CMTA 40 years of serving our community!
Charcot-Marie-Tooth Association
1983–2023

2022 ANNUAL REPORT

MAKING A BETTER TOMORROW TODAY

THE CMTA HAD ITS BEST FINANCIAL YEAR EVER IN 2022 WITH REVENUE TOTALING $10,493,765.

Dear Friends:

The CMTA had its best financial year ever in 2022, with revenue totaling $10,493,765 reflecting the value donors place on our commitment to research, community support and stewardship of funds.

Since the CMTA instituted its Strategy to Accelerate Research (STAR) in 2008, the field of CMT research has grown by leaps and bounds. We have invested more than $23.5 million in STAR to date—$4.8 million in 2022 alone. In 2022, we supported more than 50 projects and studies, partnering with leading academic labs, clinical centers and pharmaceutical and biotech companies to advance scientific knowledge, increase clinical trial readiness and accelerate progress towards treatments for CMT. Today, CMTA-STAR is the largest philanthropic funder of CMT research in the world.

The CMTA continued to expand its research portfolio in 2022, appointing a chief research officer to handle the explosive growth. It includes therapy approaches for virtually all types of CMT. In addition to CMTA-sponsored research projects, our “toolbox” of cellular and animal models for evaluating therapy candidates has attracted numerous partners interested in positioning a therapy for CMT.

The year saw significant and growing pipeline positioning for the commencement of new first-in-human clinical trials. Researchers advanced both genetic therapies and small molecule approaches for multiple forms of CMT. Our long-term investment in developing biomarkers drew strong interest from pharmaceutical and biotech companies.

With CMTA support, the Inherited Neuropathy Consortium’s clinical registry grew to more than 7,000 CMT patients in 2022. Volunteers contributed new functional outcome measures, MRI scans, quality of life and electrophysiological and genetic data, providing an unrivalled data source to advance our knowledge of CMT progression and support future clinical trials.

The CMTA’s Patients as Partners in Research platform grew to over 6,100 participants covering 47 CMT subtypes by year-end, ensuring and facilitating broad CMT patient representation and engagement in research.

The year also saw explosive growth in patient services. We added two Centers of Excellence, bringing the total to 50 worldwide and making specialist care accessible to an increasing number of people. We added two new branches to our network of support groups and made plans for a second Camp Footprint to launch in 2023 on the west coast. We added a new support group called COMPASS for young people aged 18-30 and sponsored nine virtual education meetings on subjects ranging from mental health to useful gadgets for living with CMT.

As the saying goes, “Individually we are all one drop, together we are an ocean.” In 2022, the patients, volunteers, staff, researchers and board of the CMTA came together as never before in a mighty ocean with the power to rid the landscape of CMT.

Sincerely,
Gilles Bouchard, CMTA Board Chair
Jon Pastor, CMTA Interim CEO

Gilles Bouchard,
Chairman of the Board

Jon Pastor,
CMTA Interim CEO

Gilles Bouchard, Chairman of the Board

Jon Pastor, CMTA Interim CEO

RESEARCH SPENDING

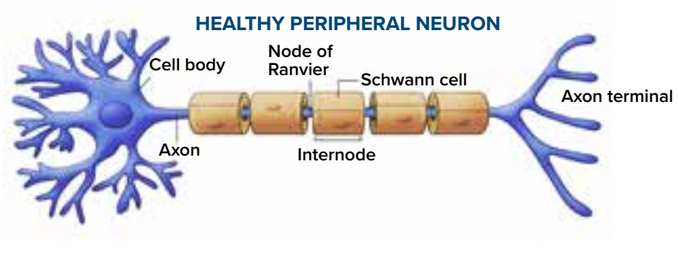
2018	2019	2020	2021	2022
$2.02 MILLION	$2.74 MILLION	$2.93 MILLION	$3.47 MILLION	$4.8 MILLION

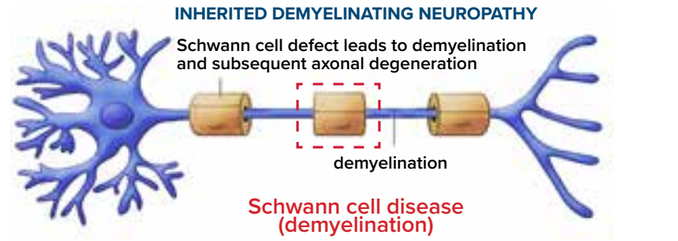
THE CAUSES OF CMT

NERVES ARE BUNDLES OF FIBERS, MOST OF THEM WRAPPED IN MYELIN. MYELIN IS AN INSULATING AND PROTECTIVE COATING, FORMED BY SCHWANN CELLS, WHICH ALSO MAKES NERVE IMPULSES TRAVEL MUCH FASTER (FROM 1 TO >50 METERS/SECOND). PROBLEMS WITH NERVE FIBERS, OR AXONS, CAUSE AXONAL CMT (CMT2).

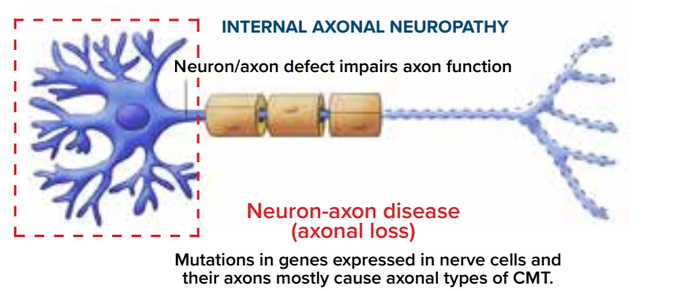
MUTATIONS IN ANY ONE OF MORE THAN 100 DIFFERENT GENES CAN CAUSE CMT NEUROPATHIES. MUTATIONS IMPACT DIVERSE CELLULAR FUNCTIONS, RESULTING IN MANY DISEASE SYMPTOMS. IN SOME CMT TYPES, THE MUTATION CREATES TOO MUCH OF A MOLECULE THAT HAS A TOXIC EFFECT ON NERVES, WHILE IN OTHER TYPES THE MUTATION RESULTS IN TOO LITTLE OF A MOLECULE, REDUCING NERVE FUNCTION. MUTATIONS IN GENES EXPRESSED BY SCHWANN CELLS MOSTLY CAUSE DEMYELINATING CMT, WHILE MUTATIONS IN GENES EXPRESSED IN NERVE CELLS AND THEIR AXONS MOSTLY CAUSE AXONAL TYPES OF CMT.

Mutations in more than 100 different genes cause CMT neuropathies.
They have diverse cellular functions, resulting in many disease mechanisms.





Mutations in genes expressed by Schwann cells mostly cause demyelinating CMT - but eventually this destroys the axons as well.



Mutations in genes expressed in nerve cells and their axons mostly cause axonal types of CMT.

In some CMT types the mutation has a toxic effect (gain of function) and in other types the mutation results in loss of function.

THE INHERITED NEUROPATHY CONSORTIUM (INC)

INC is an integrated, international group of academic medical centers, patient support organizations and clinical research resources dedicated to conducting clinical research into different forms of CMT and improving patient care. Funded primarily by NIH with supplemental funding from the CMTA and the Muscular Dystrophy Association, INC plays a key role in developing the infrastructure necessary to evaluate CMT therapies and conduct clinical trials.

The CMTA continued to fund the Inherited Neuropathy Consortium in 2022 with a new $206,000 grant for additional clinical trial preparations, including further development of critical outcome measures and biomarkers, covering four of INC's 20 sites. The grant will support training for at least six full-time trainees who are interested in pursuing CMT-related research, as well as additional postdoctoral fellows and students. INC is working with pharmaceutical and academic partners on multiple clinical trials that are underway or in the planning stages, including treatments for CMT1A, CMT1B, CMT2A, CMT1X, GAN and other rarer forms such as SORD recessive neuropathy.

Longitudinal assessments and natural history studies are critical for clinical trial readiness and delivery, and INC sites have developed world-leading protocols and training systems to make sure assessments are carried out to the highest possible standards. With previous CMTA support, INC enrolled almost 7,000 patients into its registry and developed CMT-specific clinical outcome assessments (COA) to measure disability in adults and children with CMT. INC also identified several biomarkers, including MRI imaging, skin biopsies, plasma markers and using wearable sensors to obtain sensitive gait and balance data during activities of daily living, which yielded a "digital biomarker" with enhanced responsiveness to change.

TOOLBOX DEVELOPMENT

To position CMT as an attractive disease for industry investment, the CMTA has invested considerably in the development of our preclinical toolbox. This growing collection of cell lines, best-in-class animal models and cell-based assays is made available to academic and industry researchers to test their novel treatments. Our investment makes CMT research more accessible and reduces barriers to developing CMT treatments. Combined with the CMTA's unique turn-key preclinical testing support infrastructure, we provide guidance to Alliance partners to ensure their experiments are conducted in the right models, in the right way, to determine as quickly as possible if their therapy shows promise.

STAR ADVISORY BOARD

The CMTA's STAR Advisory Board is overseen by Katherine Forsey, PhD, the CMTA's chief research officer, and comprises a Scientific Advisory Board (SAB), a Therapy Expert Board (TEB) and a Clinical Expert Board (CEB). Each plays a critical role in furthering the CMTA's mission to support the development of new therapies to treat CMT, to improve the quality of life for people with CMT, and, ultimately, to find a cure. The SAB provides scientific input for ongoing or proposed projects, the TEB evaluates the translational quality of ongoing and proposed projects and the CEB provides expert guidance and support to the CMTA's Alliance Partners around clinical trial planning and delivery. The CMTA expanded its Advisory Board by three members in 2022 (denoted by an asterisk on the list below) to reflect the evolving needs of STAR.

John Svaren, PhD, SAB Chair
University of Wisconsin

Mark Scheideler, PhD, TEB Chair
HumanFirst Therapeutics LLC

Mike Shy, MD, CEB Chair
University of Iowa

Mary Reilly, MD, CEB Co-Chair
National Hospital for Neurology, London, UK

Frank Baas, MD, PhD, SAB
University of Amsterdam, The Netherlands

Diana Bharucha-Goebal, MD, PhD, CEB Children's National Hospital Washington DC and the National Institutes of Health (NIH)*

Robert Burgess, PhD, SAB
The Jackson Laboratory, Bar Harbor, Maine

Joshua Burns, PhD, CEB
University of Sydney, Australia

Bruce Conklin, MD
University of California San Francisco*

Maurizio D'Antonio, PhD, SAB
San Raffaele Scientific Institute, DIBIT, Milan

Laura Feltri, MD, SAB
University at Buffalo

Richard Finkel, MD, CEB
St. Jude Children's Research Hospital, Memphis, Tennessee

Vera Fridman, MD, CEB
University of Colorado Anschutz Medical Campus and Hospital*

Steven Gray, PhD, SAB
University of Texas Southwestern Medical Center

Scott Harper, PhD, SAB
The Ohio State University School of Medicine

David Herrmann, MD, CEB, TEB
University of Rochester

Tage Honore, PhD, TEB
Aestus Therapeutics Inc.

Christopher Klein, MD, CEB, TEB
Mayo Clinic, Rochester, Minnesota

Kleopas Kleopa, MD, SAB
Cyprus Institute of Neurology & Genetics

Lars J. Knutsen, PhD, TEB
Discovery Pharma Consulting LLC, Cambridge, UK

Jun Li, MD, PhD, SAB
Houston Methodist Hospital and Weill Cornell Medical College

Rudolf Martini, PhD, SAB
University of Würzburg, Germany

Michael McDermott, PhD, CEB Consultant
University of Rochester Medical Center, New York

Klaus-Armin Nave, PhD, SAB
Max Planck Institute of Experimental Medicine, Germany

Davide Pareyson, MD, CEB
Besta Institute, Milan, Italy

Brian Popko, MD, SAB
University of Chicago

Mario Saporta, MD, PhD, SAB
University of Miami

Steven Scherer, MD, PhD, CEB, SAB
University of Pennsylvania

Claes Wahlestedt, MD, PhD, TEB
University of Miami

Lawrence Wrabetz, MD, SAB
University at Buffalo

Stephan Zuchner, MD, PhD, SAB
University of Miami

MAJOR INITIATIVES

GENE THERAPY

Gene therapy involves the introduction of genetic material (DNA or RNA) into the cells and tissues of an individual, reducing the need for drugs or surgery. It includes replacing a faulty (missing or mutated) gene that causes a disease with a healthy copy of the gene; deactivating or "silencing" a mutated gene that is functioning improperly; increasing the output of a normal gene to compensate for the silence of a defective gene; or editing part of a mutated toxic gene using a "cut and paste" method.

In gene therapy, an inactive virus package or other non-viral "vector" delivers the therapeutic payload to the target cell in hopes of changing how the genes work to restore proper functioning. Different gene therapies have to be developed to address the unique disease mechanism for each type of CMT. For CMT types caused by loss of function (mostly CMT 4 and X), genetic therapy focuses on gene replacement. For CMT types with a toxic gain of function (mostly CMT 1 and 2), therapy may either silence (or partially reduce) the toxic overproduction of the target gene or try to repair (edit) the mutation. The CMTA supports gene therapy development for many types of CMT, including CMT1A, CMT1X, CMT2A, CMT2D, CMT2E, CMT2F, CMT2S, CMT4A and CMT4C, utilizing a spectrum of different technologies, including AAV delivery, gene silencing, gene replacement, genome editing using CRISPR-Cas9 and antisense oligonucleotides (ASOs). Success with any of these CMT types will bring advances for all CMT types as delivery approaches and lessons can be broadly applied.

One of the biggest challenges in gene therapy is delivering therapeutic payloads to specialist cells in the furthest reaches of the peripheral nervous system. The CMTA is supporting efforts to develop innovative solutions to this challenge.

BIOMARKERS AND CLINICAL TRIAL READINESS

Because clinical trials are expensive and time-consuming, CMT pharmaceutical partners want to design clinical trials that will quickly determine a new therapy's efficacy. Industry is interested in diseases where the clinical trials are short and in diseases that have multiple accurate and objective ways to measure the therapy's effectiveness. Consequently, one of the most urgent needs in the CMT field is to find faster, more accurate and more objective ways to assess improvements in dysfunction of the peripheral nerves in patients with CMT.

The CMTA was an early supporter of INC's development of neuropathy assessments with validated scoring for adults, which was followed by similar pediatric and infant neuropathy assessments. But since CMT is a slowly progressive disease, neuropathy scores by themselves are not sensitive enough to detect short-term changes, and therefore not adequate to serve alone as a clinical trial measure of improvement. To address this, the CMTA sponsored a number of biomarker efforts extending across various CMT types.

In 2022, a novel muscle MRI method developed by the team at Queen's Square National Hospital for Neurology, London, an INC site and a CMTA Center of Excellence, was approved as the primary outcome measure in a CMTA-funded clinical trial. The CMTA funded the trial with a three-year grant to INC. This non-invasive technique is capable of detecting changes in CMT progression within a 12-month period and is a hugely valuable tool as we look ahead to the commencement of additional clinical trials.

GENE DISCOVERY

Fewer than 50 percent of CMT Type 2 patients know which gene causes their disease. If the gene isn't known, gene therapy development or application are not possible, and the patient will likely be forced into an ongoing "diagnostic odyssey." This is why the CMTA is actively pursuing advancements in gene discovery, including supporting the most important genomic initiative led by INC, the GENESIS project. In 2020, the GENESIS project discovered the most common recessive CMT2 gene–SORD neuropathy; by 2022 a new treatment advanced to Phase II clinical trials for CMT-SORD.

AXON DEGENERATION

Several genes are involved in axon degeneration. SARM1 is the most notable. The SARM1 gene codes for a protein that functions as an enzyme, affecting the levels of NAD+, a metabolite necessary for certain chemical processes in the body. All nerve cells have axons whose proper functioning is essential in signaling muscles to contract. Axons are vulnerable to degeneration due to several destructive injury-induced triggers.

In some types of neuropathy, a CMT-induced injury to the nerves causes inflammation, activating SARM1, which reduces the levels of axonal NAD+ and causes axonal degeneration. Inhibiting the activation of SARM1 has the potential to prevent this cascade of events. Several companies are working to develop compounds that inhibit SARM1, which may prove to be a successful therapeutic for blocking injury-induced axonal degeneration pathways. The CMTA is supporting studies to identify which types of CMT will be most responsive to SARM1 targeted treatments.

HDAC6 INHIBITORS

While the many genes associated with CMT make it unlikely that a single treatment will work for all forms of the disease, preclinical studies with HDAC6 inhibitors, which have been shown to reduce motor and sensory deficits, have demonstrated promising results in several mouse models of different types of CMT. Based on these results, scientists believe that HDAC6 inhibitors might be beneficial in treating a wide array of neurodegenerative conditions including demyelinating and axonal CMTs.

CMTA-STAR
ALLIANCE POWER

STAR
Strategy To Accelerate Research

The CMTA works with a consortium (the STAR Alliance) of pharmaceutical, biotechnology and contract research service industries, along with nonprofit research organizations, university research laboratories and the National Institutes of Health (NIH). In the last six years, the number of Alliance partners has skyrocketed from five to more than 40. The CMTA also works with STAR Advisory Board members and specialist consultants to support and advise companies that want their candidate treatments tested in CMT models.

Utilizing decades of experience in model development and study design, the CMTA provides counsel on ways to test potential treatments on appropriate models and provides support with interpreting results. Through this network, the CMTA offers access to safety and toxicology services and advice to help Alliance partners navigate complex regulatory and approval pathways, supporting those bringing forward treatments to take the steps required for clinical trials and eventual rollout to the patient community.

CMTA-STAR'S RESEARCH PORTFOLIO BY TYPE

As the largest philanthropic funder of CMT research in the world, the CMTA invested $4.8 million in 2022, broken down as follows.

CMTA-STAR'S PORTFOLIO FOR CMT1A

CMT1A is the single most common form of CMT, affecting some 70 percent of all Type 1 cases and 57 percent of all CMT cases. It involves the duplication of the PMP22 gene on chromosome 17, which leads to the destruction of the myelin, or protective coating, around the peripheral nerves. As the nerves die, the muscles around them follow suit. Of the four CMT types currently in preclinical testing, CMT1A has attracted the highest interest due to its prominence in the CMT patient population.

The CMTA's current research portfolio for Type 1A includes projects attacking the disease from every angle in an aggressive, multi-pronged effort involving small molecule, biological and gene therapy research by academic experts, pharmaceutical industry partners and investigators worldwide. Ultimately, we will need a combination of complementary therapies to help all CMT patients and it is with this in mind that we continue to expand our portfolio approach.

During 2022, the CMTA sponsored 12 research initiatives covering CMT1A at a cost of $1,246,206. Six were completed and three new projects were initiated. Six of the initiatives were cross-type (see p. 18). In addition, the CMTA provided support to 18 CMTA-STAR Alliance partners, who invested $1,834,120 in preclinical studies in 2022.

WEARABLE SENSORS AS FUNCTIONAL BIOMARKERS (COMPLETE)

With $64,788 in CMTA support, researchers at the University of Rochester used wearable sensors to measure how well CMT1A patients walked and balanced at home, both day and night. These new tools will help them see if new treatments are working. Researchers monitored 15 individuals with CMT1A and 15 healthy individuals and found that those with CMT1A have more trouble with balance and with walking than healthy individuals. This means wearable sensors may now be incorporated into natural history studies and monitoring patients during clinical trials.

TARGETING SREBP REGULATION TO LOWER PMP22 EXPRESSION IN CMT1A (COMPLETE)

Researchers in the ***Svaren Lab*** at the University of Wisconsin have shown that "turning down" the overactive PMP22 gene in CMT1A can help improve symptoms. With $60,000 in CMTA support, phase one of this project tested a purified form of an FDA-approved treatment for elevated triglycerides on mice with CMT1A to see if this turned down the overactive PMP22 gene. Researchers found that it reduced the activity of the SREBP pathway, which then turned down the PMP22 gene. In addition, they performed pilot tests with a different version of the same treatment thought to be better at penetrating the peripheral nerve.

ALTERNATIVE HUMAN STEM CELL-BASED STRATEGY FOR CMT1A (ACTIVE)

In an innovative two-year project, the FIERCE lab at Hasselt University in Belgium is using stem cells extracted from donated human dental pulp to generate human Schwann cells that have an extra copy of the PMP22 gene. Screening and testing potential new treatments using Schwann cells in a dish is much quicker and cheaper than testing in animal models of the disease, which will help to accelerate research. The CMTA supported this project with a grant of $98,890.

ALLIANCE PARTNER ACTIVITY FOR TYPE 1

Confidential Partner A: A leading global pharmaceutical company that identified CMT as a strategic focus contacted the CMTA about a possible collaboration. After reviewing previous test results, this company, which owns small molecules previously tested by another partner, asked us to continue the evaluation as a new testing Alliance partner. Studies conducted in the past year in the CMT1A mouse and rat models have not shown a conclusive benefit.

ToolGen: The CMTA testing resource is "therapy agnostic" and can be used to evaluate genetic therapies, biologicals and small molecule approaches to treatment. Our first alliance partner in the new area of gene editing has been working with us to determine if their approach can correct the CMT1A defect and restore normal function in rat and mouse models of CMT1A. Work on this exciting new approach is ongoing, and aimed at providing a therapy option that can be shown to have benefits to patients in clinical studies to follow.

Cell therapy company ***Cellatoz*** is applying stem cell-derived neuronal regeneration-promoting cells (NRPCs) to the treatment of CMT1A. When injected into the muscle of an animal model of CMT, its lead therapy—CLZ-2002—remyelinated sciatic nerves and accelerated regeneration of the nerve and skeletal muscle. The FDA granted CLZ-2002 orphan-drug designation in 2022. The CMTA is providing key knowledge leader feedback and senior-level guidance.

Orthogonal has been developing a novel biological approach to treat CMT and asked for our help in evaluating its candidate in both Type 1 (CMT1A) and Type 2 (CMT2E) animal models. These studies showed some promising results in both models, and together we completed studies to provide additional evidence of a positive effect on the myelination and survival of peripheral nerves in the CMT1A mouse model.

Addex Therapeutics is a Swiss-based biopharmaceutical company that owns small molecules that are GABA-B receptor selective. This is the same target as used in the Pharnext studies described below and represents a second-generation molecule that may be more potent, with fewer side effects.

AAVogen is a gene therapy company with an advanced therapy approach to treat musculoskeletal disorders. We worked with them in 2022 to position this approach for CMT1A, seeking to slow loss of muscle and strength as the disease progresses. However, market conditions did not allow AAVogen to pursue this second disease indication at this time.

The CMTA is working with ***Pharnext*** in a patient advocacy capacity, supporting recruitment to its current ongoing PREMIER trial, a pivotal Phase III clinical trial of PXT-3003 to treat CMT1A.

Confidential Partner B is a publicly listed company that has already placed a therapy to treat neurodegeneration on the market. It will next pursue anti-sense treatment of CMT1A, using ASOs to target messenger RNA. This company approached the CMTA for help in preclinical testing, and we are underway with a series of studies to evaluate this therapy.

Confidential Partner C developed a delivery system for antisense oligonucleotides (ASOs) and silencing RNAs that seeks to overcome the challenges in getting genetic-based therapies to the right part of the peripheral nervous system. A series of studies was initiated via an Alliance partnership with the CMTA, making use of our preclinical testing infrastructure. However, following the acquisition and completion of a merger with a large pharmaceutical company, this alliance was discontinued.

Shift Pharmaceuticals is a privately held, early-stage company developing antisense oligonucleotides (ASOs) to treat a variety of genetic disorders. The CMTA is collaborating on a project using ASOs to treat CMT1A, providing extensive preclinical planning that Shift will use to expand its NIH funding.

CMTA-STAR'S PORTFOLIO FOR CMT1B

During 2022, eight active sponsored research projects covered CMT1B; six are ongoing and two were completed during the year. One new project covering 1B started in 2022. Seven of the projects were cross-type projects (see p. 18). The total value of CMTA-sponsored CMT1B projects active during 2022 was $1,540,690.

1B BIOMARKERS AND OUTCOME MEASURES (ACTIVE)

With CMTA support of $529,971 over three years, researchers at multiple global INC sites led by the University of Iowa are working to track disease progression and identify biomarkers of disease severity in CMT1B. They have enrolled 65 patients with CMT1B and will examine them annually over three years using physical assessments and collecting blood, skin biopsy and MRI imaging to develop biomarkers. This critically important, first-of-its-kind work in CMT1B will be used to determine overall disease severity and whether new treatments are successful.

CMTA-STAR'S PORTFOLIO FOR CMT1X

Caused by mutations in the GJB1 gene, CMT1X is the second most common type of CMT, causing around 10 percent of all cases. More than 400 different mutations in GJB1 can cause CMT1X. The GJB1 gene encodes connexin 32 (Cx32), a gap junction protein expressed in peripheral nerve Schwann cells. The gene is X-linked (found on the X-chromosome), and the mutations cause a loss of function. Although both men and women are affected, manifestations tend to be later onset and less severe in women, some of whom may remain asymptomatic.

The total value of CMTA-sponsored CMT1X projects active during 2022 was $1,399,127, distributed across 11 projects. Six are ongoing, three were initiated in 2022 and five were completed. Seven projects covered multiple CMT types, including 1X (see p. 18).

Confidential Partner J: Following positive results from a previous CMTA-MDA co-funded project in the Kleopa lab, this top-tier pharma partner has taken an option to license the CMT1X gene therapy and is currently testing this promising therapeutic further. This exciting advance demonstrates how STAR investment catalyzes outside interest in CMT treatment development.

TWO NEW MOUSE MODELS OF CMT1X - EXPANDING THE RESEARCH TOOLBOX

Existing animal models of CMT1X do not fully represent the disease mechanisms caused by the broad range pf mutated Cx32 proteins. Without well-characterized animal models, research is hampered. To more fully represent the spectrum of human CMT1X-associated mutations, the CMTA awarded the University of Illinois at Chicago and the University of Pennsylvania $169,741 to develop two new CMT1X mouse models. Both developed representative symptoms of CMT and will be used to improve our understanding of CMT1X and in studies of potential new treatments. Full details of the new models were published in the Experimental Neurology journal in November 2022.

METABOLIC THERAPY FOR CMT1X (ACTIVE)

In people with CMT1X, cell-to-cell communication within the peripheral nervous system is affected, leading to a breakdown in nerve signals and progressive muscular atrophy (wasting or loss of muscle tissue), weakness and loss of sensation in the limbs. With CMTA funding of $95,302, researchers from The Jackson Laboratory and the University of Wisconsin used a mouse model of CMT1X that had previously shown a clear neuropathy. The team found the speed of signals along nerves—as well as the connection of these nerves with muscles—was reduced in the CMT1X mice compared to the wild types. At a molecular level, they observed increased neurodegeneration in CMT1X mice compared with the wild type. The team treated CMT1X mice with a drug called triacetin, which is commonly used as a food additive and found naturally in foods such as papaya but observed no effect.

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
1A	Pharnext	Small Molecule	P3
	Orthogonal Neuroscience	Biological	Preclinical
	Shift Pharmaceuticals	Gene Therapy	Preclinical
	STAR Alliance Partner A	Small Molecule	Preclinical
	STAR Alliance Partner B	Gene Therapy	Preclinical
	Armatus	Gene Therapy	Preclinical
	Toolgen	Gene Therapy	Preclinical
	Cyprus Institute	Gene Therapy	Preclinical
	Jackson Laboratory	HDAC6/Target Validation	Preclinical
	Jackson Laboratory	SARM1/Target Validation	Preclinical
	Research Foundation for the State Unv. of NY (SUNY)	Small Molecule	Preclinical
	University of Texas Southwestern	Gene Therapy	Preclinical
	University of Wisconsin	Small Molecule	Preclinical
	University of Wisconsin	Target Validation	Preclinical
	University of Wisconsin	Gene Therapy	Preclinical
	Addex Therapeutics	Small Molecule	Preclinical*
	University of Rochester, NY	Biomarkers (wearables)	Preclinical*
	STAR Alliance Partner C	Gene Therapy	Preclinical*
	Hasselt University, Belgium	New Cell Model	Laboratory
	New York Stem Cell Foundation	Stem Cell Lines	Laboratory
1B	Jackson Laboratory	HDAC6/Target Validation	Preclinical
	Ospedale San Raffaele (OSR)	Small Molecule	Preclinical
	Research Foundation for the State Unv. of NY (SUNY)	Small Molecule	Preclinical
	University of Iowa and INC sites	Biomarkers/Natural History Study	Preclinical
	University of Wisconsin	Target Validation	Preclinical
	New York Stem Cell Foundation	Stem Cell Lines	Laboratory
1X	Cyprus Institute	Gene Therapy	Preclinical
	Jackson Laboratory	HDAC6/Target Validation	Preclinical
	Jackson Laboratory	SARM1/Target Validation	Preclinical
	Jackson Laboratory	Metabolic Therapy	Preclinical
	University of Iowa and INC sites	Biomarkers/Natural History Study	Preclinical
	University of Texas Southwestern	Gene Therapy	Preclinical
	University of Wisconsin	Gene Therapy	Preclinical
	University of Illinois (Chicago)	Animal Model	Laboratory*
	New York Stem Cell Foundation	Stem Cell Lines	Laboratory
ALL TYPES	ARQ Genetics	Gene Expression	Preclinical
	Charles River	Animal Breeding	Preclinical
	Cleveland Clinic	Histology	Preclinical
	Frontage Laboratories	Chemical Analysis	Preclinical
	HumanFirst Therapeutics (HFT)	Consultancy	Preclinical
	Jackson Laboratory	Animal Models	Preclinical
	PsychoGenics	Preclinical Testing Partner	Preclinical
	University of Iowa and INC sites (2019-2022)	Research & Clinical Tools	Preclinical
	University of Iowa and INC sites (2022-2025)	Research & Clinical Tools	Preclinical
	WuXi	Chemical Analysis	Preclinical
	New York Stem Cell Foundation	Stem Cell Lines	Laboratory

*Indicates project completed

With CMTA support totaling $529,971, an international team of research clinicians from five Inherited Neuropathy Consortium sites across the United States, the United Kingdom and Italy are conducting the first large-scale longitudinal natural history study of CMT1X.

1X BIOMARKERS AND OUTCOME MEASURES (ACTIVE)

With CMTA support totaling $529,971, an international team of research clinicians from five Inherited Neuropathy Consortium sites across the United States, the United Kingdom and Italy are conducting the first large-scale longitudinal natural history study of CMT1X to develop outcome measures and biomarkers of disease severity that can be used to measure how well potential therapies are working. They have enrolled most of the planned 60 patients with CMT1X and will examine them annually over the course of three years to collect blood, skin biopsy, and MRI imaging biomarkers to track disease progression and determine overall disease severity. In conjunction with the CMT-FOM (Functional Outcomes Measure), CMT-HI (Health Index), and CMT-ES (Examination Score) assessments, researchers believe combined natural history and biomarker data could be used to determine if a potential treatment is working.

CMT1X FAMILY COHORT

The CMTA supported the donation of stem cells by a family cohort of CMT1X patients to the New York Stem Cell Foundation for use in CMT research. A family cohort is useful because it allows for the identification of genetic similarities among family members. By collecting stem cells from multiple family members, researchers can compare and study these cells to gain insights into the underlying mechanisms of the disease, helping us learn more about CMT1X. This $45,000 investment benefits all people with CMT1X and can aid in the development of targeted treatments and therapies.

CMTA-STAR'S PORTFOLIO FOR TYPE 2

CMT2, the axonal form of CMT, accounts for about 22 percent of CMT cases. CMT2A (MFN2 mutation) is the most commonly known subtype, accounting for an estimated 11 to 23 percent of all CMT2 cases. Some of the genetic causes of CMT Type 2 have not yet been identified. The CMTA's Patients as Partners in Research data shows that over 40 percent of people with Type 2 do not know their genetic cause (specific subtype); other sources put this figure at over 60 percent. The CMTA is supporting gene discovery efforts to help identify these missing genetic causes.

Research advances have identified several common strategies that can be used to bring CMT2 therapies to clinical trials. The CMTA's research strategy for CMT2 is an aggressive, multipronged effort involving gene discovery, genetic therapies, small molecule and biological research by academic experts, pharmaceutical industry partners and investigators worldwide that can benefit all types of axonal CMT. This is paired with clinical trial readiness efforts to expand natural history data, and biomarker identification to track disease progression, increasing our ability to quickly measure the impact of new treatments.

TYPE 2A PROJECTS

The CMTA spent $2,261,960 on eight sponsored CMT2A projects in 2022. Of these, six are ongoing, two were initiated in 2022 and two were completed. Six projects covered multiple types (see p. 18). In addition, six STAR Alliance Partners invested $1,714,121 in 2A studies through the CMTA's preclinical testing program.

CMT2A BIOMARKERS (ACTIVE)

With CMTA support of $572,055, INC researchers in an international collaboration led by the University of Iowa are working to monitor and track disease progression and identify biomarkers of disease severity in CMT2A. Working at multiple sites in the United States and the United Kingdom, researchers are actively enrolling study participants who have CMT2A so that they can develop blood, skin biopsy, and MRI imaging biomarkers to be used for determining overall disease severity. In conjunction with the CMT-FOM (Functional Outcome Measures), CMT-HI (Health Index), and CMT-ES (Examination Score) assessments, the combined natural history study and biomarkers data could be used to show if a potential treatment is working during a clinical trial.

VARIANTS OF UNKNOWN SIGNIFICANCE PROJECT (ACTIVE)

CMT is caused by mutations in more than 100 genes, and the number keeps growing. Today, more than 60 percent of patients with CMT2 are unable to obtain genetic confirmation of their diagnosis. Researchers at the University of Miami are working to close this gap. With CMTA support of $391,902, they are building a database that holds sequenced DNA data from CMT patients. Now at 2,500 datasets from patients in 30 countries, researchers have used the database to make several new gene discoveries for CMT, including the SORD gene in 2020, which is now in a Phase III drug trial. The eventual goal is to have 10,000 DNA datasets from CMT patients worldwide that researchers can analyze to identify the unknown causes for not only CMT2 forms, but for all forms of CMT where the genetic cause is not yet known.

ALLIANCE PARTNER ACTIVITY FOR TYPE 2

Confidential Partner D is the U.S. subsidiary of an international pharmaceutical company strategically focused on solving diseases that represent mitochondrial disorders. The CMTA is collaborating with this Alliance partner on two fronts: testing its candidate small molecule therapy in the CMT2A rat model via our preclinical testing network and testing its candidate therapy in a cell-based model of "CMT2A in a dish." This work started in 2022 but was terminated following the company's merger with a large international pharma company.

Confidential Partner E was formed to develop small molecules that can stimulate the activity of mitofusin proteins: CMT2A is caused by mutation of the Mitofusin 2 gene. **The CMTA is supporting development of this most promising therapy for CMT2A** by testing the efficacy of the small molecules in our rat models of the disease. Preclinical testing commenced in 2022.

CMTA Alliance Partner Orthogonal, which is developing a novel biological approach to treat CMT, partnered with the CMTA to evaluate its advanced drug candidate in both Type 1 (CMT1A) and Type 2 models. These studies have concluded and provided data showing several effects on performance in a mouse model of CMT2E, and both performance and marker effects in a mouse model of CMT1A. The study advanced to detailed investigation of the site of action of the drug in the experimental models. While these results confirmed that the drugs act at the junction of the nerve and the muscle, additional further work aimed at looking for improvement to the nerve itself did not show improvement.

Confidential Partner F is a publicly traded company built around a highly novel system to screen drugs with a known mechanism of targeting to affect a disease "signature." Its focus is on using highly representative human and animal disease models. Partner F has licensed a human CMT2A stem cell line from the CMTA for use in these studies, in which stem cells are turned into motor neurons in a dish. It identified several potential targets and agents that can regulate the activity of these targets and tested them in the cell lines to determine effects. After successful initial reports, they advanced to preclinical testing with the CMTA. While the results indicated the drug treatments had some effect, they were not sufficiently compelling to warrant further investigation.

Confidential Partner G is seeking to develop a novel gene-editing approach to CMT2A. It advanced detailed study planning with us aimed at preclinical testing of its approach in the CMT2A rat model. The work in a large study cohort of CMT2A rats was expected to start in our testing alliance network in 2022, but the company was unable to engineer an approach that would work in a rat model.

Confidential Partner H, an international pharmaceutical company that developed the drug candidate previously tested with us by another partner has entered a direct Alliance partnership with the CMTA. The alliance represents a strong commitment to focus on further testing of similar candidate therapies in animal models representing two different forms of CMT, including CMT2A. While the studies did not show further improvement than earlier shown in the CMT2A rat study, discussions about collaborating on additional CMT projects are underway.

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
			Discovery / Research Tools / Preclinical / Phase 1 / Phase 2 / Phase 3
2A	Envigo	Animal Model	Preclinical
2A	Gladstone Institutes (University of California, San Francisco)	Gene Therapy (CRISPR)	Preclinical
2A	Jackson Laboratory	HDAC6/Target Validation	Preclinical
2A	STAR Alliance Partner E	Small Molecule	Preclinical
2A	Orthogonal Neuroscience	Biological	Preclinical
2A	STAR Alliance Partner F	Stem Cell Licensing	Preclinical
2A	STAR Alliance Partner I	Stem Cell Licensing	Preclinical
2A	STAR Alliance Partner J	Animal Model Licensing	Preclinical
2A	STAR Alliance Partner H	Small Molecule	Preclinical
2A	University of Iowa and INC sites	Biomarkers/Natural History Study	Preclinical
2A	STAR Alliance Partner D	Small Molecule	Preclinical*
2A	STAR Alliance Partner G	Gene Therapy	Preclinical*
2A	New York Stem Cell Foundation	Stem Cell Lines	Laboratory
2D	Jackson Laboratory	SARM1/Target Validation	Preclinical
2D	Jackson Laboratory	HDAC6/Target Validation	Preclinical
2E	Gladstone Institutes (University of California, San Francisco)	Gene Therapy (CRISPR)	Preclinical
2E	Jackson Laboratory	SARM1/Target Validation	Preclinical
2E	Jackson Laboratory	HDAC6/Target Validation	Preclinical
2E	The Ohio State University	Gene Therapy	Preclinical
2E	Orthogonal Neuroscience	Biological	Preclinical
2E	New York Stem Cell Foundation	Stem Cell Lines	Laboratory
2E	University of Miami	Small Molecule	Screening Platform*
2F	Gladstone Institute (University of California, San Francisco)	Gene Therapy (CRISPR)	Preclinical
2F	Jackson Laboratory	HDAC6/Target Validation	Preclinical
2F	University of Iowa and INC sites	Biomarkers/Natural History Study	Preclinical
2S	Jackson Laboratory	SARM1/Target Validation	Preclinical
2S	Jackson Laboratory	HDAC6/Target Validation	Preclinical
UNKNOWN TYPE 2 VUS	University of Miami	Gene Identification	Discovery
UNKNOWN TYPE 2 VUS	Genesis Foundation	Gene Identification	Discovery
4	4A – Envigo	Animal Model	Preclinical
4	4A – University of Texas Southwestern	Gene Therapy	Preclinical
4	4A, 4C, 4J – Jackson Laboratory	HDAC6/Target Validation	Preclinical
4	4B – Ospedale San Raffaele	Small Molecule	Preclinical
4	4C – Cyprus Institute	Gene Therapy	Preclinical*
SORD	Applied Therapeutics	Small Molecule	Phase 3

*Indicates project completed

LICENSING

In addition to the Alliance partner pre-clinical studies, we have facilitated the transfer of the CMTA's CMT2A rat model, and CMT2A patient-derived stem cell lines to pharma companies (Partner J) and university laboratories (Partner I) that wish to use them to explore new potential therapies for CMT2A. The CMTA will continue to provide this service to accelerate research beyond our own programs.

OTHER TYPE 2 PROJECTS

The total value of all Type 2 projects in 2022 (including CMT2A and cross-type initiatives) was $3,428,156, distributed across 12 sponsored research projects. Seven are ongoing, two of those were new projects initiated in 2022, and five were completed. In addition, seven STAR Alliance partners invested $1,897,538 across Type 2 studies through the CMTA's preclinical testing program.

THERAPEUTIC INACTIVATION OF CMT2 DISEASE ALLELES WITH CRISPR (ACTIVE)

Ongoing gene editing research in several forms of CMT2 (CMT2A, CMT2E, and CMT2F) is showing promise. Gene editing, via CRISPR-Cas9, is a therapeutic approach that attempts to fix a faulty gene. Researchers are working to fix the cause of CMT at its source: the mutation within the gene. In a major and highly promising CMTA-funded project, the CMTA awarded researchers at the Gladstone Institute $664,261 for their in vivo work demonstrating that it is possible to turn off various mutations that cause different forms of CMT2 by editing the responsible gene via CRISPR-Cas9. Research shows that turning off the mutation that is causing CMT in animal models results in disease rescue.

GENE THERAPY STRATEGIES FOR CMT2E (ACTIVE)

CMT2E is caused by various mutations in the NEFL gene that encode the neurofilament light chain protein (NfL), an important protein in peripheral axons. Some CMT2E-causing mutations lead to high NfL accumulation in peripheral nerve axons, while other mutations lead to an absence of NfL in the axons. With CMTA support of $256,036, researchers at The Ohio State University are trying to develop a gene therapy approach that could work for CMT2E regardless of which NEFL gene mutation is responsible. The team is currently screening for molecules that reduce NfL expression and for AAV delivery vector candidates and plan to combine both into a single therapy.

HUMAN SCREENING PLATFORMS FOR CMT2E DRUG DEVELOPMENT

With CMTA support of $220,000, researchers at the University of Miami are rapidly testing drugs to treat CMT2E, a form of axonal CMT caused by a mutation in the NEFL gene. Using neurons in a dish derived from CMT2E stem cells, researchers are performing high-throughput screening (HTS) and high-content screening to identify drugs that can repair the motor neuron's damaged axons. Previous CMTA-supported research in HTS led to the development of a drug currently in Phase III clinical trial for CMT1A.

CMT2F BIOMARKERS AND OUTCOME MEASURES (ACTIVE)

With CMTA support of $302,071, INC clinical researchers are working at several international CMTA Clinical Centers of Excellence to track disease progression and biomarkers of disease severity in CMT2F that can be used to gauge whether potential therapies are successful. Researchers at sites in the United States, the United Kingdom and Italy are actively enrolling study participants with CMT2F so they can develop blood and calf muscle MRI biomarkers to be used for determining overall disease severity. In conjunction with the CMT-FOM (Functional Outcomes Measure), CMT-HI (Health Index), and CMT-ES (Examination Score) assessments, researchers believe combined natural history studies and biomarker data could be used to quickly identify if a potential treatment is working.

CMTA-STAR'S PORTFOLIO OF CROSS-TYPE INITIATIVES

While CMT has many genetic causes, certain advancements are common to virtually all types. Commonalities include the development of gene therapy delivery vehicles, improving genetic diagnostics and extending them to currently unclassified types of CMT, providing the biomarkers that enable and stimulate clinical trials, preventing axon degeneration and developing inhibitors.

ATASE INHIBITION FOR 1A AND 1B (COMPLETE)

With a CMTA-STAR grant of $88,889 over two years, researchers at the University of Wisconsin tested a new treatment on animal models with ***CMT1A*** and ***CMT1B***. They found that blocking certain enzymes can help eliminate harmful proteins that build up in the myelin sheaths of peripheral nerves and make the disease worse. Researchers gave the mice a compound that blocks the enzymes—ATase1 and ATase2. Each mouse showed improvement in symptoms over several months, which means this treatment could work for all CMTs that affect the myelin sheaths of the peripheral nerves.

IMPROVING PROTEASOME FUNCTION TO TREAT 1A AND 1B (ACTIVE)

In ***CMT1A*** and ***CMT1B***, an accumulation of "un-degraded" proteins become toxic to the peripheral nerves, leading to symptom onset and worsening. Using a CMTA-STAR grant of $204,785, investigators at the Research Foundation for the State University of New York developed a unique approach for reversing these disease processes by treating animal models of CMT with a combination of two readily available drugs. The combination reduced the toxic accumulation of these un-degraded proteins, improving both peripheral nerve health and symptoms.

SCHWANN CELL-TARGETED GENE THERAPY APPROACHES FOR CMT1A AND CMT1X (ACTIVE)

CMT1A, CMT1X and other demyelinating forms of CMT are caused by disruptions in the genes that control Schwann cells—the specialized cells that make and regulate peripheral nerve myelin. With CMTA support totaling $162,052 across three projects, an international team of researchers from the University of Wisconsin, the University of Texas Southwest and the Cyprus Institute in Cyprus is developing new ways of delivering gene therapy treatments directly to the Schwann cells that make and regulate peripheral nerve myelin, making use of specially designed adeno-associated virus (AAV) vectors to deliver DNA to target cells. The group believes that gene therapy that either repairs or replaces the faulty gene in CMT provides the best chance for a cure. Work in this area will benefit all forms of demyelinating CMT that involve Schwann cells.

INHIBITION OF SARM 1 (COMPLETE)

The axon—the part of the peripheral nerve that carries the signal—degenerates in every form of CMT. The enzyme SARM1 regulates the normal peripheral nerve axon life cycle. Previous research in mice with ***CMT2A***, supported by the CMTA, has shown that blocking this enzyme can help preserve the axons. With CMTA support of $110,000, researchers at The Jackson Laboratory studied mice with ***CMT1X*** and ***HSN2C*** to see if blocking SARM1 also worked in them. The results were not as good as they were in the mice with CMT2A; the nerve cells looked normal, but still didn't function properly. This research shows that SARM1-blocking is not a one-size-fits-all approach for treating CMT and plans are currently underway to check if this approach might work in other types of CMT, including ***CMT2D***, ***CMT2E***, and ***CMT2S***.

MECHANISMS OF AXONAL DEGENERATION IN LATE-ONSET CMT1B/CMT2J/CMT2I (ACTIVE)

Mutations in the MPZ gene cause the demyelinating CMT type ***CMT1B***. This gene is also tied to the axonal forms ***CMT2J/CMT2I.*** SARM1 is an important enzyme that regulates the normal peripheral nerve axon life cycle. With CMTA support of $260,243, an international team of researchers from the Research Foundation for the State University of New York and San Raffaele Scientific Institute in Milan, Italy, tested whether blocking SARM1 could help preserve axons in CMT1B/CMT2J/CMT2I. They studied mice with CMT2J (sometimes referred to as late-onset CMT1B) and compared them to mice with CMT2J that did not have the SARM1 enzyme. The results were not as good as previously demonstrated in mice with CMT2A, but researchers were able to demonstrate that the absence of the SARM1 enzyme—as well as SARM1 blocking—has potential benefits early in the late-onset CMT1B/CMT2J/CMT2I disease course.

HDAC6 AND CMT (COMPLETE)

Researchers at The Jackson Laboratory found that an enzyme called HDAC6 promotes damage in the axon, the part of the peripheral nerve that carries the signal. These axons become damaged in all forms of CMT. With CMTA support of $44,507, they discovered a protein in the blood, neurofilament light chain (NfL), that increases as axon damage worsens, making it a potentially suitable biomarker. The team found that mice with ***CMT1X*** have a very robust level of NfL compared to mice with other forms of CMT, suggesting that CMT1X and different forms of axonal CMT ***(CMT2)*** are good candidates for HDAC6 inhibition-based therapy.

ADDITIONAL FUNDED PROJECTS

AAV MEDIATED GENE THERAPY FOR CMT4C (COMPLETE) Researchers in Cyprus have treated mice that have ***CMT4C*** with gene therapy designed to fix the faulty SH3TC2 gene that causes this severe form of CMT. With CMTA support of $122,100, researchers at Cyprus University developed a special AAV9 vector for administering SH3TC2 gene therapy to both younger mice and older mice. This approach allowed the team to assess therapy benefits early in life versus later in life. The team demonstrated an improvement in disease severity in all mice that received this gene therapy. These exciting results leave the treatment well-placed to advance to pre-clinical testing and Phase 1 clinical trials with the support of commercial partners.

PRECLINICAL AND CLINICAL STUDIES IN CMT4B NEUROPATHIES (ACTIVE)

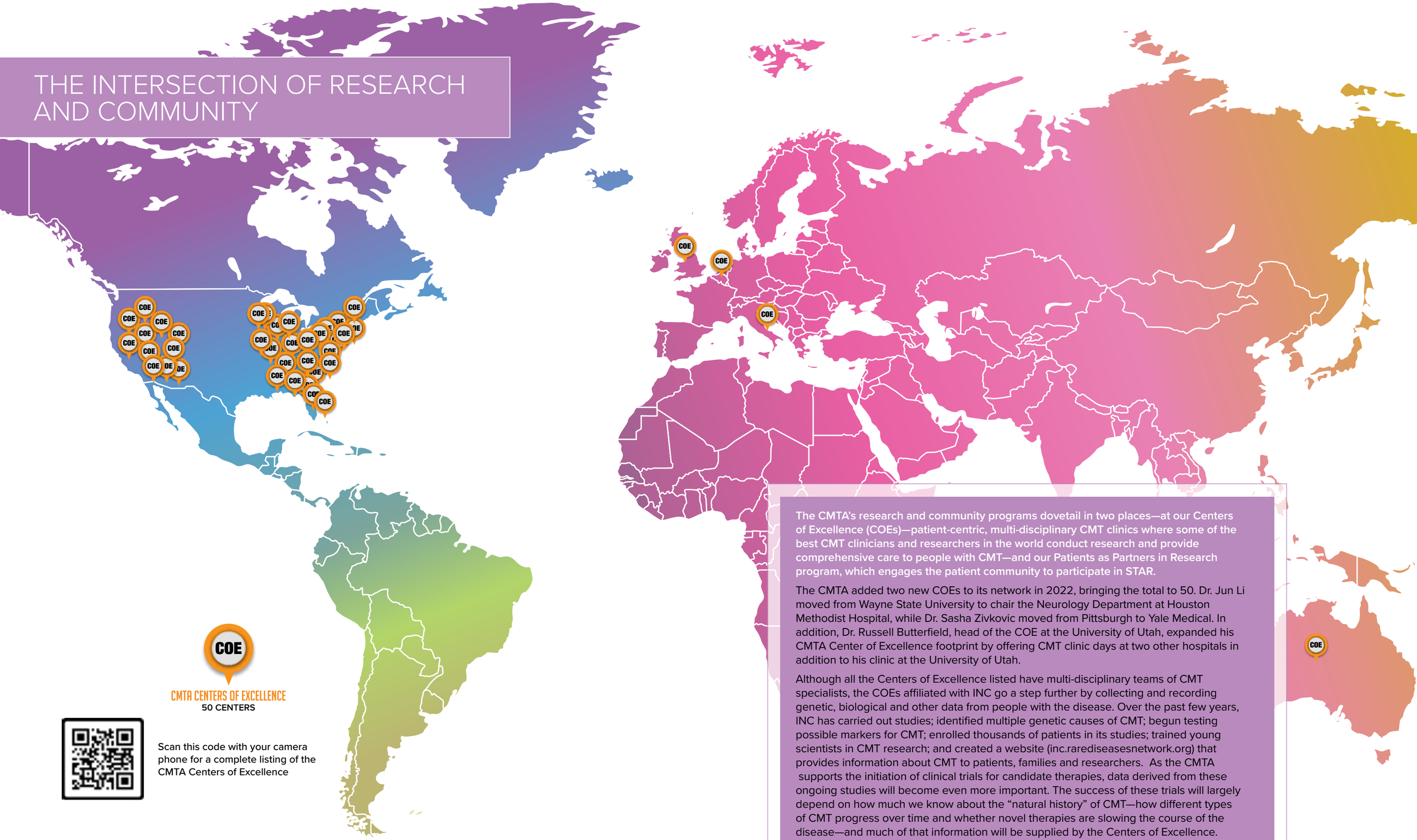
Niacin, given as one of the FDA-approved drugs for lowering cholesterol, activates an enzyme called TACE, an important enzyme in the pathway that regulates peripheral nerve myelin. With CMTA support of $201,000, researchers at the San Raffaelle Scientific Institute in Milan, Italy, treated mice that have ***CMT4B1*** with a daily dose of the drug for 150 days. The team demonstrated that neurofilament light chain (NfL) levels (a biomarker of nerve damage) decreased, indicating an improvement in nerve axon health. They also demonstrated an improvement in nerve conduction at the end of treatment, indicating an improvement in peripheral myelin health.

HEREDITARY SENSORY NEUROPATHY SERINE (SENSE) TRIAL (ACTIVE)

With an award of $354,826, CMTA-STAR Advisory Board member Dr. Mary M. Reilly and her team at the UCL Queen Square Institute of Neurology in London are planning a 12-month double-blind, placebo-controlled clinical trial to assess whether L-serine is an effective drug treatment to slow or stop disease progression in ***HSN1***, which is caused by mutations in the SPLTLC1/SPTLC2 genes. More importantly—and the reason the CMTA decided to fund the trial—the study will also assess whether magnetic resonance imaging (MRI) can accurately detect changes in fat accumulation in the lower limb muscles of people with HSN1. This is the first clinical trial to use and validate MRI muscle fat fraction as a primary outcome measure in an inherited neuropathy.

With CMTA support of $122,100, researchers at Cyprus University developed a special AAV9 vector for administering SH3TC2 gene therapy to both younger mice and older mice.

THE INTERSECTION OF RESEARCH AND COMMUNITY



CMTA CENTERS OF EXCELLENCE
50 CENTERS

Scan this code with your camera phone for a complete listing of the CMTA Centers of Excellence

The CMTA's research and community programs dovetail in two places—at our Centers of Excellence (COEs)—patient-centric, multi-disciplinary CMT clinics where some of the best CMT clinicians and researchers in the world conduct research and provide comprehensive care to people with CMT—and our Patients as Partners in Research program, which engages the patient community to participate in STAR.

The CMTA added two new COEs to its network in 2022, bringing the total to 50. Dr. Jun Li moved from Wayne State University to chair the Neurology Department at Houston Methodist Hospital, while Dr. Sasha Zivkovic moved from Pittsburgh to Yale Medical. In addition, Dr. Russell Butterfield, head of the COE at the University of Utah, expanded his CMTA Center of Excellence footprint by offering CMT clinic days at two other hospitals in addition to his clinic at the University of Utah.

Although all the Centers of Excellence listed have multi-disciplinary teams of CMT specialists, the COEs affiliated with INC go a step further by collecting and recording genetic, biological and other data from people with the disease. Over the past few years, INC has carried out studies; identified multiple genetic causes of CMT; begun testing possible markers for CMT; enrolled thousands of patients in its studies; trained young scientists in CMT research; and created a website (inc.rarediseasesnetwork.org) that provides information about CMT to patients, families and researchers. As the CMTA supports the initiation of clinical trials for candidate therapies, data derived from these ongoing studies will become even more important. The success of these trials will largely depend on how much we know about the "natural history" of CMT—how different types of CMT progress over time and whether novel therapies are slowing the course of the disease—and much of that information will be supplied by the Centers of Excellence.

A COMMUNITY THAT CARES

MT RAINIER, WASHINGTON WALK 4 CMT

Thomas McCullough, Shawn McCullough, Asher Wixson, Rowan Wixson, Rachel Wixson, Maggie McCullough, Lisa Weber, Lily Weber. Sitting: Peter Wixson

2022 WALK 4 CMT BY THE NUMBERS:

$269,138 raised for CMT research

19 walks with more than 1,000 walkers

Riverton, Utah, had the largest walk with 200 participants

8 walks raised over $10,000

3 walks raised over $25,000

Washington DC raised $47,969 with more than $125,000 since 2020

BRANCHES

In addition to being the largest funder of CMT research in the world, the CMTA is also the largest provider of community services in the world. As an organization, we strive to create a CMT community in which people feel embraced and engaged. The CMTA's branches are the touchpoint between the national organization and patients, funneling news, information, research updates and tips for living with CMT to supporters. The CMTA provides information and support, while its members raise money and awareness.

Branch leaders provide CMT patients in their localities a way to interact with others dealing with the same problems and to hear from speakers on a wide array of topics, including surgery, physical therapy, shoe fitting and bracing. There were more than 63 branches in the United States in 2022, two in Canada and one in Mexico.

In 2022, eight new leaders took control of existing branches. and two new branches joined the network—State College, Penn., and Long Island, New York. The network held 95 branch meetings in 2022, attended by nearly 900 community members.

Many branches reported great success in transitioning back to in-person branch meetings from the COVID-era online meetings that sustained many members of the community during that isolating time. Members were thrilled to be able to meet in person again, enjoying a renewed sense of connection and energy for being together.

EDUCATION

Another important component of the CMTA's mission is education, which takes multiple forms. On Oct. 1, 2022, some 569 people from 36 countries attended the virtual CMTA Patient & Research Summit, with another 3,781 views of the summit recordings online.

In addition, the CMTA sponsored nine virtual education meetings in 2022, on topics including mental health, useful gadgets, the Distant Cousin Project, tools for managing tough times, CMT-related breathing impairments, help for kids at school, self-advocacy, bracing and surgical outcomes. More than 750 people attended these webinars.

While the Patient & Research Summit and webinars are directed at people with CMT and their families, educating the general public about CMT is another vital part of the CMTA's mission. Those efforts also take several different forms, chief among them "Awareness Month," every September. The theme of Awareness Month in 2022 was "Rock and Roll into a World Without CMT." People were encouraged to honor the CMT rockstars in their lives by donating $5 to put their names on the CMTA's Virtual Hall of Fame. People without CMT were encouraged to take the CMT Music Challenge, playing instruments with thick socks, gloves or oven mitts over their hands to simulate the effects of CMT.

Social media plays a big part in Awareness Month, and users of the CMTA's social media channels were presented a variety of awareness-raising options including adding guitar-shaped frames to their online pictures, changing their Facebook profiles and using the hashtags #CMTA22, #CMTA wareness, #1in2500 in their posts.

The Seattle walk at the beautiful Harbour Pointe Middle School was led by Emily Osborne, who started it to meet other people with CMT in her community. And while Lisa Weber was thrilled to hear that the Seattle Walk 4 CMT was taking place in person again, she couldn't attend. Instead, she formed a virtual team, named it Team McWeberSon and trekked more than five miles. Lisa relished discussing their matching "Walk4CMT, One Step Closer to a Cure" T-shirts with fellow hikers and engaging in meaningful conversations.

In 2022, new volunteers stepped up to lead both the Denver and New Jersey walks. Laurie Branvold in Denver initially planned a walk for her family and friends but decided to open it up to the entire CMT community in Colorado where more than 20 walkers raised over $7,000. Meanwhile, Nicole Hudson took on the New Jersey Walk 4 CMT, drawing more than 150 participants and raising almost $40,000.

The CMTA Boston Branch had over 60 walkers.

WALKING 4 CMT

The CMTA's unique, patient-led Walk 4 CMT program brings together awareness, fundraising and camaraderie. In 2022, CMT patients and their families gathered in person for 19 walks spanning the country from coast to coast. With a mix of long-time community members and new faces, these walks raised almost $270,000.

The Valley Forge Walk returned for its second year in 2022 and on a beautiful October day, 100 teams walking at Perkiomen Valley Park raised some $19,000. Kayla Amoroso said her team, "It's a Gene Thing," will continue to fight, spread awareness and fund research to find a cure for all those affected by CMT.

THE FUTURE OF THE CMTA IS IN GOOD HANDS

YOUTH COUNCIL

BACK ROW:
Hannah Hockenson
Evan Zeltsar
Toby Fantl
Elsa Groenink
Sebastian Bruce
Abby Thompson
Joseph McCullough
Jonah Berger

FRONT ROW:
Hannah Roberts
Riley Williams
Hannah Spencer
Emmily Stufflet
Ashlyn Montisanti
Lily Sander

YOUTH PROGRAM

CAMP FOOTPRINT

The CMTA's Youth Program began as a series of field trips for youth whose parents were attending patient conferences. It has grown exponentially since it was formalized and now comprises a full array of services for young people with CMT.

The heart of the CTMA's Youth Program is Camp Footprint, a one-week sleepaway camp exclusively for kids with CMT. After converting to online camp in 2020 and 2021, Camp Footprint welcomed 117 campers and 72 staff members back to Fombell, Pennsylvania, in August 2022.

Camp Footprint gives kids aged 10 to 18 the chance to feel understood and to blend in.

Former camper/now counselor Erin Black, 19, explained it this way: "Imagine walking around with a backpack full of bricks for 360 days, but then one day someone tells you that you can take it off for five days and feel free, joyful and empowered. For one week, CMT isn't an ugly, painful neurological disease—it's a superpower." With the pandemic over, Camp Footprint (motto "One Step at a Time") again gave kids with CMT a chance to participate in all the regular camp activities like swimming, horseback riding, campfires and music.

CMT parent Kari Holzgang explained how camp affected her daughter: "My daughter Melia came back this weekend with one of the greatest gifts she has ever received, the gifts of acceptance and (more importantly) self-acceptance. I want to thank you and the other volunteers for providing these special gifts to her. It was evident that you and the other volunteers put together such a wholesome and well-thought-out week of fun-packed activities filled with reachable

CAMP DIRECTORS Jonah Berger, Laurel Richardson and Jeana Sweeney “Rockin it” at Camp Footprint

The Super Nurses of Camp Footprint

goals, opportunities to make friends, live outside her comfort zone (but just enough!), and tears and laughter (a necessary balance!) that it has really changed her life. Until now, she has had no peers that understand what she is going through.”

Based on the success of Camp Footprint, which launched in 2016, the CMTA began planning for a West Coast camp in 2022. For families west of the Mississippi, “Camp Footprint East” was geographically challenging and families whose children attend schools that start in August needed an early-summer alternative to the late-summer East Coast camp. Planners decided to follow the East Coast pattern closely, replicating existing plans and infrastructure. They identified a home for Camp Footprint West—B’Nai B’rith Camp in Lincoln City, Ore. Two hours from the Portland airport and five minutes from the Pacific Ocean, the camp offers the same activities as the Pennsylvania camp, is close to emergency services and is ADA compliant.

The Youth Program established a new support and advocacy group in 2022 aimed at accommodating youth who have aged out of its core program, which provides services to those 8 to 18. COMPASS is for young adults with CMT between the ages of 19 and 30, a time of transition in any life, from youth to college to employment and beyond.

The Youth Program also initiated a “Boxes of Sunshine” project in 2022, sending care packages to newly diagnosed youth and youth awaiting surgery for CMT. A community member volunteered to pay for the first round of 200 boxes, and in the first eight months of the program, 96 were delivered.

Some 75 members of the CMTA youth community published a book, “Walk a Mile in My Braces,” in 2022 to welcome newly diagnosed kids to what they refer to as the Tribe of the Funky Feet. The book was not about the disease and its symptoms, but rather a celebration of young people who live with it. Dancers from 12 states and five countries participated in the Youth Program’s second annual Dance 4 CMT in 2022, raising more than $12,000. And in another quantitative measure of the importance of connections, the Youth Council database grew in 2022 from 88 members to 261.

CMTA ONLINE COMMUNITY 2022

The CMTA’s online community provides information, support, and resources to people living with CMT. At the close of 2022, the CMTA had a total of just over 53,000 fans across all social media platforms. During the year, the number of Facebook followers grew by 972, bringing our total to 39,866. On Instagram, we had a net growth of 1,007 followers, raising that audience to 7,498. Our LinkedIn audience grew by 30 percent to 1,702.

All of the CMTA’s branches have Facebook groups. The CMTA also hosts five main Facebook discussion groups with an international reach: The CMTA Discussion Group is the largest with over 21,000 members; CMTActive has 1,594 members; CMTA Parents has 1,664 members; CMTA Youth group has 283 members; and the Cycle 4 CMT group has 243 members.

The number of new users on the website increased from 416,400 in 2021 to 696,062 users in 2022. There were over 882,640 sessions on the CMTA’s website in 2022 and 1,307,877 page views. The CMTA’s Monthly Giving webpage had 350,699 unique pageviews in 2022 compared to 267 in 2021, thanks to a Google ad campaign that drove traffic to the site.

FUNDRAISING

THE LEGACY SOCIETY

The CMTA reorganized its planned giving program as the Legacy Society in 2020 and in 2022 three remarkable individuals whose philanthropic spirit knew no bounds contributed $4.9 million to the bottom line. These individuals championed the CMTA throughout their lifetimes, acting as donors, advocates and volunteers. Their unwavering dedication and bequests are a testament to their belief in our ability to make positive change and transform lives. We mourn their passing and are grateful for their commitment to the CMTA. The impact of their legacy will be felt for generations to come. The CMTA also built out a new Legacy Society website in 2022, cmtalegacy.org, which offers information on a wide variety of opportunities to donate, including bequests, IRA rollovers, beneficiary designation gifts, charitable trusts and more.

INNERVATORS

An increasing number of individuals joined our monthly giving program, Innervators, in 2022. This growth not only bolstered financial stability but also deepened connections with donors, fostering a sense of shared purpose and impact. Income from the Innervators program increased from $55K in 2021 to $125K in 2022. Diane Covington explained why she's an Innervator: "One of the best things my involvement with the CMTA has brought me is acceptance. I've learned to live comfortably in my skin, as imperfect as it is, with grace and resilience. I am grateful for all the incredible research that is leading to a cure, andI hope it will help my children and grandchildren live their lives without CMT. For me, the challenge of living with a slowly degenerative disease is made easier because I've been able to improve my mental health and confidence by exposure to all the positivity in *The CMTA Report*. Knowing that I am not alone and that there are many others with CMT living good, full lives is inspiring."

Vermont Cycle 4 CMT

YEAREND APPEAL

The CMTA's end-of-year giving campaign captured the hearts and minds of our community in 2022, raising a record $705,000. Through strategic communication, personalized appeals, and enhanced donor engagement, we inspired a groundswell of generosity that exceeded all expectations. The collective response to our campaign not only showcased the dedication of our supporters but also reaffirmed the strength of our mission and the belief in our organization's ability to make change.

BOARD MEMBER FUNDRAISERS

Each year, members of the CMTA Board of Directors hold fundraisers for the CMTA and 2022 was no different—altogether they raised $413,578.

Cycle 4 CMT, helmed by board members Chris and Elizabeth Ouellette, raised more than $256,810 in new donations. "The first year, it was mostly family and close friends. I didn't know how to run an event or mark trails, and people who meant to ride 10 miles ended up riding 20. But we raised $60,000 for the CMTA's STAR research program," laughed Chris. In its ninth year, the Cycle 4 CMT had almost 150 participants from coast to coast, bringing the event's grand total raised for CMT research to $2 million.

Board member David Coldiron with his wife Christina, daughter Hazel, (age 10 who has CMT), and daughter Clara, age 9

CMTA Board Member David Coldiron raised $84,623 with a 2022 Kentucky Derby party, almost triple what his 2021 Derby party brought in. The fundraiser featured live music, fabulous bites, mint juleps, Derby viewing, live and silent auctions and a bourbon tasting. Board Member Phyllis Sanders, well known for her past Essex House fundraisers in New York City, conducted a letter-writing campaign in 2022 that brought in $31,300, and Board Member Herb Beron brought in $47,659 with the TeamJulia swim, dedicated to his daughter.

BOARD OF DIRECTORS

The members of the Board of Directors bring a unique combination of professional competence and personal commitment to governing the activities of the CMTA. As business owners, managers, doctors, lawyers, or public servants, they have the expertise to oversee the organization's operations and formulate its strategy for funding research and finding a cure. As individuals with CMT or closely related to someone with CMT, they are dedicated to helping people affected by the disease." Together they contributed $839,872 to the bottom line in 2022.

Gilles Bouchard, Chairman
Kevin Sami, Treasurer
Herb Beron, Secretary
Dan Chamby
David Coldiron
Thomas W. Dubensky, Jr., PhD
Pete Foley
Gary Gaspar
Alan Korowitz
David Norcom
Steve O'Donnell
Chris Ouellette
Elizabeth Ouellette
Jon Pastor
Phyllis Sanders, Esq.
Steven Scherer, MD, PhD
Michael Shy, MD
John Svaren, PhD
Craig Zeltsar
Special Advisor to the Board Bruce Chizen

BOARD OF ADVISORS

The CMTA Board of Advisors comprises a panel of experts in a wide variety of fields—occupational and physical therapy, orthotics, foot surgery and more—who stand ready to offer insights into some of the important, but not neurological, issues facing people dealing with CMT.

Gregory Carter, MD, MS
Ken Cornell, CO
Bob DeRosa
Katy Eichinger, PT, DPT, NCS
Ashraf Elsayegh, MD, FCCP
Tim Estilow, OTR/L
Shawna Feely, MS, CGC
Valery Hanks, OTR/L, C/NDT
Sarah Kesty
Kate Lair
Bethany Noelle Meloche
Tom Meloche
David Misener, BSc (HK), CPO, MBA
Elizabeth Misener, PhD, LMSW
Christine Murray, MD
Sabrina Paganoni, MD, PhD
Glenn Pfeffer, MD
Kenneth Raymond
Clark Semmes
Carly Siskind, MS, CGC
Greg Stilwell, DPM
David Tannenbaum, LCSW

CMTA STAFF

(as of Dec. 31, 2022)

Amy Gray
Chief Executive Officer

Jonah Berger
National Youth Programs Manager
jonah@cmtausa.org

Katherine Forsey, PhD.
Chief Research Officer
katherine@cmtausa.org

Sarah Gentry
Technology Manager
Sarah@cmtausa.org

Sarah Kaider
Digital Marketing Manager
sarahk@cmtausa.org

Kim Magee
Director of Finance and Administration
kim@cmtausa.org

Laurel Richardson
Director of Community Outreach
laurel@cmtausa.org

Jeana Sweeney
Chief Engagement and Gifts Officer
jeana@cmtausa.org

Elizabeth Ouellette
CMTA Board Member/Staff Volunteer

2022 BY THE NUMBERS

PERFECT 100
★★★★ Charity Navigator 4-Star ranking

$4.8 Million
Invested in STAR

92%
of every dollar donated spent on mission

$10,493,765 Million
Raised in donations

6,100
Patients as Partners in Research

19
WALKS 4 CMT

63
BRANCHES

50 CMTA CENTERS OF EXCELLENCE

$269,138
raised by WALKS 4 CMT

569
ATTENDEES AT
Patient/Family Conference

117 CAMP FOOTPRINT CAMPERS

72 CAMP FOOTPRINT COUNSELORS

1,307,877 PAGE VIEWS
on cmtausa.org

95
BRANCH MEETINGS

50+ Research Projects

40+ Research Partners

$23.5M+
in Research Funding to date

53,000
SOCIAL MEDIA FOLLOWERS

CONSOLIDATED STATEMENT OF FINANCIAL POSITION DECEMBER 31, 2022

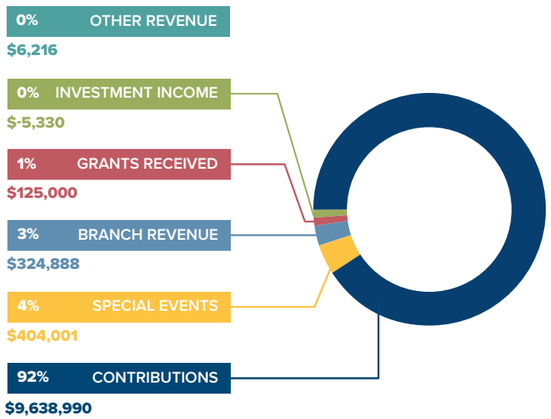
MISSION EXPENSES

TOTAL MISSION EXPENSES
$6,091,426

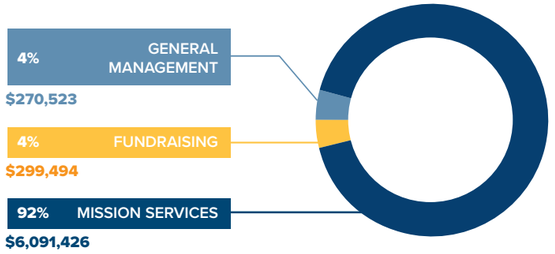
RESEARCH
81% - $4,818,479

EDUCATION & AWARENESS
19% - $1,272,947

TOTAL REVENUE
$9,638,990



TOTAL EXPENSES
$6,661,443



CMTA CORPORATE PARTNERS

AETREX WORLDWIDE, INC.
ALLARD, USA
GENEDX
TURBOMED ORTHOTICS

THE CMTA IS:

The largest philanthropic funder of CMT research in the world.

The provider of the most CMT patient services in the world.

The recipient of Charity Navigator's "Perfect 100" score for exceeding industry standards and outperforming other organizations that do similar work. Less than 1 percent of the thousands of charities rated by Charity Navigator have earned perfect scores.

CMTA
Charcot-Marie-Tooth Association

P.O. Box 105 • Glenolden, PA 19036 • 800-606-2682

CMTAUSA.ORG

9-2022