wings. I love hot wings. It's very difficult to eat them when your pinching motion from your finger to your index finger is very weak. It's very embarrassing as well. Because fine motor strength is deteriorating, it is difficult to hold the wings with the thumb and index finger. As the CMT condition progresses, fatigue and weakness continue to be a major concern. Walking long distances, climbing stairs, transporting groceries from the car into the house are major tasks, along with carrying out daily life skills.

Although I struggle with these limitations, I am concerned for my physical abilities as I age. Like opening jars, and these complicated packages. CMT has definitely affected my mental health in a small way. Particularly, my self-image and physical confidence. As a young man, I always took pride in my self-image because I grew up in foster care, not having much or the best of anything, I did not have much to feel good about myself. As a child knowing that I was limited in what I could do and could not do, because of the CMT, I stayed to myself. Over the years, I have exercised and tried to eat right and tried innovative ways to cope with the CMT's physical limitations. For example, I discovered that a slim piece of string could be used to make zippers more effective when attached to my pants and jackets. The

string idea was done because of too many near close bathroom accidents. Because the pinching motion in my hands made it difficult to grab the zippers. These challenges although time consuming on a daily basis have not altered my attitude. In fact, I have become determined to not let CMT condition give me a negative self-concept. CMT does put limits on my physical abilities, but it will not limit my self-confidence and the building of positive social relationships.

I learn to accentuate the social skills and how to build meaningful relationships because, having CMT, I realize we need help from other people. It is my hope, that in my lifetime, or in the lifetime of others, that a cure will be found for this troubling condition. So, I, and others could have a more physical quality of life.

Session 3 – Patient Perspectives on Treatments for CMT:

Joy

Good afternoon. My name is Joy. I'm from Seattle, Washington, and I have CMT1A. There's nothing I can do for you. There's no treatment or cure. When I was 14 years old, this is how a neurologist diagnosed my mom, brother, and me with this hereditary neuromuscular disease that would progressively get worse as we got older.

CMT is considered rare as it's estimated to affect approximately 1 in 2,500 people in the US, but that's approximately the same as MS, so it's so frustrating that I have to explain it to every doctor I meet. Why don't more doctors know about CMT? And friends that asked, what happened to you? When I show up at event on crutches or in a boot or cast because my dropped foot and weak ankles continually cause me to injure myself. I've always made excuses for not participating in physical activities, but I've never discussed my CMT, which luckily was very slowly progressing.

I did eventually have to start acknowledging it and discussing it with my husband, Toby. Part of the reason we decided not to have kids was because I understood it could make my symptoms progress much more quickly, and the chance of our kids having CMT, maybe a lot worse than mine, was 50/50.

After I turned 40, I struggled to walk up the stairs with my weak legs and poor balance, and soon, two stairs without a railing I couldn't even do. I started walking like a stork, hiking my knee up to get my feet to clear the ground without tripping. It was time to get some braces or AFOs to allow me to walk a little faster, for longer distances, and hopefully give me some energy return, because walking any distance like a stork became exhausting.

The state of bracing for people with neuromuscular disease is quite honestly disgusting to me. While amputees now have state-of-the-art blades for running and skiing and wearing pretty shoes, we are offered a custom molded brace that's ugly, bulky, limits mobility, and does nothing but prevent the ankle from rolling. And off the shelf, one size fits all carbon fiber brace which offers little individualized correction, or the \$15,000 option that I was lucky enough to have my dad help me pay for, custom molded, carbon fiber Helios braces that correctly align my ankle, knee, and hip, and have some spring in them which provides so much needed pep in my step and energy return. I prayed these would be the answer to living a normal life, and they do help me walk and stand unaided with better balance. But they added new challenges.

Finding the right shoes to accommodate the bulky brace, they didn't work well on hills or beaches, and they still make me feel disabled. It has finally been acknowledged that the phrenic nerve which conducts signals for breathing to the diaphragm can also be affected, and not just in rare types. Diana, Lainie, and I have lost our moms to CMT related respiratory failure. I'd do almost anything for a treatment to help me regain the strength in my diaphragm muscle. I'm terrified of the flu and pneumonia, and I'd love to be able to lay flat for a massage or in a dentist chair without having to sit up every ten minutes to catch my breath. I'm sick and tired of being hassled by TSA over my leg braces and BiPAP when I travel. Wouldn't it be awesome to ditch them both?

Recently, I helped HNF draft a letter to CMT patients announcing hope is on the horizon. Pharnext PXT3003 clinical trial is proving the combination can regulate the production of the extra protein my body is producing so that the damage can be halted, and I may even be able to regain some function. If my 12- and 14-year old nieces have CMT and the pediatric trial is started soon, their progression could be halted by age 15. Grace can continue playing volleyball and Anna can keep running, as she puts it, like a wolf through the moonlit woods at night. She's definitely got a flair for drama.

It seems too good to be true. For nearly 35 years now I've been told, there's nothing I can do for you. Now, I optimistically await the news of when this drug will be available to me, my brother, and my nieces. I'm excited about PXT3003, but my mind is whirling with questions too. Will I be able to access it via compassionate use or right to try? Will I be able to afford it if I have to take it every day for the rest of my life? Will I still have to spend hours looking for shoes that accommodate my leg braces, and walk with a cane or worse, a wheelchair? Will I be able to walk side by side on the beach in Maui and hike at Mount Rainier side by side with my husband again? What I'd give just to be able to go for a walk with my two Labrador Retrievers.

In just 30 short years, I watched my mom go from very active to limited mobility to a wheelchair to death by respiratory failure, secondary to CMT, when she was only 70 years old. I'm haunted by the shadow her life was casting over mine, but I'm starting to get really excited about the hope on the horizon.

Stephanie

Hello. My name is Stephanie. I'm 40 years old, and I have a rare and severe form of hereditary neuropathy called TRPV4 related hereditary neuropathy, also known as Charcot-Marie-Tooth type 2C scapuloperoneal spinal muscular atrophy. Having this disorder has not stopped me from pursuing the higher education, having a career, and getting married, but it has made a huge impact on how I live and experience life, and it necessitates endless adaptation.

To start, I was born with foot deformities, torticollis, and hip dysplasia. As a result, I had corrective foot surgeries in infancy, but was still never able to stand or walk on my own due to severe foot weakness. At 18 months, I received my first walker, a pair of KAFO's, or long leg braces, and with a strong upper body, was able to walk. Later in childhood, I developed severe scoliosis and had a partial spinal fusion at eight years old to prevent further curvature, restrictive lung disease, and digestive problems. My braces, walker, crutches, and spinal fusion allowed me to attend school, play with friends, and be active with my family.

I've also always had vocal cord weakness, or stridor. I needed a tracheostomy during my spinal fusion for airway access. I practice vocal exercises to optimize my weak voice, but it remains high, quiet, and breathy, which makes it difficult for others to understand me, especially in loud settings.

Starting around age ten, I developed significant hand weakness, which manifested with a typical claw hand pattern of hereditary neuropathy.

In early adulthood, I developed significant respiratory insufficiency with severe sleep apnea, and have been dependent on a BiPAP with supplemental oxygen at night ever since. My BiPAP breathes for me when I stopped breathing during sleep due to diaphragm paralysis, reduces the burden on my weak respiratory system, allowing rest and completely saved my life. I would not be here with you today without having had it. I stopped walking altogether at age 25 due to respiratory insufficiency, fatigue, and increased hand weakness and pain from using crutches.

I'm in pain from using crutches. I've exclusively used my wheelchair since. Although using a wheelchair comes with many accessibility limitations. It has given me the freedom to move more quickly and efficiently and reduce my hand pain and fatigue. I recently received my first pair of hearing aids. Because my disorder has caused hearing loss. I'm mostly independent of activities of daily living but I have to use assistive devices and adapt most of them. But they take significantly longer for me to perform than the average person.

I use an adjustable bed at night, shower bench, and hand-held shower head since I can't stand in the shower. I'm limited in how I style my hair since I can no longer hold my arms above my head. I avoid clothing, buttons, and zippers, due to hand weakness, and am limited in the types of shoes I can wear because of my foot deformities and foot fusions. I had to invest in renovating my kitchen and closets, to lower counters and install pull-down rods and shelves for access. While I love to cook, I struggle to hold knives and utensils, and opening packages is very difficult. Grocery shopping, cleaning the house, and doing laundry is so difficult that I've had to hire help. I use a manual wheelchair with a smart-drive, push-assist to get around. I drive a wheelchair ramp van, with a lowered floor kneel system, driver side transfer seat, and hand controls.

But of all my symptoms, the respiratory weakness and its severe fatigue that goes along with it, make the most impact on my daily life. I have to sleep more than the average person. I often have to leave work and important family and social gatherings early or miss them altogether due to extreme fatigue. And I'm not able to fly, or travel, as much as I want with my husband. Because of the respiratory insufficiency and vocal cord paralysis that goes along with my rare form, it can be life threatening.

Unfortunately, for me and others with my disorder, there's currently no treatment available other than supportive therapies. There are children with my disorder who have never been able to walk, who need permanent tracheostomies to be able to breathe, and who are dependent on a ventilator. We are in desperate need of accelerated research and the basic science to understand the exact mechanism of our disorder and in to functional treatments that could improve the quality and length of our lives. I am in need of treatments to extend my life expectancy, to keep me off of a ventilator full-time in the future, to reduce fatigue so I can work more hours, spend more time doing advocacy work, participate in social activities and family gatherings, and to strengthen my muscles to make ADL's easier. I need treatments that will improve my respiratory function, so I do not live in fear during cold and flu season, because of my higher risk of airway obstruction and respiratory failure. I thank you so much for this opportunity.

Kristin

Good afternoon. I'm Kristin, mother of Parker, and living with CMT4C. CMT4C is one of the more rare types, so it affects everyone differently. For me, it's impacted my balance, my coordination, my muscles have atrophied, my vocal chords are affected, and my diaphragm no longer works. It's hard for me to walk without the use of leg braces and crutches. They help me maintain my balance and prevent falls. With them I am able to enjoy life with my son. We are able to explore the zoos and parks. We can enjoy the beaches and family outings. They allow me to continue walking when my doctor suggested using a wheelchair.

Unfortunately, leg braces are not without their own burden. They are big and clunky, they are heavy and awkward, they are expensive, even with insurance coverage, and makes buying nice shoes nearly impossible, and they aren't the most comfortable to wear. They also do not guarantee that you won't fall. My crutches help me maintain my balance, especially on uneven ground, but they put a lot of strain on my hands and wrists. And with the disease that causes arm and hand weakness, this is eventually going to be a problem. I won't be able to rely on them for much longer.

With vocal cord dysfunction and diaphragm paralysis I need to be extra cautious around those who are sick. If I catch even a simple cold, it sends me into respiratory failure and admitted in to the hospital. I've been in the hospital three times this past year. Each time being a little more serious and requiring a little more intervention. The very last time, I spent the week in the ICU and on a ventilator, something I really never want to experience again. Nor do I want my son to ever have to see me like that again. I depend on a BiPAP at night; it gives my lungs a break from working so hard. So far, it's kept me out of the hospital and breathing a bit easier. Unfortunately, because diaphragm paralysis is not something widely known about, there's been no standard of care developed for those affected. There's no standard treatment.

After my doctor found out I had diaphragm issues, it took over a year for me to obtain a BiPAP and two more hospitalizations. Without that standard of care, treatment for diaphragm paralysis is anyone's best guess. And that's really scary when it's your health on the line. When I was first diagnosed, so many things ran through my mind. I was relieved to know what I was up against, but I was scared learning Charcot-Marie-Tooth Disease was progressive. I was a semester away from completing my nursing degree. I was an active EMT that had volunteered on the weekends, and now I have this little boy who relied on me.

My house wasn't set up for someone with a disability. We had carpets that made it hard to navigate, steps that I couldn't get up, and now baby clothes and toys that were not user friendly. I couldn't snap those little onesies. We had to make sure we got pants and shirts without those buttons. Baby swings, kid toys, and equipment made my house a minefield, impossible to navigate without falling. The stroller became my new best friend. I had progressed so much during pregnancy, I was relying heavily on my wheelchair.

When Parker was born, using a wheelchair no longer seemed like a good option while I could still walk. I wanted to enjoy my time with him. I started taking him for short walks, further and further each time, until I had regained some of the strength I had lost. As time passed, I walked with crutches more and more, and used my chair less and less. I continued to do the exercises that I know will help, I tried to eat more balanced, and continued to remain as active as possible.

I follow-up with my neurologist to help me manage my pain with the use of daily medication. Without it, I wouldn't be able to get out of bed or live a normal life. Without the medication, I'm bed-bound and unable to move. Taking Parker on walks to the zoo and to the parks would no longer be possible. Enjoying my life with him would be over. Now, with the new restrictions and mandates that are continually placed on pain medications, I fear the day my neurologist says you will no longer be allowed to prescribe it. I know I would be forced to use my wheelchair more and lose the ability to enjoy my life with my son. If I become bed-ridden, that terrifies me.

Living with this disease causes a tremendous amount of frustration. No matter how hard I try to get stronger and keep my body in good physical shape, I will always have CMT as an underlying issue. It rips out everything that I've worked for. After my last stay in the ICU for respiratory failure, I'm coming back even weaker, and more uncertain of my future. For the first time in a very long time, I'm scared. I can't help but worry about my future. I wonder if it will be cut short. Am I receiving the right treatment? I don't want to leave my son behind. I hate having him watch me when I get sick. I see the fear in his eyes. Am I giving him the life he deserves, the life I had always envisioned for him. I wanted so much more for him. And me. All the things that I had taken for granted are now at the forefront of my thoughts when I lay down at night. I won't allow that fear to rule my life.

We need a treatment that will halt progression of Charcot-Marie-Tooth Disease. We need people to take it seriously and understand how disabling and life-altering it truly is. We need people to find medications that will help all of us.

Lori

Hello. I'm Lori from Upstate New York. In March of 2008, my husband and I were told that Hannah, our youngest of three daughters, had Giant Axonal Neuropathy or GAN. GAN is one of the most severe forms of inherited neuropathy and impacts every nerve cell in the body. We were told Hannah would continue to weaken. She would lose the ability to walk, speak, swallow, and would eventually succumb to pneumonia in the second or third decade of her life.

GAN is ultra-rare with about 75 known cases worldwide. At the time of Hannah's diagnosis, there was one investigator in the world studying GAN. There were no treatments, no best practices, and no translational research underway. After picking ourselves off the ground, we decided to fight. On July 21st, 2016, Hannah received the first in-human intrathecal gene therapy gene transfer, funded grassroots by an army of supporters. That is the trial that Dr. Thomas referenced at the beginning of our afternoon session.

I must tell you that the single most stressful day of my life was awaiting the results of Hannah's pulmonary function test. She needed the score of at least fifty percent to satisfy inclusion criteria for the gene therapy clinical trial to the central nervous system. The second most stressful day of my life should have been the day Hannah received that injection with the AAV9 viral vector. Hannah is a homozygous deletion meaning she makes no endogenous protein. The four patients before Hannah were missense mutation patients. So, while the protein didn't work, the immune system knew it, knew it was there. If the immunosuppression protocol failed, and Hannah launched a T-cell response to the transgene, it would have very likely been fatal. We knew what we were signing up for.

Instead of intense fear on the morning of Hannah's injection, we felt relief and optimism about Hannah's future for the first time in nearly a decade. The only definite thing was the GAN was killing Hannah. The injection was her only chance at having any quality of life. Her tomorrow looked grim. She was fragile. She weighed 58 pounds. She would go to the nurse's office at school, sometimes twice a day, to nap. She would rarely make it to the restroom in time, both at home and at the long hallways at school. She couldn't feed herself. If she was finally able to get food on a utensil, it would fall off while en route to her mouth. She would cry in frustration. She was having difficulty grabbing things and navigating her iPhone. Her vision was worsening. She would experience bouts of vertigo several times a day without even changing positions. One pinky developed a contracture. Her strider was worsening. Drool began running out of her mouth and food began falling out of her mouth when she ate. She developed sleep apnea. Her legs would buckle when standing while supported.

We knew from other GAN patients how rapidly Hannah would decline if she were to lose the ability to be weight-bearing. With certainty, if Hannah hadn't received this injection, twenty-six months ago, a common cold this coming winter could take her life.

The natural history of GAN reveals a dramatic change in these children in just a six-month period. While I'm not privy to the data from this current AAV trial, I can say with certainty, that Hannah is much stronger in all proximal muscle groups. Her balance proprioception and fine motor skills are dramatically better, she can feed herself without frustration, she can grab a bottled water, bring it to her lips and take a sip without spilling, episodes of vertigo are greatly reduced and now only occur if we lay her down too quickly, like to get in bed at night. Her stamina is greatly improved, no more naps in the nurse's office during her school day. Her vision is stable out twenty-four months. Muscle control of her eyes is much better, and we definitely noticed this in photos pre and post gene therapy. The comparison is really staggering. Her pulmonary function is stable out twenty-four months and urinary urgency is better than baseline. She's thriving and now weighs eighty-one pounds. I'm eager to see if Hannah's leg strength will show any improvement at her next visit.

We feel incredibly blessed. From a quality of life standpoint for Hannah, my husband and I, Matt, and Hannah's caregivers, I feel continence of bladder and bowel and the ability to stand to transition to the toilet are critical. Because of this we can still travel freely with Hannah and spend hours at a theme-park without having to figure out where to lay down an eighty-one-pound child to change a soiled diaper. We can fly across country, she can use the bathroom at school like her peers. However, we notice Hannah has been having choking episodes while eating. If she doesn't swallow twice per mouthful, food that's drenched in saliva at the back of her tongue will slide down her throat as she's focused on the new mouthful of food. Her speech is now high-pitched at times and it's really been striking to me today. I knew it wasn't vocal paresis, because if I asked her to speak really loudly in a low voice, she can, it's her diaphragm that's being impacted.

When Hannah came down with the flu last winter, as we all know all too well, the flu vaccine didn't have coverage last winter, her body temperature dropped to 94.9. These are indicators that we must move quickly to get a trial underway targeting the autonomic nervous system. Preliminary studies in Dr. Steven Gray and Rachel Bailey's labs, they're both now at UT Southwestern, indicate we can use the same vector construct as the current IND, even in rats, pre-immunized weeks prior by intrathecal route, with the same vector. This is amazing. That's a win we didn't anticipate.

From a neuroanatomy standpoint, neuropathologist Diane Armao confirmed the areas we see pathology in our GAN knockout rat, are the same areas responsible for the human autonomic phenotype we're

seeing in GAN patients. If we're able to launch an autonomic gene transfer IND for the treatment of GAN, we expect this intervention to help with body temperature control, sleep apnea, swallowing, weak speech, likely from a weak diaphragm, constipation, bladder control, respiration, and abnormal heart rate which appears late in the disease process. I hope we are before you, FDA CBER, for a pre-IND meeting in January. Like ALS, any intervention for GAN that halts or even slows disease progression, is a huge win. Every week that slips by for a patient with GAN or CMT4J or 2E or 2C or 4C or CMT2A or CMT6, and many others, results in severe functional loss and puts patients at risk.

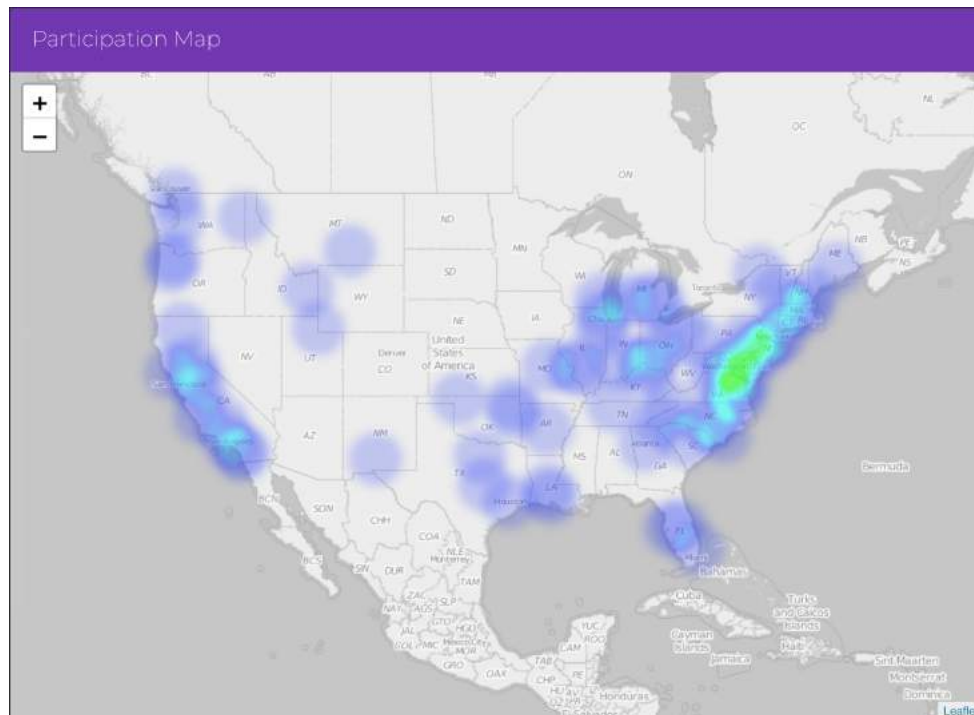
We've had a repeated theme. Be a voice. Speak out. And I'm going to take this moment to speak out to Oprah Winfrey, Bill Gates, Warren Buffett, Sarah Blakely, and whoever else has the financial means, to help the Hereditary Neuropathy Foundation, start checking off these diseases one by one. The inherited neuropathy community is, I believe, the most underserved community on the globe. In this small conference room, small ballroom, there are people from four different countries. This is a different aspect of global health. The technology is there to treat these diseases. What's missing is the attention and funding. Please reach out to the Hereditary Neuropathy Foundation. Precious and innocent lives depend on us all. Thank you.

APPENDIX 2 – Polling Questions

The meeting began with several polling questions to understand the demographics of the attendees. The first two general questions were open to all participants in the meeting.

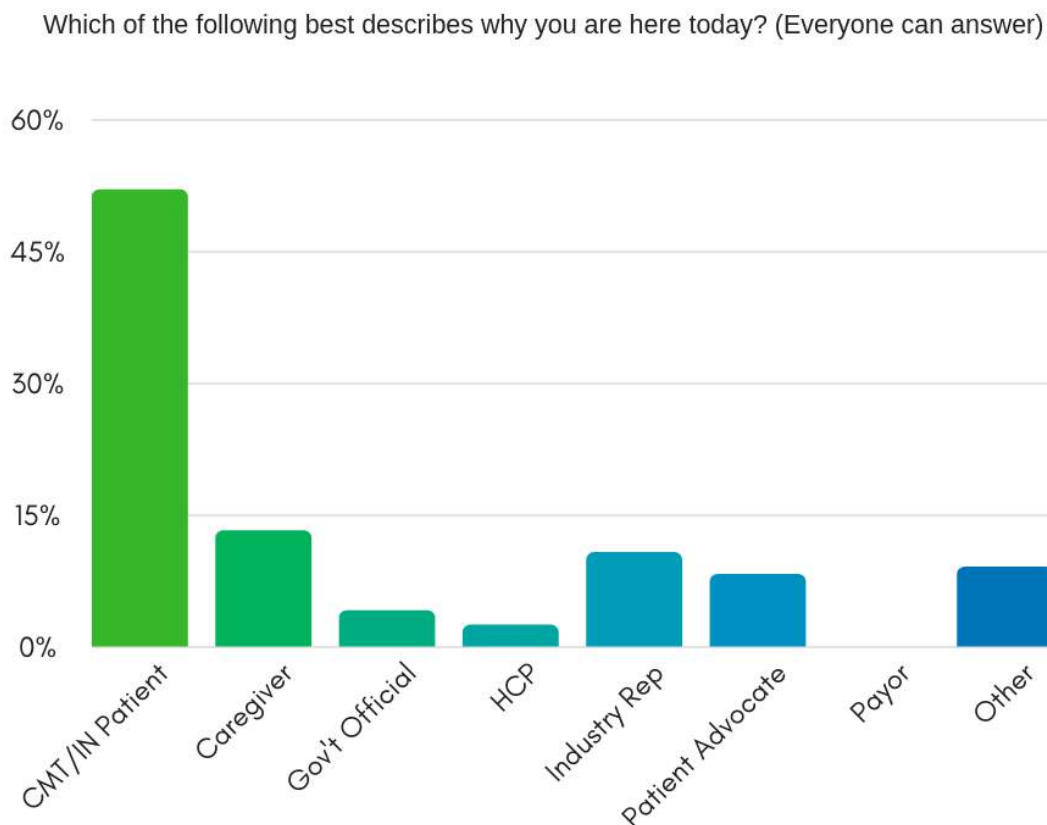
General Polling Question 1:

In which time zone do you live?



This poll revealed that 91% of the participants were US-based. Most of the participants were based in the Eastern time zone (70%), and the Central, Mountain and Pacific time zones were also represented.

General Polling Question 2:



This poll showed that 52% of the participants were CMT/IN patients and 13% were caregivers. Others in attendance came primarily from industry, advocacy organizations, and government.

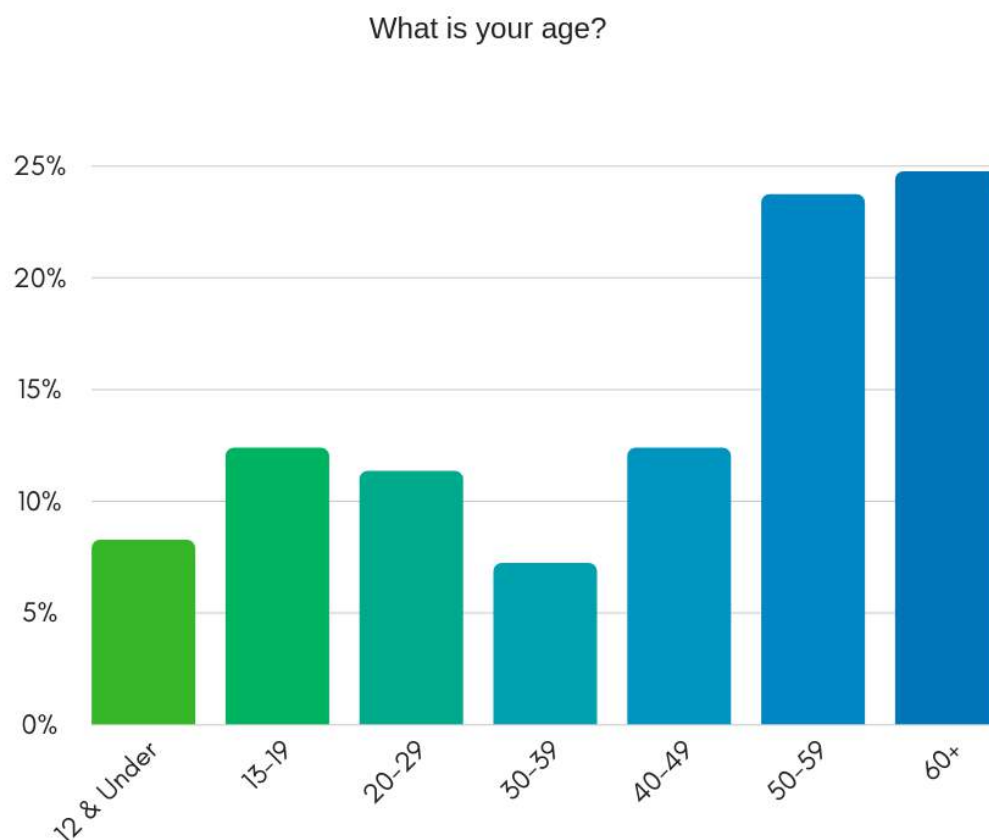
The following demographic questions were available only to patients and caregivers. Throughout the remainder of the polling, caregivers answered questions on behalf of the patients they represented. Those who were both caregivers and patients were instructed to answer the questions only once, on behalf of themselves. For cases in which both the caregiver and patient they care for were present at the meeting, caregivers were instructed to participate to get a caregiver perspective.

Demographic Polling Question 1:

What is your gender (or the gender of the patient you represent)?

The poll responses showed that the gender representation was balanced, with slightly more females than males.

Demographic Polling Question 2:



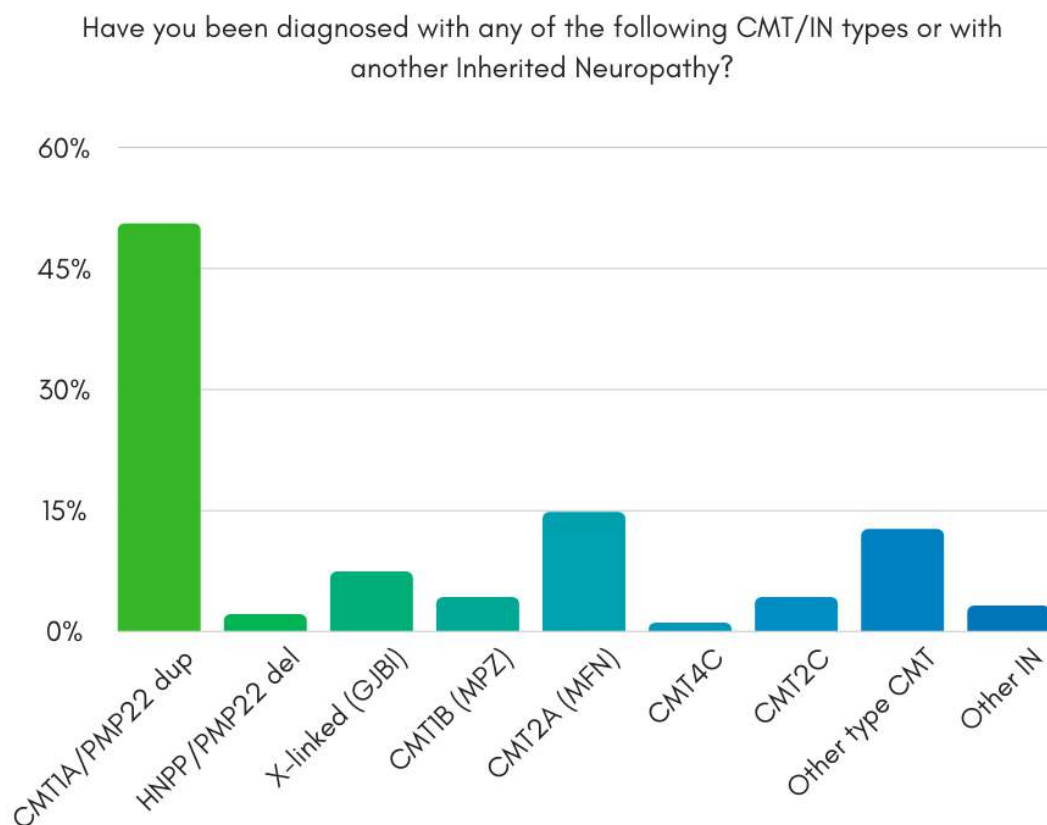
The poll results revealed a good representation across all the different age groups, with the highest percentages in the 50 to 59 years age group (24%) and 60 years and older age group (25%).

Demographic Polling Question 3:

Have you (or the patient you represent) ever had genetic testing?

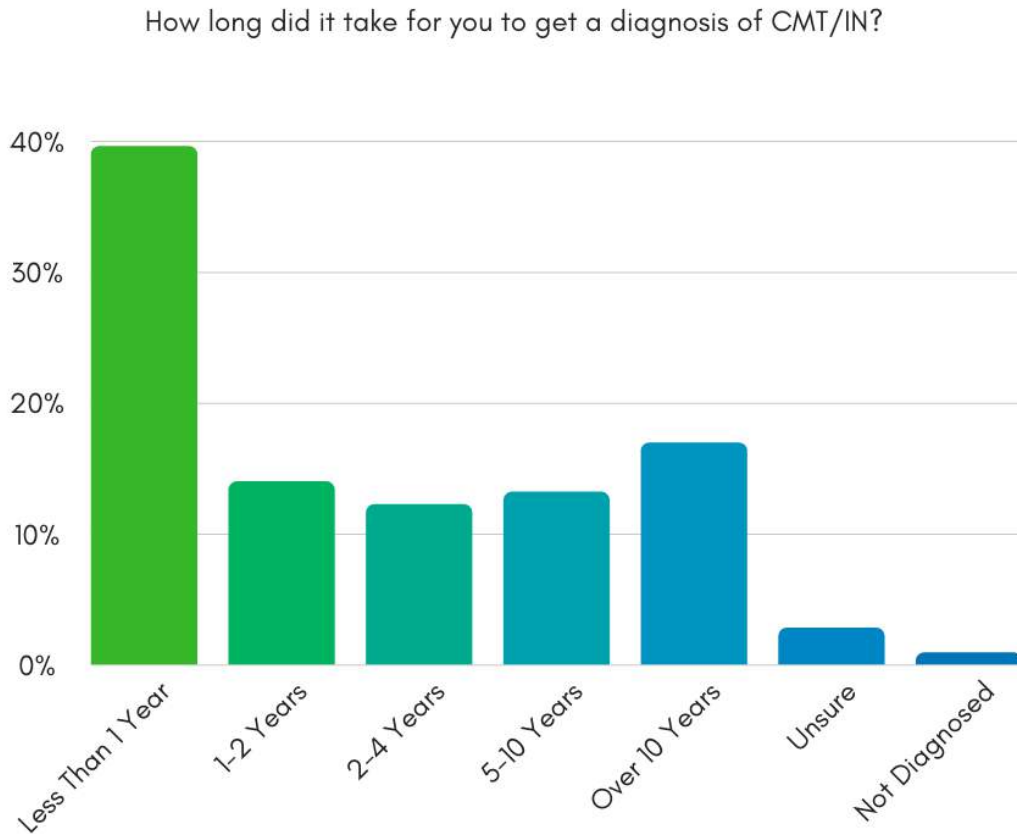
The poll results showed that 71% of participants have had genetic testing, while 29% have not.

Demographic Question 4:



The poll results showed about half of the participants have been diagnosed with CMT1A (PMP22 duplication). After CMT1A, the most common diagnoses are CMT2A (MFN; 15%) and other types of CMT (13%).

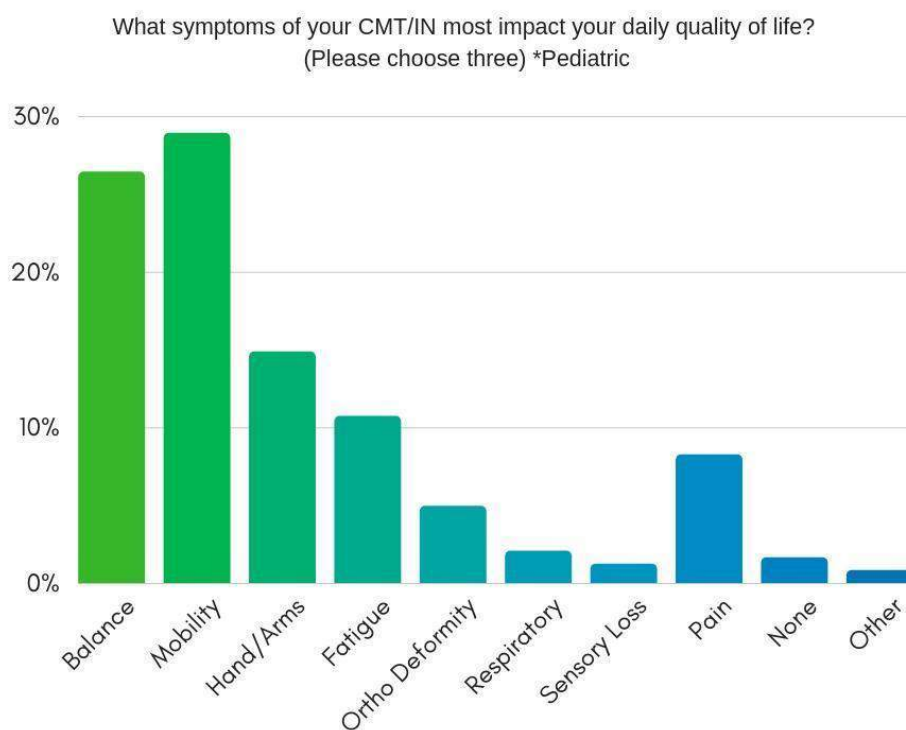
Demographic Question 5:



The poll results revealed that for 40% of participants, it took less than one year to receive a diagnosis. Collectively, for many it took much longer, including 17% for whom it took over ten years to receive a diagnosis.

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

Polling Question 1:

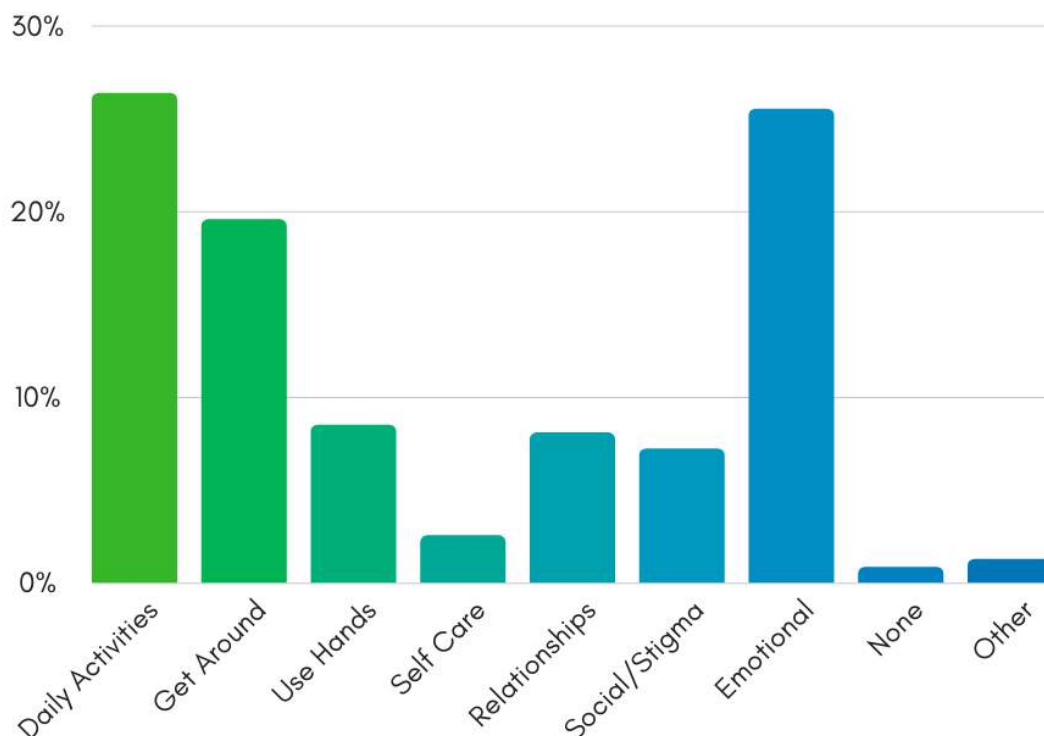


This poll reveals that the top three symptoms with the most impact on the daily life of pediatric and young adult patients are as follows:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

Polling Question 2:

As a result of living with CMT/IN, which of the following impacts are most significant to you?
(Please choose up to three)

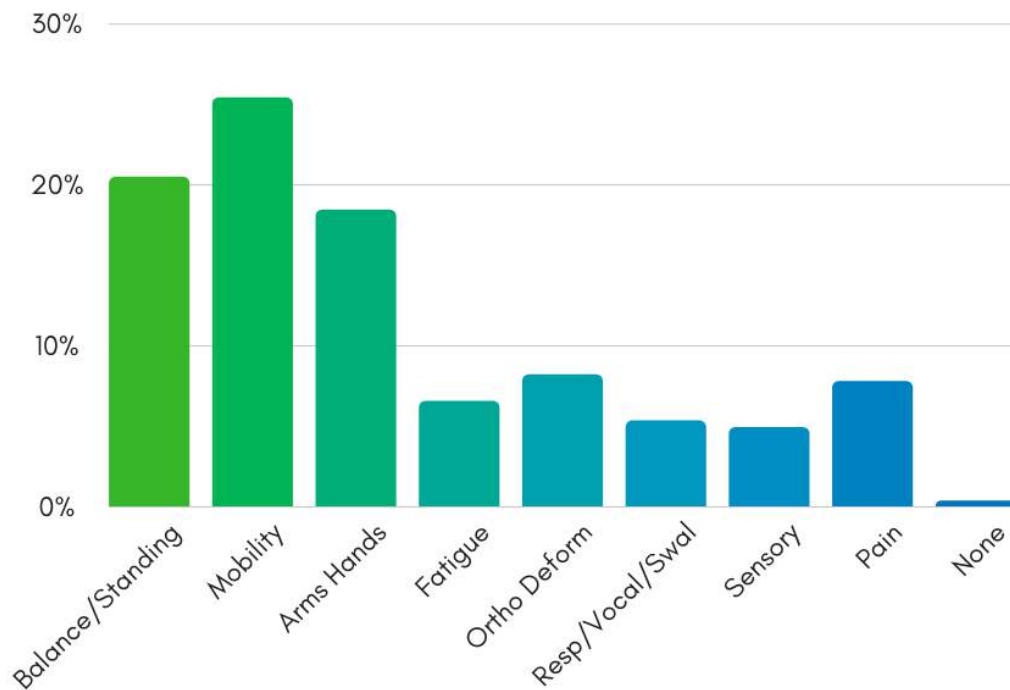


This poll showed that the following social or emotional consequences are the most significant to pediatric and young adults:

- 1) Ability to participate in or perform daily activities (such as work, school, sports, driving, hobbies, etc.)
- 2) Emotional impacts (such as fear, embarrassment, self-esteem, depression, anxiety, etc.)
- 3) Ability to get around (such as stairs, walking, getting up from sitting without using your hands)

Polling Question 3:

As the disease progresses, development or progression of which of the following symptoms of CMT/IN worries you the most? (Please choose up to three)

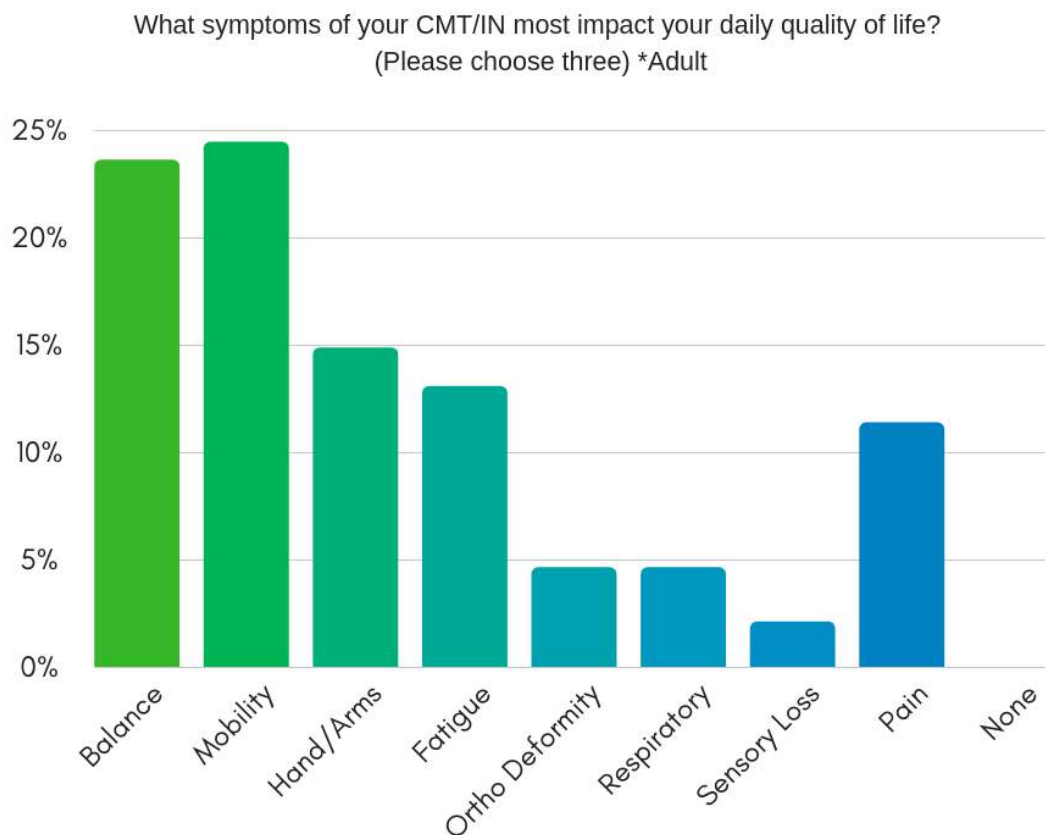


This poll reveals that progression of the following symptoms worries pediatric and young adult patients the most:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

Polling Question 1:

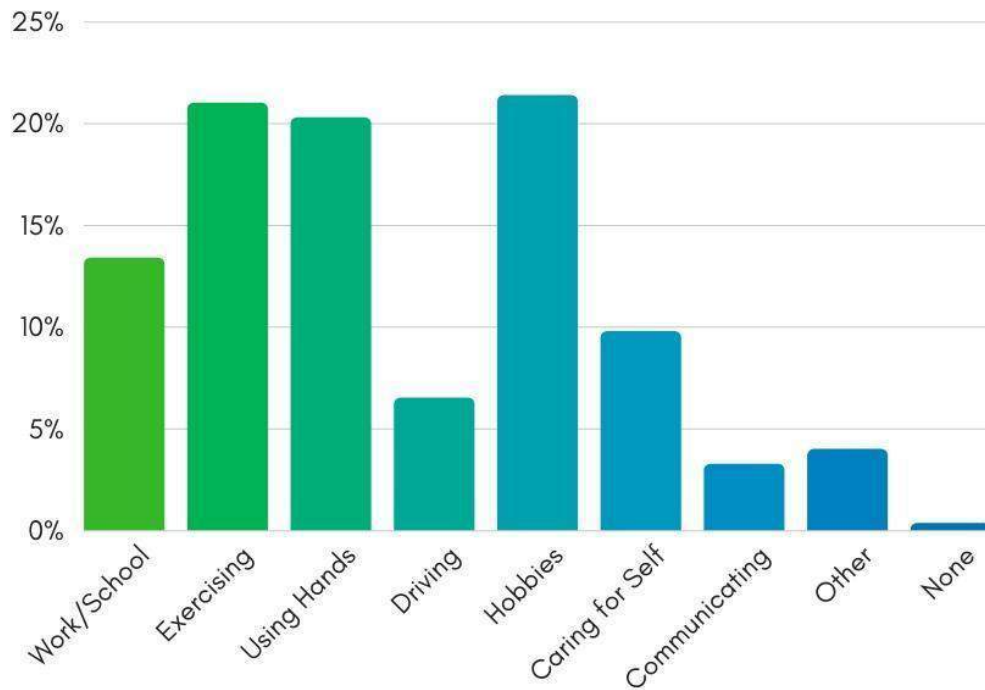


This poll reveals that the top three symptoms with the most impact on the daily quality of life of adult patients are as follows:

- 1) Mobility issues (such as foot drop, walking, tripping, frequent falls)
- 2) Balance / ability to stand (such as ankle weakness)
- 3) Coordination with hands and arms (such as difficulty grasping, gripping, holding objects or fine motor skills)

Polling Question 2:

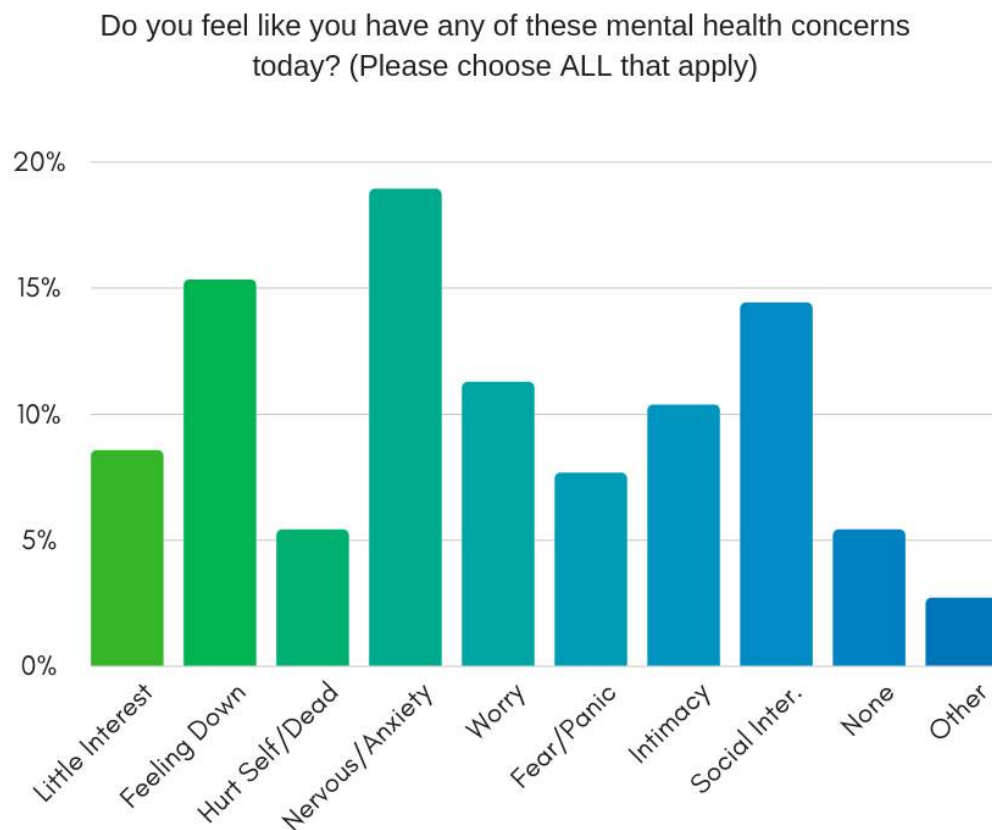
What specific aspects of daily life are most challenging because of CMT/IN?
(Please choose ALL that apply)



This poll showed that the following aspects of daily life are most challenging to adults:

- 1) Exercising
- 2) Hobbies (such as gardening, sewing, painting, sports)
- 3) Using your hands (such as handwriting, typing, cutting food and handling utensils)
- 4) Working or going to school

Polling Question 3:



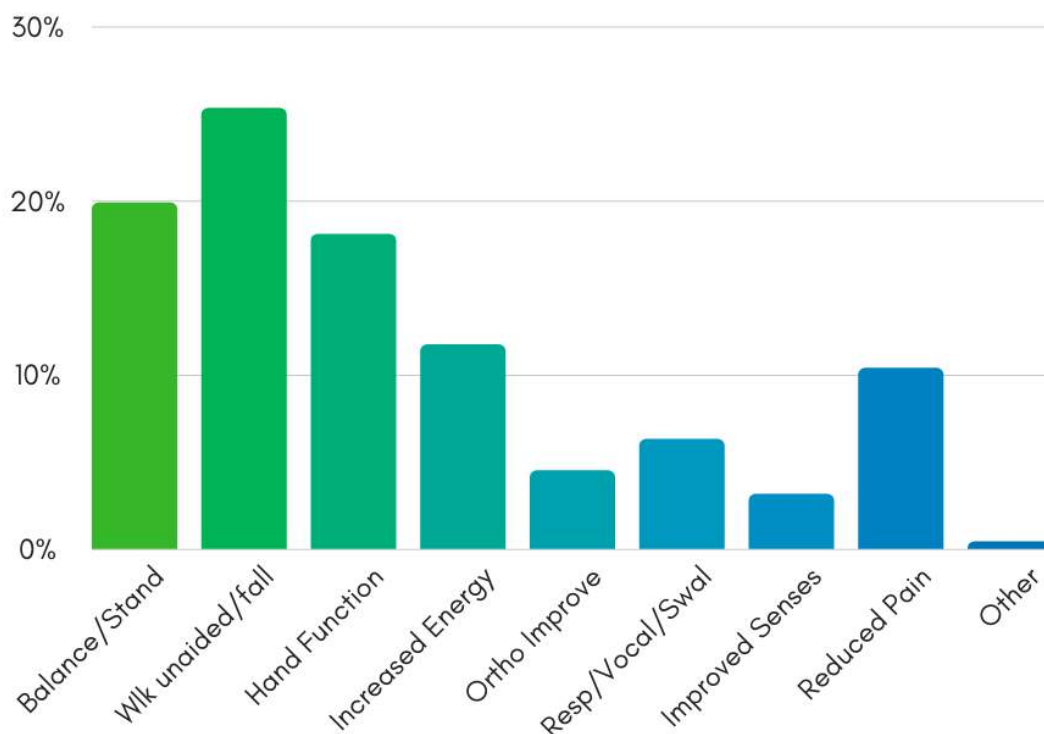
This poll reveals that the following mental health concerns are most felt by adults living with CMT/IN:

- 1) Feeling nervous and anxious, or on edge
- 2) Feeling down, depressed, or hopeless
- 3) Interacting socially, such as friends or family

POLLING RESULTS AND COMMENTARY FROM GROUP FACILITATED DISCUSSION

Polling Question 1:

When considering treatment options, which of the following benefits would you consider to be most meaningful? (Please choose up to three)

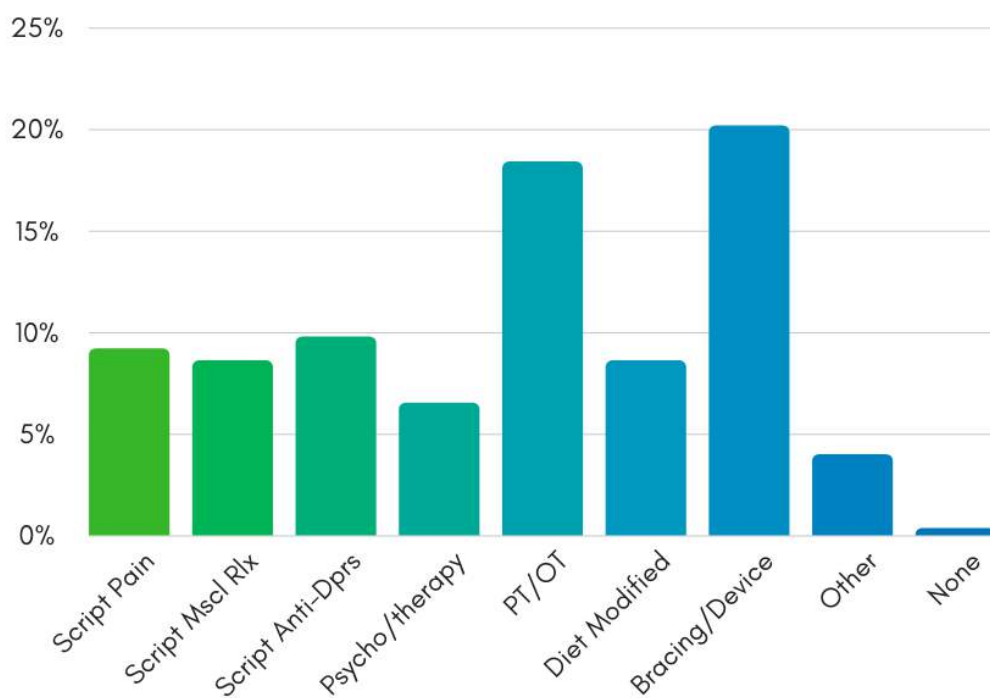


This poll reveals that the top three treatment benefits that would be most meaningful to patients are as follows:

- 1) Ability to walk unaided / reduced falls
- 2) Ability to balance / stand
- 3) Improved hand function (such as grip strength, fine motor skills)

Polling Question 2:

Have you ever used any of the following medications or therapies to help reduce symptoms of CMT/IN? (Please choose ALL that apply)

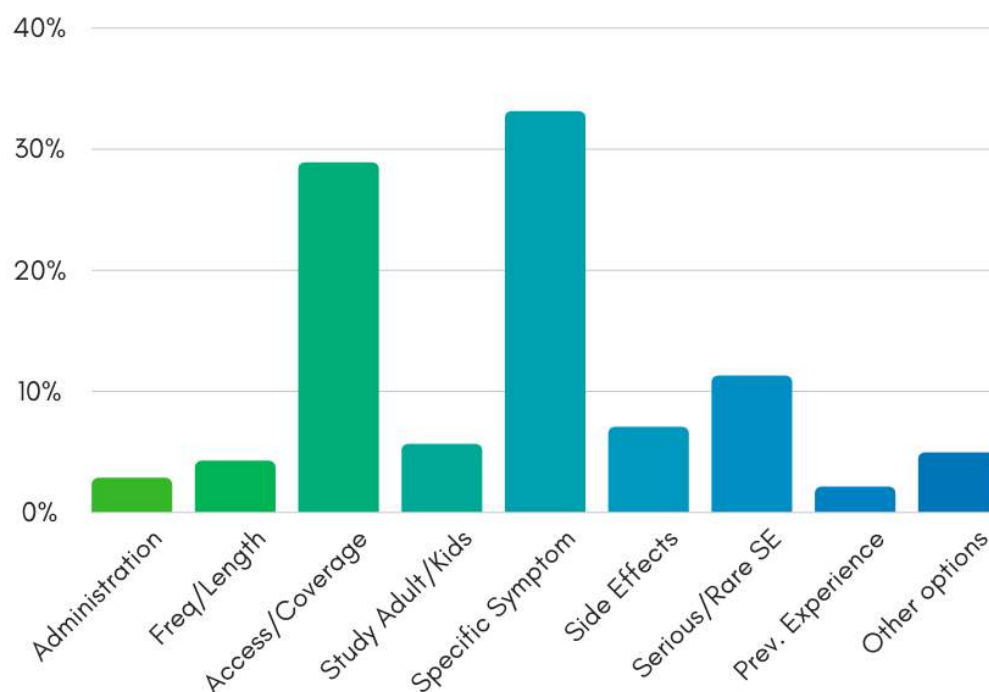


This poll showed that the most commonly used medications or therapies are as follows:

- 1) Bracing or adaptive devices (such as AFOs [ankle-foot orthosis], crutches / cane, scooter, wheelchair)
- 2) Physical therapy / occupational therapy
- 3) Complementary therapies (such as acupuncture, meditation, massage, exercise)

Polling Question 3:

Which would you rank as most important to your decision about whether to use a medication to help manage your CMT/IN symptoms?
(Please choose two)

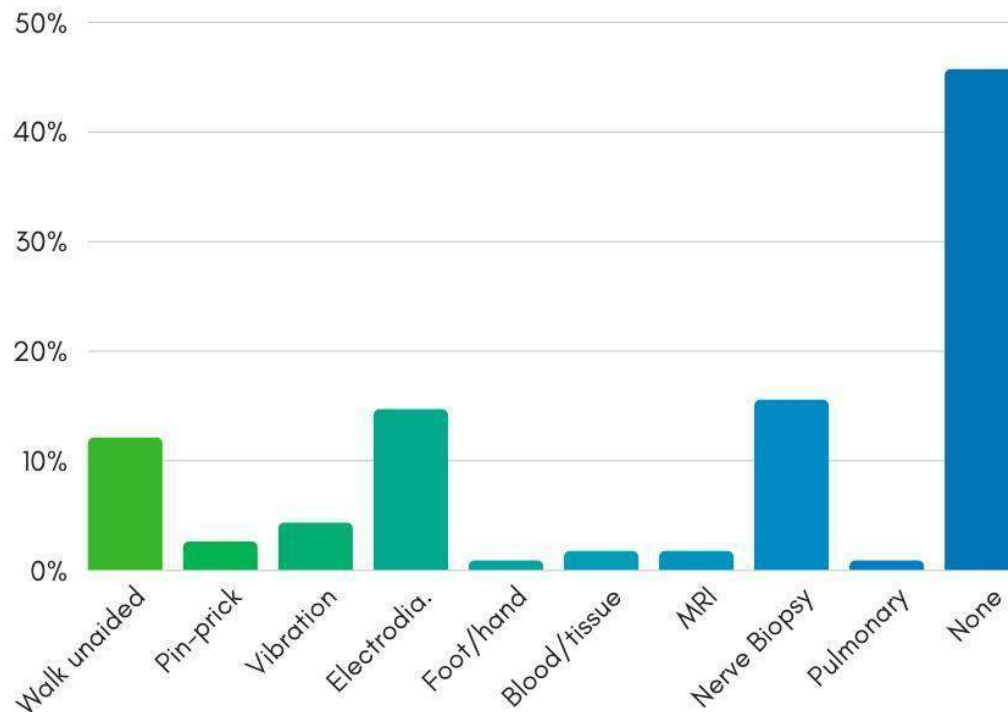


This poll reveals that the following are most important in making a decision about taking a medication:

- 1) How much the medication showed benefit for a specific symptom
- 2) Your access to treatment (such as insurance coverage)

Polling Question 4:

Which of the following measurements would discourage you from participating in a clinical trial? (Please choose ALL that apply)

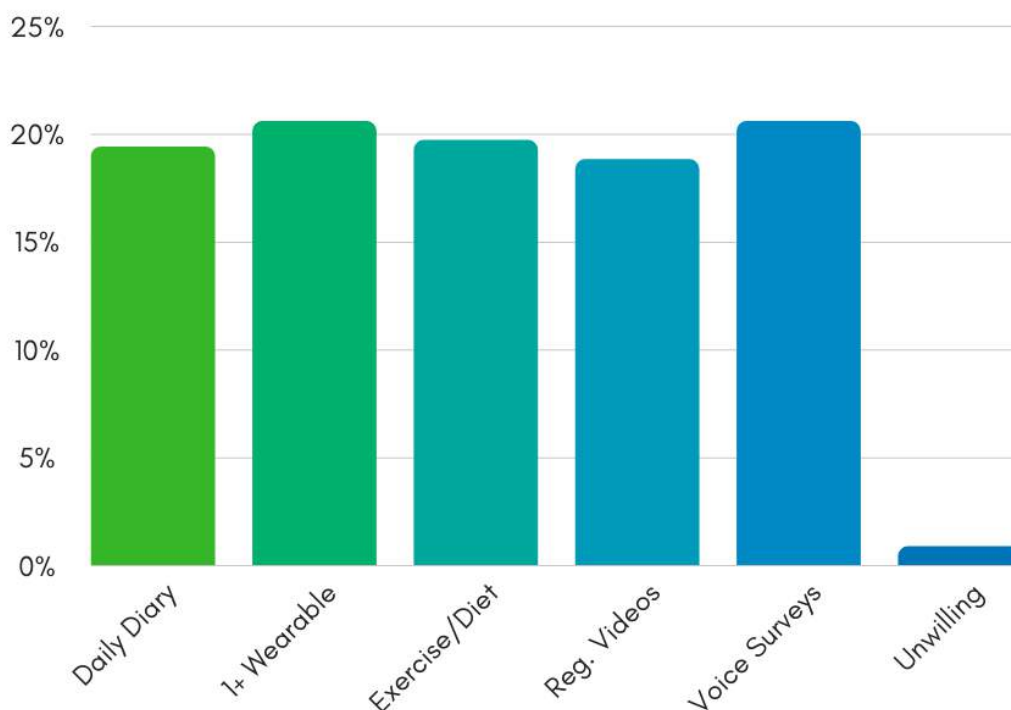


This poll reveals that the following measurements would discourage clinical trial participation:

- 1) None – for 46% of respondents, no measurements would discourage them from participating
- 2) Nerve biopsy
- 3) Electrodiagnostic testing (such as NCV, EMG)
- 4) Walking unaided for a specified distance, as quickly as possible

Polling Question 5:

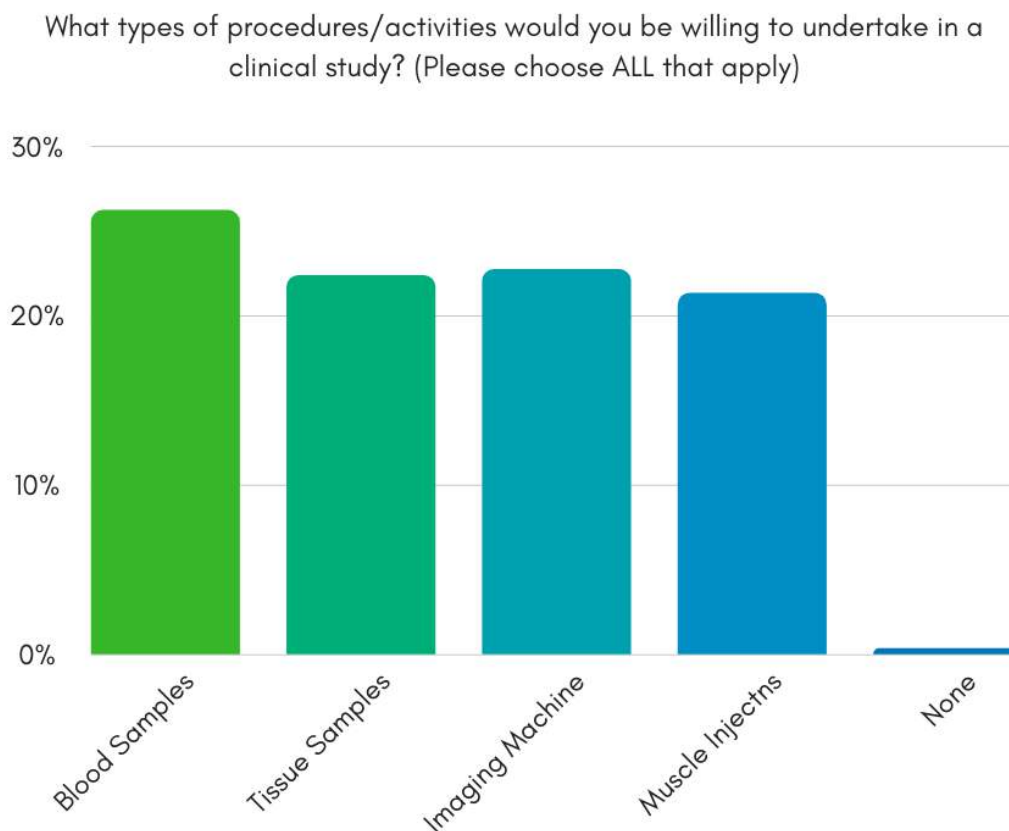
If you were to participate in a 6-month clinical study, what would you be willing to do at home as part of the study? (Please choose ALL that apply)



This poll reveals that about 80% of the respondents would be willing to do all the following things at home as part of a clinical study. Only three respondents responded that they would not be willing to do anything at home.

- 1) Wear one or more devices to monitor activity (such as ankle sensor, armband)
- 2) Answer a brief questionnaire by calling a toll-free number
- 3) Maintain a specified exercise and/or diet regimen
- 4) Fill out a daily electronic diary/questionnaire
- 5) Submit a videotape on a regular basis (such as weekly, monthly)

Polling Question 6:



This poll reveals that 80% of the respondents would be willing to undertake the following procedures/activities in a clinical study. Only one respondent responded that they would not be willing to undertake any of these procedures/activities.

- 1) Providing blood samples
- 2) Lying inside an imaging machine for long periods of time (such as MRI)
- 3) Providing tissue samples (such as skin, nerve, muscle biopsy)
- 4) Receiving injections into muscle on a periodic basis of an investigational/experimental drug therapy (such as diaphragm, peroneal, hands)
- 5) None

ACKNOWLEDGEMENTS

Many thanks to our generous sponsors including:

- Acceleron Pharma
- Athena Diagnostics
- Charcot-Marie-Tooth Association (CMTA)
- Ceres
- Cresco Labs
- Cydan
- Everylife Foundation
- Flex Pharma
- Ionis
- Muscular Dystrophy Association (MDA)
- Pharnext
- Southern Vermont Wellness / Champlain Valley Dispensary

“The Voice of the CMT Patient” video was developed using *True Reply Voice Activation Technology* Voice in partnership with Inspire.

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Muscular Dystrophy Association: Amanda Haidet-Phillips, Brittany Hernandez, Lucja Grajkowska



About Hereditary Neuropathy Foundation (HNF)

[HNF, a non-profit 501\(c\) 3 organization](#) whose mission is to increase awareness and accurate diagnosis of CMT and IN, support patients and families with critical information to improve quality of life, and fund research that will lead to treatments and cures. In 2007, HNF developed the [Therapeutic Research in Accelerated Discovery \(TRIAD\) program](#), a collaborative effort with academia, government and industry, to develop treatments for CMT. TRIAD involves many groups that span the drug discovery, drug development and diagnostics continuum.



About Charcot-Marie-Tooth Association (CMTA)

The Charcot-Marie-Tooth Association (www.cmtausa.org) is a patient-led non-profit organization dedicated to finding a cure for CMT. The CMTA's Strategy to Accelerate Research (STAR) program brings top researchers together with pharmaceutical and biotechnology partners to accelerate scientific breakthroughs and develop therapies. The CMTA also offers community services to help patients and families live their best life with CMT. These include over 70 local branches, an Advisory Board of Experts, Camp Footprint exclusively for teens with CMT, annual Patient & Family Conferences and online support communities.



About the Muscular Dystrophy Association (MDA)

MDA is committed to transforming the lives of people affected by muscular dystrophy, ALS and related neuromuscular diseases. We do this through innovations in science and innovations in care. As the largest source of funding for neuromuscular disease research outside of the federal government, MDA has committed more than \$1 billion since our inception to accelerate the discovery of therapies and cures. Research we have supported is directly linked to life-changing therapies across multiple neuromuscular diseases. MDA's MOVR is the first and only data hub that aggregates clinical, genetic and patient reported data for multiple neuromuscular diseases to improve health outcomes and accelerate drug development. MDA supports the largest network of multidisciplinary clinics providing best in class care at more than 150 of the nation's top medical institutions. Our Resource Center serves the community with one-on-one specialized support, and we offer educational conferences, events, and materials for families and healthcare providers. Each year thousands of children and young adults learn vital life skills and gain independence at summer camp and through recreational programs, at no cost to families. For more information visit mda.org.