RARE AS ONE NETWORK CYCLE 1 IMPACT REPORT

Chan Zuckerberg Initiative

DECEMBER 2024

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Cover: Science in Society grantees, including members of the Rare As One Network, and other key stakeholders in the rare disease ecosystem, gather at the Science in Society 2023 Meeting.

Ann Geffen (left), Executive Director of the TANGO2 Research Foundation, and Medha-Deoras Sutliff (right), former Executive Director of the EHE Foundation, at the Rare As One Network 2022 Meeting. Ann and Medha were both hired during the grant period.

Members of the APBD Research Foundation community meet up at the Rare As One Network 2022 Meeting. Left to right: Natacha Pires, Executive Director; Deberah Goldman, Vice President of the Board of Directors; Harriet Saxe, member of the Board of Directors; and Orhan Akman, a member of the APBD Research Foundation Scientific and Medical Advisory Board from Columbia University.

Patient leaders collaborating to advance progress against rare developmental and epileptic encephalopathies meet up at the Science in Society 2023 Meeting. (Left to right) Amber Black, Operations Manager of TESS Research Foundation; Leah Schust Myers, Founder and Executive Director of FamilieSCN2A Foundation; Amanda Johnson, Executive Director, of ASXL Rare Research Endowment; JayEtta Hecker of Decoding Developmental Epilepsies; Jenny Burke, Board Chair of FamilieSCN2A Foundation; Gabi Conecker, Executive Director and Co-Founder of SCN8A Alliance; and Kim Nye, Founder and Executive Director of TESS Research Foundation. TESS Research Foundation is a RAO Network Cycle 1 grantee; FamilieSCN2A Foundation is a RAO Network Cycle 2 grantee; and SCN8A Alliance was in 2024 selected as a RAO Network Cycle 3 grantee. ASXL Rare Research Endowment also received support from CZI through the Rare As One Project.

Marianne Clancy (center), Executive Director of Cure HHT, connects with fellow participants at the Science in Society 2023 Meeting.

Welcome

Dear reader,

Today, approximately 10,000 rare diseases collectively affect over 400 million people around the world. Half of these diseases affect children, one-third of whom will die before their 5th birthday. Meanwhile, it takes an average of six years for a rare disease patient to obtain a diagnosis. The physical, social, mental health and economic impact of these diseases on patients and their families and caregivers are devastating, and even greater for those from underserved and underrepresented communities. The vast majority of these diseases are poorly understood, with limited knowledge of the underlying biology or natural history. Many do not have an International Classification of Disease (ICD) code and almost all are lacking diagnostic and treatment biomarkers or clinical trial endpoints. Small, scattered patient populations, and a lack of systematized data collection in most of these disease areas, pose significant challenges for research. *Fewer than 10% of rare diseases have a FDA-approved treatment*.

In 2015, in a letter drafted to their newborn daughter from a hospital delivery room, Mark Zuckerberg and Priscilla Chan announced the launch of the Chan Zuckerberg Initiative (CZI), a new kind of philanthropy that would leverage science and technology, community-driven solutions and collaboration to address complex, societal challenges, with an overarching mission to build a better future for everyone. As part of that mission, they established CZ Science, with an audacious goal to make it possible to cure, prevent or manage all diseases by the end of the century. Inspired by the growing number of patient-led, rare disease organizations seeking to

Fewer than 10% of rare diseases have a FDA-approved treatment.

drive forward research, in 2019, CZI's Science in Society Program launched the Rare As One (RAO) Project, a program aiming to elevate patient communities as central stakeholders in research. Foundational to the program is the Rare As One Network, currently consisting of 94 patient-led rare disease organizations funded across multiple grant cycles. The first cycle of the Network consisted of 30 patient-led rare disease organizations, funded with $600,000 each over a period of three years, to accelerate research in their disease areas by (i) developing and expanding a network of researchers;

Ron Garber (left), who co-founded the Yaya Foundation for 4H Leukodystrophy in honor of his daughter, embraces Andra Stratton (right), Program Manager for the Rare As One Network, at the Rare As One Network 2022 Meeting.

Rachel Alvarez (center), Executive Director of Cure CMD, and her husband, Jesse (right) connect with Nathan (far left) and Allison Peck (left), founders of Cure VCP Disease, a Rare As One Network Cycle 2 grantee, at the Rare As One Network 2022 Meeting.

Bina Maniar (right), Founder and CEO of Project 8p Foundation, and Luke Rosen (left), Co-Founder of KIF1A.ORG, reconnect at the Rare As One Network 2022 Meeting.

(ii) convening their patient and research communities; (iii) aligning research priorities in a prioritized research agenda; and (iv) strengthening their organizational capacity so as to better support their communities and continue to drive forward research well beyond the grant period.

Hoping to catapult progress, organizations funded as part of the Network were typically early in their development. On average, Cycle 1 organizations were less than 6 years old with average operating budgets of $375,000. The majority were entirely volunteer-led and few leaders of these organizations had prior non-profit or scientific expertise. Rather, they found themselves stepping up to roles they never expected or wanted when they or their loved ones were diagnosed with a disease for which medicine had no answers. Driven to create a better future for themselves, their loved ones, and future patients, these leaders left behind their previous lives, and brought their unique background and skills — as stay-at-home moms, social workers, actors, lawyers, scientists, educators — to this work, along with love, urgency and a relentless determination unparalleled in research.

Leading a rare disease organization is enormously challenging. On top of managing medical, economic and other challenges, these leaders find themselves needing to become proficient in a host of fields including marketing, fundraising, communications, community building, event planning, scientific research, intellectual property, drug development, and more. Recognizing that funding alone would be insufficient to support leaders facing such a breadth of needs and challenges, we stood up the Rare As

We stood up the Rare As One Network as an incubator-style program to help build the capacities of the organizations and their leaders, optimize their efforts and equip them to sustain themselves and their research efforts well beyond the grant program.

Kristen Groseclose (left), Co-Founder and Director of Development of the Smith-Kingsmore Syndrome Foundation, a Rare As One Network Cycle 2 grantee, and Sandra Ojeda (right), Science Director of the Glut1 Deficiency Foundation, connect during a poster session showcasing patient-driven research at the Rare As One Network 2022 Meeting.

One Network as an incubator-style program to help build the capacities of the organizations and their leaders, optimize their efforts and equip them to sustain themselves and their research efforts well beyond the grant program, and to enable them to work alongside, learn from, and support one another. In addition to funding, grantees were offered organizational capacity building trainings and coaching in leadership, hiring, finance and operations, fundraising, grant writing, event planning and more; monthly mentorship via a partnership with the Milken Institute's FasterCures TRAIN program; access to a mental health support group; scientific capacity building trainings and science advising; access to a shared tool to identify scientific and other synergies; and regular opportunities to share learnings and collaborate with one another via an online discussion forum, Network calls, and multiple virtual and in-person convenings.

Cycle 1 of the RAO Network launched in February 2020, just as news of the COVID-19 pandemic broke. As in-person convenings became an impossibility, and research around the world

Julie Raskin (left) CEO, and Mahlet Mesfin (right), former Research Manager,of Congenital Hyperinsulinism International, and Paul Thornton (center), Medical Director of the Cook Children's Medical Center Hyperinsulinism Center, connect at the Rare As One Network 2022 Meeting.

Kurt Losert (second from left), CEO of the Fibrolamellar Cancer Foundation, a Rare As One Network Cycle 1 grantee, speaks on a panel with fellow rare disease leaders at a 2024 CZI-hosted workshop on applications of AI to rare disease diagnosis. (Left to right) Moderator Ruth-Anne Pai, Rare As One Science Consultant at the Chan Zuckerberg Initiative; Kurt Losert; Terry Jo Bichell, CEO of COMBINEDBrain; Zohreh Talebizadeh, Senior Director, RARE-X Research Program at Global Genes.

ground to a halt, we had concerns the grantees might struggle to achieve the basic objectives of these grants. But instead, we became first-hand witnesses to the indelible spirit of these patient leaders, as they pushed forward, supporting their communities through immensely challenging times, innovating to circumvent COVID-imposed restrictions, and continuing with unwavering resolve to drive forward research in their disease areas — not only meeting all of the key grant objectives, but going far beyond. We saw Cycle 1 organizations leveraging operational capacity building support in ways that resulted in major shifts in their organizational practices, enhancing their sustainability and ability to drive science forward; leveraging scientific capacity building support to make key scientific hires and collectively engage nearly 3,000 researchers in their rare disease areas; convene their communities regularly in research roundtables, workshops, and — once the global pandemic lifted — international in-person scientific convenings; and comprehensively survey their communities and lead the development of a shared patient-prioritized research agenda in each of their disease areas.

Far beyond these core grant objectives, RAO grantees built strong patient communities, identifying and engaging patients from around the world; provided mental health supports for their communities; launched awareness campaigns addressing diagnosis and diversity and equity-related challenges; supported the development of ICD codes; and funded and partnered in research, aligned with community-established priorities. Importantly, they advanced biomedical science by building or supporting the development of essential research-enabling assets and infrastructure, including Centers of Excellence, natural history studies, registries, biobanks, cell lines and

> These small but mighty patient-led organizations, collaborating and working in partnership with global researchers, clinicians, industry, regulators and policy-makers have significantly transformed their fields.

Jennifer Canvasser (left), Founder and Executive Director of the NEC Society, connects with Rebecca Ganetzky (right), Director of Mitochondrial Biochemical Diagnostic Test Development at Children's Hospital of Philadelphia, during a poster session at the Rare As One Network 2022 Meeting. Dr. Ganetzky has extensive experience caring for patients with Pearson Syndrome, and attended the meeting in her capacity as an advisor to The Champ Foundation, another Cycle 1 grantee.

animal models that are enabling critical, data-driven insights into rare disease mechanisms, characterization, and progression; published diagnostic and treatment guidelines; and partnered with industry and regulators to support clinical trial design and recruitment. These small but mighty patient-led organizations, collaborating and working in partnership with global researchers, clinicians, industry, regulators and policy-makers have significantly transformed their fields.

Cycle 1 organizations have also partnered in many ways to accelerate research across diseases, forming working groups around areas of scientific synergy and need, attending one another's conferences, and funding collaborative research projects. Now technically 'alumni', Cycle 1 leaders have become informal 'mentors' to new grantees, while also continuing to learn, receive support, and collaborate with others across this growing Network. The Network has also become a valuable test bed for the development of new scientific tools and platforms as it is regularly sought after by researchers for partnership on projects. Collectively, these organizations and research partners are driving forward novel patient-centered research and demonstrating that the Network is more valuable than the sum of its parts.

This report, developed in partnership with Cycle 1 of the RAO Network, provides a snapshot of the tremendous

Stephen Rossi (left), Chief Scientific Officer of PSC Partners Seeking a Cure, and Sonya MacParland (right), Associate Professor of Immunology at the University of Toronto, discuss developments in primary sclerosing cholangitis (PSC) research at the Science in Society 2023 Meeting.

Lex Cowsert, Chief Scientific Officer of the DADA2 Foundation, speaks at the Science in Society 2023 Meeting. Dr. Cowsert's remarks focused on patient-driven efforts to further diagnosis for DADA2 patients, and for other patients across rare disease areas.

scientific momentum and progress these organizations have inspired, and highlights the impact that a network of similarly placed and determined patient advocates can have when provided with baseline funding, support and opportunities to collaborate with one another. While the accomplishments and impact of each of these organizations is tremendous, for all of them, there is further to go, and meanwhile, lives hang in the balance. These 30 organizations (and the additional cycles we have funded) represent a small portion of the rare disease communities that are in critical need of treatments and cures. Through our work with the RAO Network, we seek to better understand the challenges facing these communities and to identify cross-cutting, systematic approaches to accelerating science and improving the research ecosystem. We invite you to join us in driving forward and enabling critical rare disease research and in supporting, empowering and elevating the work of patient-led rare disease organizations around the world.

In partnership, and with deep admiration for all of the leaders of Cycle 1 of the RAO Network, and all rare disease patients and families,

Tania Simoncelli
Vice President, Science in Society

Heidi Bjornson-Pennell
Senior Program Manager, Science in Society and Lead, Rare As One Network

Andra Stratton
Program Manager, Rare As One Network

Left to right: Andra Stratton, Heidi Bjornson-Pennell, and Tania Simoncelli.

Impact At A Glance

In their grant agreements, the 30 patient-led rare disease organizations of the Rare As One Network Cycle 1 each committed to build and strengthen a collaborative research network, host at least one international scientific convening, and align their community through development of a prioritized research agenda.

The Cycle 1 grantees achieved these targets and much more. Surpassing our expectations, in just three years, they enabled research progress and scientific breakthroughs in their disease areas in a wide range of ways, and their efforts are bearing fruit.

Collectively, the 30 organizations...

- Substantially engaged more than 3,000 new researchers
- Developed 29 prioritized research agendas
- Funded, co-authored and/or contributed data to 182 publications
- Held 144 scientific convenings
- Supported 355 research projects
- Collaborated with 96 industry partners

24
Organizations developed or contributed to the development of cell lines

26
Organizations have built or collaborated in the building of a registry

20
Organizations were involved in clinical trials

25
Organizations have designed or collaborated in the design of a natural history study

27
Organizations developed or contributed to the development of disease models

18
Organizations developed or have contributed to a biobank

13
Organizations have supported centers of excellence

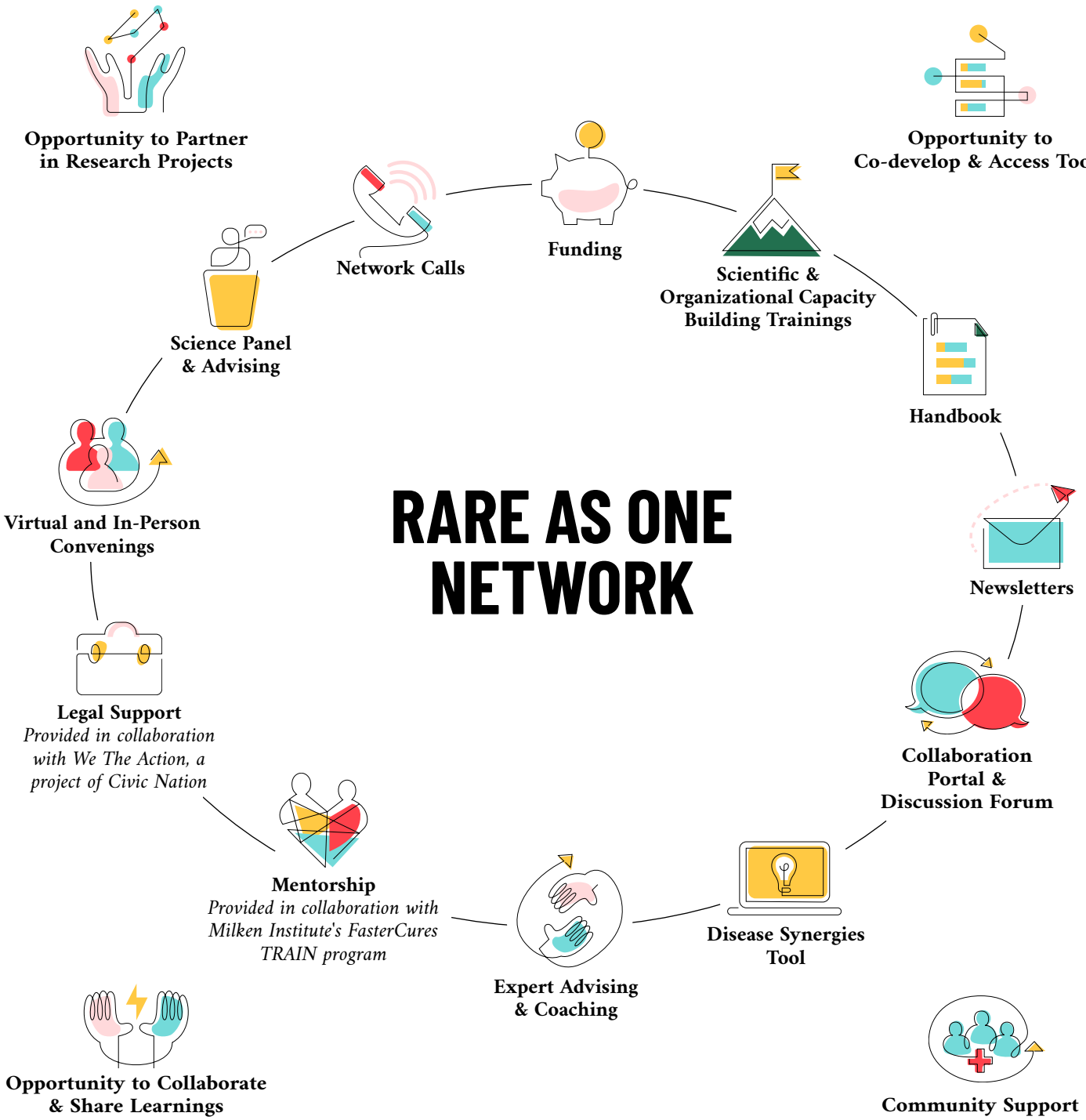
Publications

During their grant period, the organizations of the Rare As One Network Cycle 1 contributed to or funded research described in more than 180 scientific publications. Of these, 28 publications were co-authored by — or acknowledged contributions of — Rare As One Network Cycle 1 grantee organizations. These 28 publications are captured in the visual to the right. For more information about specific publications, please see the individual grantee case studies.

CZI Support and the *Network Effect*

In addition to grant funding, Rare As One Network grantees are provided access to a range of resources aimed at supporting their efforts to build organizational and scientific capacity, essential foundational elements to advancing patient-driven research and, ultimately, scientific progress. An overview of the support provided by CZI can be found in the graphic to the right.

Additionally, one of the most significant impacts of CZI support highlighted by Rare As One Network grantees is the power of the *network effect*: by bringing leaders and communities together, and creating virtual and in-person spaces for engagement, synergies and opportunities for collaboration have naturally emerged, with significant positive effects. Members of the Rare As One Network have connected and collaborated through working groups, research collaborations, advocacy partnerships, joint publications, shared resources, and more.



Working With the Rare As One Network

From mentors to scientific advisors, and from coaches to trainers, those working with the grantee organizations of the Rare As One Network Cycle 1 have seen the power of patient communities in action. If you are interested in learning more about collaborating with the Rare As One Network, please contact rareasone@chanzuckerberg.com.

"These RAO grantees and organizations are working in areas that have traditionally been neglected so in my view they are all inspirational heroes to so many — to the doctors who take care of these patients, to the scientific community for diving deep into disease processes that are often not supported by traditional research funding, and most importantly to the often desperate patients and families that would have nowhere else to go. To these patients and their loved ones, they are often the only source of hope, comfort, and community. Being able to support these groups and the important work that they do has been nothing less than a privilege and an honor."

Tisha Wang, MD
Vice Chair, Department of Medicine; Professor of Clinical Medicine and Professor of Surgery
University of California Los Angeles School of Medicine

Tisha is a member of the RAO Science Panel, researchers and clinicians who advise and support members of the Rare As One Network as they work to build their scientific capacity.

"As a RAO Science Panelist, I found the interaction between physician-scientists and grantee organizations very valuable for both groups. These meetings brought together different medical disciplines and patient advocates for a variety of disorders. We were able to share insights about patient priorities, strategic planning, acquiring research partners, developing new treatments, grant mechanisms and just brainstorm. The dedication of volunteers motivated by personal and family experiences with the medical community was inspiring and their achievements were eye-opening. I was gratified to have had the opportunity to participate in both group discussions, and on a one-to-one basis with a representative of one of these amazing advocacy groups"

Phyllis Speiser, MD
Associate Professor, Institute of Molecular Medicine, Feinstein Institutes for Medical Research; and Emerita Professor, Pediatrics, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Northwell Health

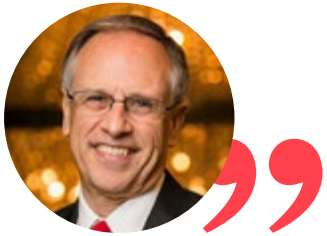
Phyllis is a former member of the RAO Science Panel, researchers and clinicians who advise and support members of the Rare As One Network as they work to build their scientific capacity.

"In a few short years, newly formed entities have established multi-stakeholder engagement with scientists, industry partners and patient-families. It is so gratifying to see how they are able to bring awareness and research progress in such a short period of time.

Through the RAO program, new organizations are able to put research resources like cell lines, mouse models and tissue repositories in place in record time, [aided] by financial and institutional resources. I have watched a mentee organization establish a fundraising and awareness strategy where there was none and bring on scientific leadership to set a research agenda. I feel like this took our organization about 10 years and they did it in 3 years."

Jennifer Farmer, MS
Chief Executive Officer
Friedrich's Ataxia Research Alliance

Jen supports members of the Rare As One Network through a mentorship program delivered by the Milken Institute's FasterCures.



"Only the 'rare disease' organizations can collect and provide the kind of data that will enable researchers to understand the nature of the disease. Researchers, clinicians and even pharma have very limited capacity to identify and reach out to rare disease patients and families. The rare disease organizations have a more natural 'affinity community' from which to draw the much needed data to move toward effective therapies.

[In this work, you encounter] 'everyday people' being heroes, champions, advocates, warriors beyond their own wildest dreams of what they might accomplish for their loved ones. [This is] deeply moving and makes those of us who have not experienced this life challenge wonder what we have been doing with ourselves!"

Tim Armour, MBA
Member of the Board of Directors; former President and CEO
Cure Alzheimer's Fund

Tim supports members of the Rare As One Network through a mentorship program delivered by the Milken Institute's FasterCures.

"In working with the leaders of Cycle One affiliates, I have seen so many of them move from complete reluctance to ask individual donors for contributions to being creative and bold about inviting them to make worthy impact investments. Their entire mindsets have changed as a result of this critical work yielding gifts of $100,000 to $1,500,000."

Laurie Kirkegaard
Co-Owner and Principal
NPL Impact Agency

Laurie serves as a trainer and advisor to members of the Rare As One Network, on topics including major donor engagement and fundraising strategy.

"Working with the RAO grantees has really driven home for me that these groups are the hub for all the work going on in their community. Not only do they contribute their own research to the field, but they bring together previously siloed work to ensure collaboration happens across all facets of their network. Another amazing thing about the RAO network is that the tools, resources and training provided to these groups not only make an impact in their own community, but in other communities as well. These groups share their experience and knowledge with other patient advocacy groups who can then learn from those experiences and think about how to best integrate them into their network."

Samantha Baxter, MS, CGC
Associate Director, *Genetic and Genomic Data Sharing Broad Institute of MIT and Harvard*

Sam is a member of the RAO Science Panel, researchers and clinicians who advise and support members of the Rare As One Network as they work to build their scientific capacity. Sam also supports members of the Rare As One Network to engage in the Broad Institute's Rare Genomes Project, as part of an effort to more accurately estimate disease prevalence.

Case Studies

Science in Society grantees, including members of the Rare As One Network, and other key stakeholders in the rare disease ecosystem, gather at the Science in Society 2024 Meeting.

APBD Research Foundation

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Dedicated to finding therapies and a cure, while improving the lives of those affected by APBD and other allied diseases.

Adult Polyglucosan Body Disease (APBD) is a rare monogenic disorder caused by autosomal recessive mutations in the GBE1 gene. It is characterized by a deficiency of the glycogen branching enzyme that results in an adult-onset condition with symptoms including peripheral neuropathy, bladder dysfunction, decreased energy, and, in some cases, cognitive decline. At least 160 cases have been identified worldwide, with a high prevalence in Ashkenazi Jews. There are currently no treatments.

The APBD Tour de Friends bike team raised funds for research grants by participating in the UPenn Million Dollar Bike Ride for rare disease research.

During the Grant Period

Impact Spotlight
Adult Polyglucosan Body Disease's impact on patients begins with a mutation in the GBE1 gene, with downstream effects impacting mRNA, protein levels and glycogen molecules. For the APBD Research Foundation (APBDRF), each stage of impact was an area for exploration and opportunity for potential treatment strategies.

One area of particular interest for the foundation was whether downregulation of glycogen synthesis could be therapeutic. In a study jointly funded by the APBDRF and the NIH, researchers identified two effective therapeutic targets in an APBD mouse model the APBDRF had funded years prior. The findings also built on earlier research in Lafora disease, another neurological glycogen storage disorder.

The APBDRF is confident that the results of this collaboration bring the APBD community closer to a potential therapy. More broadly, the results could have significant implications for other rare glycogen and polyglucosan body storage diseases. In this spirit, researchers funded by both the APBDRF and Chelsea's Hope Lafora Children Research Fund, a Rare As One Cycle 2 grantee, are jointly advancing efforts to define pre-clinical biomarkers and assess potential therapy candidates, which could one day benefit both patient communities.

Key research and research infrastructure achievements
Collaborated with the Rare Genomes Project on the development of a soon-to-be-published study that estimates the global genetic prevalence of related GBE1 disorders, including APBD, at 26,000.

Key publications

- *American Journal of Rare Disorders: Diagnosis & Therapy* (2020): a study on the prevalence of APBD in the United States (co-authored by a APBD Research Foundation volunteer).
- *Annals of Clinical and Translational Neurology* (2020): research on GYS1 or PPP1R3C deficiency in a APBD mouse model (funded by the APBD Research Foundation).
- *Molecular Genetics and Metabolism* (2023): a clinical practice resource on the diagnosis and management of Glycogen Storage Disease Type IV, including APBD (developed based on an APBDRF partnership with the Association for Glycogen Storage Disease and 20 experts from a range of specialties; co-authored by Deberah S. Goldman, Vice President of the Board of Directors of the APBDRF; publication acknowledges the APBDRF for 'critical review and suggestions').

Key operational achievements

Made key hires in conference and research coordination, strategic planning, special projects management, communications and development, and genetic counseling.

Key community achievements

Led a patient-focused Listening Session with the FDA, focused on ensuring future research reflects patient priorities and needs.

Natacha Pires (left), who was appointed as the first Executive Director of the APBD Research Foundation in February 2023, speaks with Heidi Bjornson-Pennell (right), Senior Program Manager for Science in Society and Lead for the Rare As One Network, at the Chan Zuckerberg Initiative Rare As One Network 2022 Meeting.

After the Grant

- The APBDRF completed their strategic plan and has continued to advance collaborative efforts, including by joining the European Glycogen Storage Disease (GSD) Value Project, an initiative aimed at developing an internationally applicable set of patient health outcomes that are relevant to individuals with liver GSDs and other GSD subtypes.
- In 2024, the APBDRF hosted a global focus group that brought together, for the first time, over 50 participants representing Glycogen Storage Disease Type IV (GSD IV), including APBD, communities to identify areas of alignment and advance therapy development.

"Our biggest gains came from connections made during our Scientific and Community Conferences and our Biomarkers Workshops, as well as [collaborative research grant] applications. The RAO grant funding, educational programs, and expert support, along with the camaraderie of the other grantees, also helped us focus on what are now promising therapeutic initiatives."

On success during grant period.

Jeff Levenson, DDS
President, APBD Research Foundation

Association for Creatine Deficiencies

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To provide patient, family, and public education, to advocate for early intervention through newborn screening, and to promote and fund medical research for treatments and cures for Cerebral Creatine Deficiency Syndromes (CCDS).

Cerebral Creatine Deficiency Syndromes (CCDS) are inherited metabolic disorders that interrupt the formation or transportation of creatine, resulting in language and motor delays, intellectual disability, behavioral problems, hypotonia and seizures. It is estimated that 1–3% of patients with intellectual disabilities of unknown origin may have Creatine Transporter Deficiency, though there are only a few hundred currently diagnosed cases worldwide. Most CCDS patients cannot lead an independent life.

Eight-year-old Louis, who has a GAMT deficiency — one of three cerebral creatine deficiency syndromes — takes medications four times per day. These treatments will allow him to live independently and avoid seizures and intellectual disabilities

During the Grant Period

Impact Spotlight

Since the discovery of Cerebral Creatine Deficiency Syndrome, Guanidinoacetate Methyltransferase (GAMT) deficiency in 1994, nutritional supplements have been the standard of care. Creatine supplements can be highly effective in improving symptoms like developmental delay, seizures, and behavioral issues, when started early in life. However, the supplements are not a cure for the disease, and significant damage can occur for patients who are not diagnosed and placed on supplements early in life.

Recognizing the critical importance of early diagnosis, Heidi Wallis and other leaders of the Association for Creatine Deficiencies (ACD) sprung into action. In May 2022, ACD's advocacy efforts, underway since 2016, were successful, when GAMT was endorsed by a review committee for addition to the Recommended Uniform Screening Panel (RUSP), a list of disorders that the Secretary of the Department of Health and Human Services (HHS) recommends states screen for as part of their state newborn screening programs. GAMT was officially added to the RUSP in January 2023.

ACD isn't stopping there. In February 2020, the organization launched a gene therapy consortium to facilitate the sharing of information and tools in order to shorten the timeline and effort required to develop gene therapy solutions for creatine deficiencies.

ACD also awarded four grants to researchers working to advance gene therapy over the following year. One grant was awarded to a researcher at UCLA to support efforts in gene therapy for GAMT deficiency. In June

2022, applying their gene therapy approach, the UCLA researcher demonstrated that they could increase creatine levels in mice that had been genetically modified to have GAMT deficiency to normal levels and restore their cognitive function.

Key research and research infrastructure achievements

- Launched the ACD-owned and -operated CreatineInfo Patient Registry and Natural History Study (120+ participants in first 7 months).
- In January 2023, held the CCDS Externally-Led Patient Focused Drug Development meeting, attended by more than 300 individuals worldwide.

Key publications

- *Molecular Therapy: Methods & Clinical Development* (2022): demonstrates via mouse model that a gene therapy for GAMT restored cerebral and myocardial creatine and resolved behavioral abnormalities (funded by the Association for Creatine Deficiencies; authors thank Executive Director Heidi Wallis for 'helpful discussions').
- *Molecular Genetics and Metabolism* (2021): a report on the first two cases of GAMT deficiency identified at birth by newborn screening in Utah (where newborn screening for GAMT began in 2015) and New York (where newborn screening for GAMT began in 2018); the publication preceded the addition of GAMT to the national RUSP in May 2022 (co-authored by Executive Director Heidi Wallis).

Key operational achievements

- Hired one full-time Executive Director and two part-time staff focused on patient registry development, social media and fundraising.
- Increased fundraising by 558% over grant period.

Key community achievements

Established a fellowship program to develop future generations of CCDS experts.

After the Grant

- In March 2023, ACD formed the Creatine Deficiency Research Center (CDRC) at the University of Utah and ARUP Laboratories, a collaboration of young researchers and seasoned experts. The first project is exploring whether delivery of AGAT and GAMT to neurons would allow for creatine synthesis within the brain, overcoming the creatine transporter deficiency (CTD) issues of crossing the blood brain barrier.
- In May 2024, ACD announced the first clinical drug trial available to its Creatine Transporter Deficiency community. The trial's priorities and outcomes were informed by ACD's Core Outcome Set (COS), a resource developed under the association's PCORI-funded project ,"**P**arents **A**dvancing **R**esearch **N**e**T**work**S**: **PAR**e**Nts**", to inform future GAMT and CTD clinical trials based on input and consensus from key stakeholders, including patients and parents. ACD began a second PCORI-funded project in September 2024, PAReNts 2.0: ExCiTE, to identify considerations needed for implementing the COS from the first grant.
- In March 2024, ACD announced funding of a research project to validate repurposable drug screening hits in human cells after a fellow's positive results in engineered cells during the RAO grant period.
- As of June 2024, The CCDS ClinGen Variant Curation Expert Panel, of which ACD is a part, has curated 181 variants including 72 variants in GAMT, 45 variants in GATM, and 64 variants in SLC6A8 and submitted these to ClinVar.

Heidi Wallis, Executive Director of the Association for Creatine Deficiencies, speaks about the organization's work to advance policies and systemic approaches to scaling genetic diagnosis at the Chan Zuckerberg Initiative Science in Society 2024 Meeting.

"Since 2020, when we received the CZI Rare As One grant, research into Cerebral Creatine Deficiency Syndromes (CCDS) has made remarkable strides. After nine years with ACD, I can confidently say this progress has been transformational for our rare disease group. Our community now has so much more hope and opportunity, with truly positive developments on the horizon. Not only is ACD at the forefront, regularly involved in pivotal collaborations with researchers, but we are helping lead the charge for change. The RAO grant was a game-changer for us, having an enduring and profound impact on CCDS families — an impact that cannot be overstated."

Heidi Wallis
Executive Director, Association for Creatine Deficiencies

The Champ Foundation

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The Champ Foundation supports research toward better treatments and a cure for single large-scale mitochondrial deletion syndromes (SLSMDS), like Pearson syndrome.

Pearson Syndrome is caused by a single large-scale deletion in mitochondrial DNA, leading to a multi-system disease affecting infants and young children. Pearson syndrome is exceedingly rare, affecting an estimated 1 out of 1,000,000 individuals, with approximately 100 cases having been reported in the medical literature. Often fatal in infancy, survivors typically transition to another SLSMDS called Kearns-Sayre Syndrome, a rare, progressive neuromuscular condition. Children with SLSMDS often require major interventions including blood transfusions, pace makers, and feeding tubes.

Elizabeth Reynolds, Co-Founder and Member of the Board of The Champ Foundation, in a family photo with her husband and co-founder, Jeff Reynolds, and their two sons. William (left) was diagnosed with Pearson Syndrome in 2015 when he was 2 months old.

During the Grant Period

Impact Spotlight
Research progress relies on the availability of patient data. For exceedingly rare diseases like Pearson Syndrome, collecting, managing, and sharing this data can be a challenge.

Since joining the Rare As One Network in 2019, the Champ Foundation has focused on breaking down these barriers to research progress by developing patient-led research infrastructure, beginning with a data repository.

By the end of the grant period in 2023, the Champ Foundation Registry had enrolled more than 120 participants, enabling patient reported outcomes and biospecimen collection, laying the groundwork to support the foundation's natural history study (NHS). The foundation also enrolled 40 participants in the NHS within 2 years of its launch, more than triple the number captured in an earlier, NIH-funded NHS over a period of nearly a decade.

Key research and research infrastructure achievements
Identified and funded two SLSMDS Centers of Excellence; provided financial support for patients and their families to travel to participate in research, see specialists, and receive clinical care from disorder-specific experts at these centers.

Key publications

- *Molecular Genetics & Metabolism* (2021): study capturing the first patient reported outcomes of children with SLSMDS (lead author, Co-Founder of the Champ Foundation, Elizabeth Reynolds).
- *JIMD Reports* (2023): study using patient reported outcomes from caregivers of children with SLSMDS (lead author, Co-Founder of The Champ Foundation Elizabeth Reynolds).
- *Nature Biomedical Engineering* (2022): reports on the development of MitoKO, a "library of base editors for the precise ablation of all protein-coding genes in the mouse mitochondrial genome"; the authors anticipate the library will establish new information on the role of mitochondria in aging, cancer and neurodegenerative diseases (funded by the Champ Foundation).

Key operational achievements
Developed policy for sharing registry data, including data use and data transfer agreements, to enable free and open access to researcher engagement.

Key community achievements

- Partnered with four other organizations and/or families of children with SLSMDS, leveraging resources, personnel and networks to develop the largest-ever RFP for single large-scale mtDNA deletion syndromes.
- Hosted patient and researcher conference in 2022 with more than 100 attendees, including families of affected children, researchers, and clinicians, up from 20 attendees at the foundation's first meeting in 2018.

The Champ Foundation hosted the SLSMDS Family and Scientific Conference at the Philadelphia Zoo. Here, 10 children with SLSMDS, alongside their siblings, pose for a group picture.

After the Grant

The Champ Foundation is taking its efforts to collect and manage data to the next level. The foundation is working to add patient-mediated integration of electronic health record data to the registry, and has already enrolled seven patients in a pilot project as of June 2024. As the foundation prepares to engage with the FDA to support clinical trial readiness, they are hopeful that the availability of integrated, longitudinal data could be transformative.

"Our conference was not just about families meeting other families. It was about showing the researchers why their work is so important. Seeing families playing at the zoo reminds researchers that our kids are not just data points or lab cells. We have to engage with families, share their stories, and more importantly, always include them."

Elizabeth Reynolds, PhD
Co-Founder and Executive Director,
The Champ Foundation

CLOVES Syndrome Community

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To support, educate, empower and improve the lives of those affected by CLOVES syndrome.

Congenital, Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis/ Skeletal/Spinal anomalies (CLOVES Syndrome) is a disease of the PIK3CA-related overgrowth spectrum (PROS), caused by a somatic genetic mutation in the PIK3CA gene, and characterized by congenital childhood onset of tissue overgrowth and complex vascular anomalies. For the approximately 2000 CLOVES patients around the world, symptoms include overgrowth of extremities, with treatment requiring operations and orthopedic procedures to reduce the size of overgrown tissues and large limb anomalies.

Kristen Davis (left), former Executive Director of the CLOVES Syndrome Community, presents a copy of "Four Leaf Clovers," a book about living with a rare disease, to PROS advocate Wilma Westenberg (right). While it was written with CLOVES syndrome in mind, Four Leaf Clovers is truly a story about embracing differences of all kinds.

During the Grant Period

Impact Spotlight

In 2020, following months of engagement with the FDA by the CLOVES Syndrome Community and other partners, Novartis launched the EPIK-P1 Study, a retrospective chart review of 59 patients with PIK3CA-related overgrowth spectrum (PROS) who had received the drug alpelisib through compassionate use. Alpelisib, originally developed and approved to treat breast cancer, inhibits the PIK3CA gene, and had been identified as a potential candidate to be repurposed for treatment of PROS patients.

In April 2022, real-world evidence generated by the EPIK-P1 study led to FDA approval of the drug for treatment of PROS. For the 30% of PROS patients found to have seen clinical benefit from treatment with alpelisib and others who could benefit in the future, the approval was a profound breakthrough. But for the CLOVES Syndrome Community, it is just the beginning of the progress and impact it wants to see for CLOVES and PROS patients.

In parallel to the approval, the organization doubled down on the potential of drug repurposing to bring benefits to all of its patients, including by creating a database of relevant inhibitors and a catalog of all

known mouse models, to enable continued research into candidates for additional drug repurposing projects. In 2022, the organization invested $100,000 in the development of a zebrafish model for CLOVES, for use in screening potential treatments.

Key research and research infrastructure achievements

- Created and published a database of all existing literature on CLOVES and PROS, and launched an Open Access Group through Open Science Framework for researchers to share information, ideas and failures.
- Developed research priorities, based on 50+ stakeholder interviews, literature review, a patient and family survey, and formal gap analysis.

Key publications

- *Science Advances* (2022): a study showing that alpelisib is efficient at preventing and improving PIK3CA-adipose tissue overgrowth and reversing metabolomic anomalies in animal models and patients (funded by the CLOVES Syndrome Community).
- *Science Advances* (2023): a study describing a microfluidic model of PIK3CA-driven vascular malformations, which demonstrated clinical phenotypes and a mechanism of disease progression (funded by the CLOVES Syndrome Community).
- *Orphanet Journal of Rare Diseases* (2022): a paper describing the journey and experience of PROS patients from the patients' and caregivers' perspectives, from onset to diagnosis to treatment and support (co-authored by Executive Director Kristen Davis).

Key operational achievements

- Expanded staff and board capacity and expertise, including a Collaborative Research Network Coordinator.
- Created a succession plan and hired a new Executive Director, allowing for continued sustainability and operations.

Key community achievements

- Began a bi-monthly PIK3CA Related Conditions Research Roundtable for basic and preclinical researchers to connect and learn from one another.
- Held first international scientific meeting in 2021, including eight other patient advocacy organizations who share a somatic mutation in PIK3CA; over 300 attendees and 33 abstracts submitted.
- Held a combined Family and Scientific Engagement Conference in 2023, featuring lay-friendly research presentations for families.
- Created an educational video on iPSC lines for patients and families.

After the Grant

- With funding from the CLOVES Syndrome Community, researchers successfully modeled the complexities of CLOVES in zebrafish for the first time, and created iPSC lines.
- In December 2023, the CLOVES Syndrome Community launched the CLOVES Patient Registry.

Noreen Fairley, the CLOVES Syndrome Community's Collaborative Research Network Coordinator, joins fellow patient leaders at the Rare As One Network 2022 Meeting.

"We believe in the power of the collective. We believe that together, we can make a change in the lives of people with CLOVES and PIK3CA Related Conditions."

Kristen Davis
Former Executive Director, CLOVES Syndrome Community

Congenital Hyperinsulinism International

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CHI supports research toward better treatments and a cure, advocates for timely diagnosis and improved standards of care, and supports people living with congenital hyperinsulinism (HI) every step of the way.

Congenital hyperinsulinism (HI) is the most frequent cause of severe, persistent hypoglycemia in newborn babies, infants and children, with symptoms including irritability, sleepiness, lethargy, excessive hunger and rapid heart rate. HI is estimated to impact approximately 1/28,000 births. The disease can have a number of causes, with those arising from genetic defects persisting throughout life. Treatment focuses on preventing or promptly treating hypoglycemia to prevent death and brain damage.

During the Grant Period

Impact Spotlight
Congenital Hyperinsulinism International (CHI) created the CHI Collaborative Research Network (CRN) and invested in infrastructure and convenings for sustained global research and advocacy collaborations.

The CRN enabled extensive collaboration among researchers and clinicians, fostering a culture of cooperation aimed at solving complex research problems. CHI CRN expert groups began executing on top priorities to end preventable brain damage and death that stems from late diagnosis, improve treatment options, and increase access to excellent care. In parallel, CHI engaged its patient community to do their part in advancing research, by expanding the HI Global Registry, a patient- and physician-reported natural history study. CHI also provides all patients with the opportunity to receive targeted genetic testing which gives individuals vital health data while supporting research.

Early CRN member successes include published data identifying the second most common genetic cause of HI, a significant breakthrough that also reminds rare disease researchers to look beyond the exome to intronic areas of the genome for coding mistakes that can cause disease. Another area of early success is CRN member research focused on understanding the mechanism of neonatal hypoglycemia.

CHI is optimistic that these results will open channels for further study and progress toward timely diagnosis, treatments, and cures.

Key research and research infrastructure achievements

- Created CHI's first Prioritized Research Agenda in collaboration with their research network, including patient and caregiver representatives. Expanded the CHI Global Registry to include physician-reported data and surveys now available in six languages; since 2019, registry data has been leveraged in five CHI-supported clinical trials for HI.
- Launched a research partnership with Children's Hospital of Philadelphia and Cook Children's Hospital, to better understand the natural history of hyperinsulinism hyperammonemia syndrome, a type of HI.
- Designated six medical institutions in the US, UK, and Europe as Centers of Excellence for HI.

The CHI Collaborative Research Network (CRN) gathers in Lisbon in 2023.

- Through a detailed collaborative process, developed the first set of international consensus treatment guidelines for HI.

Key publications

- *Hormone Research in Paediatrics* (2023): the first international care guidelines for HI (authors included CHI research staff).
- *Nature Genetics* (2023): a study identifying new molecular causes of congenital hyperinsulinism (authors include CHI CRN members).
- *Frontiers in Endocrinology* (2022): a study leveraging the CHI Global Registry to characterize HI through the experience of individuals who live with it (authored by CHI staff).
- *Frontiers in Endocrinology* (2022): an article detailing the ways in which CHI works to improve the lives of HI patients and their families, including through the Collaborative Research Network (authored by CHI staff).
- *Clinics in Perinatology* (2022): an article furthering the understanding of neonatal hypoglycemia (co-authored by a key CHI CRN member).

Key operational achievements

Expanded staff to include expertise in research, epidemiology, and major gifts.

Key community achievements

- From 2020 to 2022, CHI held six family conferences. Attendance ranged from 130 to 423 participants at each conference, with participants attending from 46 countries.
- CHI enrolled over 500 participants from 53 countries in the HI Global Registry.

After the Grant

- CHI has continued to support the growth of the CRN and its developing infrastructure.
- CHI has expanded its expert pool to bring in experts from additional fields and has developed a model research protocol for universal neonatal screening for HI.
- CRN members have also developed and published the first global consensus guidelines for treating people with HI.
- CHI CRN members are also working on novel pre-clinical and clinical research studies, supported, in part, by data from the CHI HI Global Registry, which has expanded to include eight languages and participant continuous glucose monitoring data.
- With CHI as advocacy partner, European scientists and physicians, and members of the CHI CRN, are developing a potential new photodynamic therapy treatment for HI. Funds for this project are made possible through a five-year €8.2M grant from the European Union research arm, Horizon Europe. The focus of the grant is also on advocacy for those with HI, with CHI receiving over €1.4M to strengthen natural history, develop patient-reported outcome measures, and raise awareness of clinical research and glucose as a vital sign.
- Designated two additional medical institutions in Europe as Centers of Excellence for HI.

An infant diagnosed with congenital hyperinsulinism.

"CHI CRN members are among the most committed, knowledgeable, and compassionate people I know, and the collaboration taking place is truly stunning. CHI continues to invest in the CRN infrastructure because it is the only way forward for medical breakthroughs for people with congenital hyperinsulinism."

Julie Raskin, MA
Chief Executive Officer, Congenital Hyperinsulinism International

Cure CMD

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Cure CMD's mission is to advance research toward treatments for congenital muscular dystrophy (CMD) and empower those living with CMD through engagement and support of our community.

Congenital Muscular Dystrophy (CMD) is a group of rare genetic disorders defined by muscle weakness at or soon after birth. Mutations in one of more than 30 genes cause muscle tissue to break down faster than the body can repair it. A person with CMD may have a variety of neurological and physical impairments, including the inability to walk, respiratory weakness, scoliosis, joint contractures, feeding and cardiac complications, and for some, profound cognitive impairment. There are currently no approved treatments for CMD.

CMD-affected young adults demonstrate their wheelchair hockey prowess in the film, The Tenacity of Hope.

During the Grant Period

Impact Spotlight
When Cure CMD began planning an externally-led Patient-Focused Drug Development (PFDD) meeting at their Scientific & Family Conference, the organization knew capturing and communicating the experience of those living with CMD — affected individuals and those who care for them — was a top priority.

To do this, they partnered with Living in the Light, a rare disease visual storytelling initiative, to produce a documentary film — titled, *The Tenacity of Hope* — capturing the diverse experiences and perspectives of members of the CMD community, and presented the full film live to the FDA.

Key research and research infrastructure achievements

- Revamped international registry to increase usability in research, including transferring to a new platform, expanding patient-reported data collection, improving user experience, and implementing data-sharing opt-in features.
- Expanded patient registry to serve patients with adjacent congenital muscles disorders who lacked existing registries.
- Launched a retrospective natural history study in one subtype of CMD (LAMA2) to expand knowledge of disease presentation and natural course in infancy and early childhood, and to further develop potential outcome measures.

- Funded $740,000 across 12 research grants to push the CMDs closer to clinical trials, consistent with an updated research strategy.

Key publications

- *Brain Communications* (2021): an international retrospective natural history study of LMNA-related congenital muscular dystrophy (funded by Cure CMD and co-authored by Executive Director Rachel Alvarez).
- *Cold Spring Harbor Molecular Case Studies* (2022): a patient perspective by Executive Director Rachel Alvarez, detailing her personal experience with the diagnosis and management of CMD, and her path to joining Cure CMD.
- *Neuromuscular Disorders* (2022): a workshop report on the 253rd ENMC international workshop, focused on laminopathies; describes the natural history and clinical trial readiness for one CMD subtype (Cure CMD Scientific Director Gustavo Dziewczapolski is listed as a workshop participant).

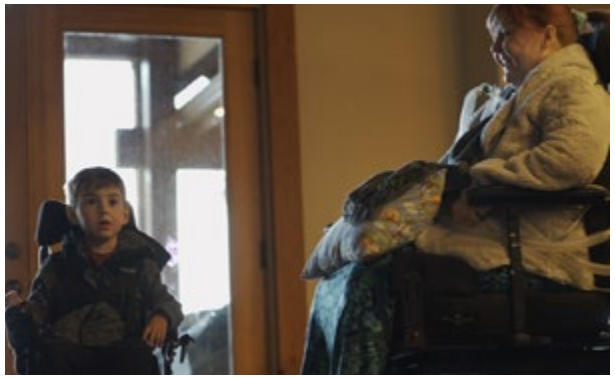
Key operational achievements

- Hired an Outreach and Engagement Coordinator, and Young Adult Programming Assistant, both living with CMD, as well as a Director of Individual and Corporate Giving.
- Executed year-end fundraising campaigns that raised more than $150,000 each year.

Key community achievements

- Outreach and Engagement Coordinator spearheaded new programming for young adults, a demographic the organization had previously struggled to engage.

Mom and son share a common care regime for those living with CMD: delivering medication through a feeding tube.



Young community member shares his perspective on CMD with Executive Director, Rachel Alvarez

- Executive and Scientific Directors joined the CZI-funded Pediatric Muscle Cell Atlas project as co-PIs focused on ensuring diversity of samples for study and communication of project milestones.

After the Grant

- Cure CMD has engaged with several pharmaceutical companies with an interest in developing treatments for CMD.
- Results of a study funded by Cure CMD indicating novel aspects of fibroblast physiopathology in a severe form of CMD were published in *Cells* (2024).
- Cure CMD executed a retrospective natural history study through their patient registry, with results published in the *Journal of Neuromuscular Disorders* (2024).
- Results from the first-ever clinical trial conducted in CMD, with Cure CMD's support, were published in *Neurology Genetics* (2024).

"Rare disease impacts more than just the affected individual. How are parents, siblings and spouses coping? What are extended family and friends going through? The experiences of everyone touched by this disease is at the heart of our work, to identify the most impactful therapeutic targets, and ultimately, improve quality of life."

Rachel Alvarez
Executive Director, Cure CMD

CureGRIN Foundation

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curegrin.org

To improve the lives of people around the world with GRI Disorders and their families through research, education and support. We work closely with scientists and the medical community to drive patient-centered research that will lead to treatments and cures.

GRI disorders are neurodevelopmental disorders affecting one out of every 2,422 births, caused by dysfunction in glutamate signaling, with symptoms including intellectual disability, seizures and sensory impairment. The few treatment options that exist include seizure medications, implantable stimulation devices, and dietary therapy.

Denise Rehner (left), co-founder of the CureGRIN Foundation, with her son Brett Rehner (right), a kindergartner who has a GRIN Disorder.

During the Grant Period

Impact Spotlight
In 2021, the Simons Foundation awarded a public-private research collaboration a $1.2M grant to test adeno-associated virus gene therapy strategies for GRIN1 and GRIN2B. The engagement and leadership of the CureGRIN Foundation was crucial to securing this funding, and making possible the multi-institutional research collaboration it supports.

The Foundation's leadership identified the funding opportunity, as well as members of their research network whose work could be a fit. Building on the organization's existing relationships with Homology Medicines (a company developing gene therapy medicines), neuroscientists, and a pediatric neurologist leading a clinical trial for GRIN, the foundation made introductions and encouraged the team to apply. The foundation anchored the application in the patient community's priorities, and successfully advocated to the funder when more time was needed to finalize materials. In the words of Dr. Amy Ramsey of the University of Toronto, the grant's lead researcher, "CureGRIN really brought us all together."

Key research and research infrastructure achievements

- Developed a research roadmap, identifying 10 essential questions to be answered toward treatments and cures; in 2023, awarded more than $600,000 in funding to five research projects.

- Hosted GRICON 2023, convening 226 attendees, including patients and family members, scientists and researchers, and industry representatives, from 14 countries and representing all nine GRI genes with known pathogenic variants.

- Supported planning for a clinical trial approved in four countries to date, including advising on relevant endpoints to the patient community.

Key publications

- *Genes, Brains & Behavior* (2022): research on vision and other sensory modalities in cognitive performance using GRIN1 knockdown mice (funded by CureGRIN Foundation).

- *The Globe & Mail* (2020): an op-ed by CEO Keith McArthur titled, "I want to cure my son of his rare genetic disease. Is that wrong?", elevating questions of disability and ableism.

Key operational achievements

Evolved from a volunteer-driven start-up to a professional organization with two full-time and two part-time positions focused on research, community support and development, and shifted staff from contractor to employee roles.

Key community achievements

- Expanded GRI genes of focus under the CureGRIN umbrella to increase collaboration and representation from a broader range of patients.

- Launched GRIConnect, a private online community for GRI families, researchers and clinicians.

CureGRIN's Meagan Hutchinson (right) presents Dr. Amy Ramsey (left) with a GRI Patient Impact Award at GRICON23 in Boston.

After the Grant

- Leveraging foundation-funded and -collected data, CureGrin completed an application for an ICD-Code and is awaiting a decision as of June 2024.

- In 2024, CureGrin held a roundtable discussion on the latest GRI research. The foundation is collaborating with GRI families, researchers, clinicians and industry representatives from around the world to plan their 2025 conference, GRICON25, an opportunity for members of the community to learn, collaborate and network.

Keith McArthur (left), Executive Director of CureGRIN Foundation, with his son, Bryson (right), who has GRIN1 Disorder.

"For those saying, 'why should we fund patient advocacy organizations, instead of just giving to researchers,' [the successful award of a $1.2M grant] is an example."

Keith McArthur, MA
Executive Director, CureGRIN Foundation

Cure HHT

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To find a cure for HHT while saving the lives and improving the well-being of individuals and families affected by HHT.

Hereditary hemorrhagic telangiectasia (HHT) is an inherited disorder characterized by malformations of various blood vessels, with symptoms including recurrent nosebleeds, vascular malformations, headaches, migraines, stroke, pulmonary hypertension, anemia, and high output heart failure. It is the second most common genetic bleeding disorder in the United States, and affects more than 1.4 million people worldwide.

Hereditary hemorrhagic telangiectasia pediatrician, Dr. Joshua Murphy, educates a young patient during the Youth Program at the 2016 National HHT Family Conference.

During the Grant Period

Impact Spotlight

Cure HHT was founded in 1991. In 2015, a drug that had been approved for cancer treatment (pazopanib) showed promise in low dose for alleviating symptoms of HHT in a small clinical trial. The drug was then sold to another company and the trial was not completed. Realizing they needed to take on a more active role in research and drug development, Cure HHT set out to raise money to purchase the drug and sponsor their own trial. In 2020, they secured $7.2 million in federal funding to launch the trial, and received orphan drug and breakthrough designations from the FDA.

Along the way, Cure HHT applied for and received a RAO grant. They leveraged the funding and support to develop a research roadmap, surveying more than 1,200 patients, 100 clinicians and 60 scientists over six months, to inform the organization's priorities. In parallel, Cure HHT created a therapeutic arm of the organization, allowing them to hire in-house experts to identify and proactively build partnerships with industry. Additionally, in 2022, Cure HHT received $2 million in federal funding per year to support U.S.-based HHT Centers of Excellence, as well as funds to launch a natural history study within 18 months.

Key research and research infrastructure achievements

- Funded 40 young investigators from six continents.
- Contributed to successful advocacy for US Department of Defense funding for the UCSF-led 'Aviator' project, aimed at streamlining three diagnostic screens into one; once the project is launched, Cure HHT will support patient recruitment for trials.
- Launched Centralized Research Hub on Hivebright platform to serve as an intranet for HHT science and medicine, including publication updates, working groups and data sharing.

Key publications

- *Annals of Internal Medicine* (2020): evidence-based consensus guidelines for the management and prevention of HHT-related symptoms and complications (funded by Cure HHT; co-authored by Executive Director Marianne Clancy).
- *Blood Advances* (2022): a report on the development and evaluation of an HHT-specific quality of life measurement instrument (funding and enrollment support provided by Cure HHT; co-authored by Executive Director Marianne Clancy and Chief Operating Officer Nicole Schaefer).

Key operational achievements

- Onboarded staff and consultants with expertise in fundraising, Salesforce, marketing and communications, education, patient registries, research and grant programs, and clinical research.
- Launched $12M Called to Cure Campaign, aimed at major donor fundraising in support of funding collaborations prioritized in the organization's research roadmap, and increasing access to diagnosis and care.

Key community achievements

Held an International Scientific Conference in Portugal in 2022, convening 325 attendees.

After the Grant

- Launched in 2022, Cure HHT's Therapeutic Arm continues to drive impact in HHT therapeutic development. Today, ten companies have active programs in HHT.
- Six biotech and pharma companies are partnering with Cure HHT to advance pipeline projects. As of November 2024, twelve active therapeutic projects are moving forward.
- As of November 2024, Cure HHT's Phase II/III clinical trial of the investigational drug pazopanib to treat HHT-related bleeding has enrolled 67 patients. Cure HHT is one of only a few patient-led organizations in the world to have sponsored their own Phase II/III trial.
- Cure HHT developed an online continuing medical education program, and continues to increase the number of new patients diagnosed and treated.
- Cure HHT Executive Director Marianne Clancy co-authored several significant publications:
  - *The New England Journal of Medicine* (2024): the results of the PATH-HHT clinical trial, which aimed to determine the safety and efficacy of pomalidomide for bleeding in HHT, and found pomalidomide treatment resulted in reduced severity of nosebleeds in patients with HHT.
  - *The American Journal of Neuroradiology* (2024): an overview and analysis of current practice around screening children with HHT for brain vascular malformations.
  - *Pediatric Neurology* (2024): a longitudinal study of de novo brain vascular malformations in patients with HHT.
- In November 2024, Vaderis Therapeutic announced FDA designation of their treatment VAD044 as a Fast Track product for the treatment of HHT. Cure HHT partnered with Vaderis Therapeutic throughout the process, including to inform trial design and support recruitment.
- In October 2024, Cure HHT hosted the 15th HHT International Scientific Conference in Mandelieu-La-Napoule, France, bringing together a record-breaking 376 attendees from 29 countries, including 72 trainees and 34 funded young scholars.
- In September 2024, Cure HHT partnered with the UCSF HHT Center of Excellence to host HHT Kids Day at the California Academy of Sciences Museum, as an opportunity for families and researchers to connect.
- In April 2024, Cure HHT launched a global outcomes registry, the HHT Connect Registry, with 275 participants. The registry will focus on quality of life and outcomes in multiple countries.
- In early 2024, Cure HHT launched the first centralized biorepository for HHT. A biobank was the resource most requested by all working groups in the organization's research roadmap development process. Within eight months of launch, 270 samples had been procured.

"We were always the connector, but not the conductor… Our organization invested in creating a Therapeutic Development Arm, bringing the necessary talent in house to help us proactively bring forward promising therapies to patients faster. We are not sitting on the sideline and hoping change comes. We are rolling up our sleeves and making it happen."

Marianne Clacy, MPA
Executive Director, Cure HHT

dada2
FOUNDATION

DADA2 Foundation

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To continually foster collaboration among patients, family, researchers and clinicians to accelerate research, raise awareness and improve the lives of DADA2 patients.

Deficiency of Adenosine Deaminase 2 (DADA2), discovered in 2014 and known to impact more than 600 patients, is a genetic disease characterized by changes in how immune, blood, and vascular systems develop and grow. These changes can cause autoinflammation or excessive inflammation throughout the body, which in some patients can lead to recurring pediatric stroke. There is no cure for DADA2, but treatment options exist to prevent life-threatening manifestations of the disease.

The Inaugural Conference on Deficiency of Adenosine Deaminase 2 or DADA2 in Bethesda, MD welcomed 69 patients and family members from six countries. The 2016 meeting occurred just two years after the discovery of the disease in 2014.

During the Grant Period

Impact Spotlight
Just eight years after the discovery of DADA2, the DADA2 Foundation and its partners had identified two shelved drug development candidates for the treatment of DADA2.

One of these drugs, an enzyme replacement candidate for the ADA2 enzyme that had originally been developed as a cancer treatment, had been shelved by the company developing it. In 2023, following months of negotiation, the Foundation entered into a transfer of ownership agreement with the company for 39 patents, the compound, and the right to develop the compound for treatment of DADA2.

Following this major step forward for the DADA2 community, the foundation aims to continue to accelerate progress, with an emphasis on sustainability and multiple shots on goal toward better outcomes for patients.

Key research and research infrastructure achievements

- Formed the DADA2 Collaborative Research Network, and engaged more than 500 clinicians and researchers in more than 39 countries in its international scientific conference.
- Made substantive progress (80% to goal) toward launching the DADA2 Patient Registry and Natural History Study.
- Supporting the development of ADA2 NOW™ Point-of-Care Testing in collaboration with In Vitro Diagnostic Solutions (IVDS), which targets quantitative reporting of ADA2 activity in blood from a finger stick in under 10 minutes.

Key publications

- *JAMA Network Open* (2023): the first publication of an international consensus statement from 35 DADA2 experts on the evaluation and management of DADA2. This paper now serves as a key resource for physicians treating DADA2 and a reference for

appealing health insurance rejection of TNF inhibitors for DADA2 (co-authored by Founder and President Chip Chambers; the DADA2 Foundation convened 35 experts and patients to develop the statement).

- *Journal of Clinical Immunology* (2024): the publication of proposed disease activity score and disease damage score for DADA2. These scoring systems will aid physicians in the initial staging of DADA2 and monitoring the progression of DADA2 over the patient's life, and enable physicians to adjust treatments as needed. These tools will be important in the foundation's planned natural history study. (co-authored by Founder and President Chip Chambers).

Key operational achievements

- Expanded staff from zero to five.
- Added peer-to-peer fundraising suite to engage patients/families in fundraising efforts.
- Fine-tuned investments in operational systems like Bloomerang, Constant Contact and Quickbooks to maximize efficiency and connection.

Key community achievements

- Due to restrictions and challenges of the COVID-19 pandemic, pivoted from an in-person convening to a virtual conference for patients, bringing together more than 100 patients and their families.
- Overhauled DADA2 website as a one-stop resource center, including an interactive human graphic to show all 130+ published signs and symptoms of DADA2.

Lex Cowsert, Chief Scientific Officer of DADA2 Foundation, speaks to fellow patient leaders and others at the Science in Society 2023 Meeting.

After the Grant

- In September 2023, In Vitro Diagnostic Solutions (IVDS) received a $300,000 NIH/NIAID Phase I Small Business Innovation Research (SBIR) grant. As of June 2024, DADA2 Foundation and IVDS are finalizing their SBIR Phase II application to conduct clinical validation in support of a 510(k) for FDA market approval for a diagnostic test for DADA2.
- The DADA2 Foundation continues to explore next steps toward application for orphan drug status and a priority review voucher for the enzyme replacement therapy they acquired during the grant period.
- The DADA2 Foundation hosted the 4th International Conference on DADA2 in Washington, D.C. in October 2023, welcoming approximately 100 researchers and clinicians from 23 countries, representing 22 specialties at 48 institutions.

"If you can get something that hits and generates revenue, that enables you to go warp speed on other things you want to do — investing money in the next drug, for example. Having skin in the game moves things along faster. Our hope is that, if we can make this happen once, then it self-perpetuates."

Chip Chambers, MD
Founder and President, DADA2 Foundation

DDX3X Foundation

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To connect families, resources, and the medical community to advance research for a treatment or cure to DDX3X Syndrome.

DDX3X Syndrome is a genetic neurodevelopmental disorder caused by a mutation in the DDX3X gene, located on the X-chromosome. It is estimated to cause 1-3% of all intellectual disabilities in females, though it remains significantly underdiagnosed. Symptoms include intellectual disability, developmental delays, low muscle tone/hypotonia, difficulty with speech, seizures, movement disorders and abnormalities of the brain, with current treatment options limited to physical, occupational and speech therapies.

Members of the DDX3X Foundation staff and community pose together.

During the Grant Period

Impact Spotlight
The DDX3X Foundation has invested in critical research-enabling infrastructure, including funding two Centers of Excellence (CoE), and launching an FDA-compliant registry and a multisite natural history study. In addition, the foundation is directly engaging in multiple research projects.

Though DDX3X Syndrome is rare, the DDX3X Foundation's work to advance scientific understanding of the DDX3X gene may have implications far beyond its own patient population. A research project funded by the DDX3X Foundation and led by Debra Silver of Duke University that aimed to investigate how disease-causing mutations in the DDX3X gene lead to impaired brain development provided new insights into the role the DDX3X gene plays in neuron generation.

The results of the study, published in 2022, provide important insights into the underpinnings of DDX3X Syndrome and biology, and may have implications for many neurodegenerative diseases, as well as some cancers.

Key research and research infrastructure achievements

- Identified and funded two CoEs for DDX3X Syndrome that will contribute to a central database of natural history data, with additional CoEs planned to launch.
- Surveyed patient community to identify issues of greatest interest for research prioritization, and developed and implemented a patient-prioritized research agenda.

Key publications

eLife (2022): mouse model study demonstrating new insights into the etiology of DDX3X syndrome, implicating dysregulated progenitor cell cycle dynamics and translation as pathogenic mechanisms (DDX3X Foundation contributed expertise and funding).

Key operational achievements

Hired a full-time Executive Director to manage operations, as well as a staff person to support donor stewardship, and part-time and contract employees to facilitate grant writing, fundraising and design.

Key community achievements

- Established a Leadership Advisory Board of parents from the disease community to involve viewpoints of families from different backgrounds, including patients ranging in age and professional background.
- Hosted free financial advocacy and literacy workshops, to support families in planning for their children's futures.
- Established International DDX3X Day, a major fundraising milestone leading to a substantial increase in the ability to fundraise with an additional major fundraising day during the year.

DDX3X community members convene.

After the Grant

- The DDX3X Foundation named the University of Pennsylvania and Children's Hospital of Philadelphia as a Center of Excellence for DDX3X Syndrome; this additional site will contribute to the DDX3X Natural History Study.
- The foundation has continued to expand its research funding, including by supporting gene therapy research at University of Texas Southwestern, moving forward preparations to fund a biomarker study, and developing a young investigator funding plan.
- The foundation plans to hold Scientific Conferences in 2024 and 2025.

"We are the convening force for doctors and researchers studying DDX3X Syndrome to ensure that, for such a small disease population, we're not duplicating efforts and get the most we can for the funding that's available."

On convening the DDX3X research community and encouraging the sharing of unpublished data.

Chelsey McCarthy, MS
Executive Director, DDX3X Foundation

The EHE Foundation

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To find treatments and a cure for epithelioid hemangioendothelioma (EHE) by advancing research and driving collaboration between patients, researchers, and clinicians.

Epithelioid hemangioendothelioma (EHE) is an ultra-rare sarcoma affecting one in a million people worldwide, that can arise anywhere in the body with a high propensity for systemic involvement, occurring most prevalently in the liver, lungs, and bones. There are no approved treatments specifically for EHE, and options vary and are inconsistent around the world. Disease progression is unpredictable, and in many cases, the cancer progresses to an aggressive and fatal stage.

Left to right: Amy Baghdadi, Medha Deoras-Sutliff, Denise Robinson and Patty Cogswell, of the EHE Foundation, meet in-person at the Rare As One Network 2022 Meeting.

During the Grant Period

Impact Spotlight
With a vision of dramatically increased research in EHE, the EHE Foundation has laid the groundwork for such research through the development of foundational infrastructure and resources, including by rolling out a biobank in 2021, and initiating the development of a patient registry and a secure research forum for researchers and clinicians to connect, both in 2022.

In parallel, the foundation prioritizes and centers patients by engaging them with educational programming and research updates. By the end of the grant period, these engagement efforts — which spanned the globe — had led to a patient community more than 2,000-strong and spanning more than 70 countries.

Efforts to build a strong foundation and engaged patient community for research participation are — quite literally — paying off. In late 2021, the foundation announced receipt of a $1 million, unrestricted gift from the Margie and Robert E. Peterson Foundation. With a strong patient community and research infrastructure in place, the foundation is poised to leverage these resources and more for research progress benefiting patients around the world.

Key research and research infrastructure achievements

- Organized two international conferences, institutionalizing ‘EHE 360’ as the leading global convening of the EHE community with the most recent event engaging 367 patient, clinician and research registrants from 13 countries.

- Launched the EHE Biobank, engaging 66 patients/caregivers, consenting 41, and completing 25 specimen collections.

- Initiated the EHE Research Grants Program, awarding five grants.
- Partnered with xCures for an observational registry study, aimed at generating research for repurposing of an FDA-approved drug for EHE.
- Engaging in collaborative effort to create international clinical management guidelines.

Key publications

- *ESMO Open* (2021): consensus- and evidence-based best practices to approach primary and metastatic EHE, developed based on a global consensus meeting of more than 80 experts from across disciplines (co-authored by former Executive Director Medha Deoras-Sutliff).
- *Cancers* (2022): an evaluation of recent research and a framework for further investigating the biology of EHE and YAP/TAZ-dependent cancers (funded by the EHE Foundation).

Key operational achievements

Hired or contracted key roles including Executive Director, Director of Research, and Biobank Coordinator.

Key community achievements

Launched EHE Community Connections series, aimed at breaking down barriers and identifying critical needs of rare cancer patients living with EHE.

After the Grant

Since the grant period's end in January 2023, the EHE Foundation has experienced exponential growth in basic, translational, and clinical researchers engaging in the disease area and has had a significant maturation of the organization's operational and research activities — serving its mission to find treatments and a cure for EHE. Achievements include:

- Expanded the collaborative research network to include over 150 sustained clinicians and basic scientists by May 2024.
- Initiated enrollment in the EHE Global Patient Registry, enrolling more than 200 participants from 24 countries by May 2024.
- Formed two new significant academic research partnerships.
- Distributed specimens from EHE Biobank for cell-line / EHE model development.
- Engaged in global drug repurposing initiatives, including stakeholders from US, EU, UK in meetings with regulators at FDA and EMA.
- Formed relationships with two industry partners initiating development projects focused on EHE.
- Supported efforts resulting in publications in *Frontiers in Oncology* and *Clinical Cancer Research* (1, 2).
- Implemented a CRM, capturing more than 3,500 constituents in more than 80 countries in 2023.
- Hired a full-time Executive Director and a full-time Director of Development and Communications, both in 2023.
- Initiated clinician and researcher newsletters.
- Strengthened partner alliance with European sister EHE organization.

The EHE Foundation's former Executive Director Medha Deoras-Sutliff (right) supports Board President Jenni Kovach (left), who was diagnosed with EHE in 2018.

"The EHE Foundation has experienced transformative growth in the past 3 years, significantly benefiting from the CZI grant and the organizational support and development investments gained as part of the Rare As One Network. Today, we are blazing trails toward our mission to find effective treatments and a cure for this ultra-rare cancer."

Denise Robinson
Executive Director and Director of Research,
The EHE Foundation

Fibrolamellar Cancer Foundation

Fibrolamellar Cancer Foundation

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To encourage, drive and fund research that will substantially improve outcomes for fibrolamellar patients.

Fibrolamellar Carcinoma (FLC) is a rare form of liver cancer, with a reported incidence rate of 0.02 per 100,000 per year. Typical symptoms include abdominal discomfort, swollen abdomen, loss of appetite, weight loss, malaise, unusual tiredness, easy bruising, jaundice, nausea, vomiting, and a palpable liver mass. Currently, the only proven curative treatments effective for a small minority of patients are surgical resection and liver transplantation.

Every year, the Fibrolamellar Cancer Foundation (FCF) brings together patients from around the world to the Vermont mountains to create a more intimate dialogue among the community and a support system they would not have otherwise.

During the Grant Period

Impact Spotlight

Collaboration has always been an important consideration for the Fibrolamellar Cancer Foundation (FCF). As with other rare diseases, having a small research network and limited budgets makes coordination of efforts critical. Still, the foundation's team could not have imagined that the $500,000 of *seed funding* they issued for separate studies, and a collaboration they suggested between research teams, would lead to a $7.5 million NIH grant a few years later.

In 2022, an expanded version of that collaboration — the *Immunotherapy Working Group* — developed a hypothesis about metabolic changes that they hoped could explain why immunotherapy had only limited success against the disease. The FCF's proactive funding of the Immunotherapy Working Group to further develop this concept ultimately resulted in FCF making its largest-ever grant commitment to Johns Hopkins University for a clinical trial, and to a biotech start-up to secure the drug supply needed for the trial and coordinate regulatory support. According to one researcher, the trial, which treated its first patient in February 2024, would not have happened, if at all, until late 2025 without the involvement and collaborative support of FCF.

The Fibrolamellar Cancer Foundation is already looking downstream: as part of its agreement with the biotech start-up, FCF's investment will be returned more than threefold if the drug candidate is commercialized, providing potential funds to support new research efforts.

Key research and research infrastructure achievements

- Built a biobanking infrastructure, which includes a new coordinator, service provider, and protocols.
- Supported research that obtained proof of concept of peptide vaccine and adoptive cell immunotherapy targeting the cancer driver.
- Supported research deepening understanding of FLC biology through analysis of FLC's transcriptome, proteome, and metabolome; including first studies at single-cell resolution.
- Supported research leading to identification of at least five steps in signaling pathways downstream from FLC's unique driver protein that might be targeted for drug therapy.
- Funded efforts resulting in the expansion of research model availability from one patient-derived xenograft line to three, as well as one cell line.

- Identified and engaged high-potential early-career investigators by funding multi-year fellowships.

Key publications

- *HHS Author Manuscripts* (2022): a roadmap of research progress in fibrolamellar cancer (co-authored by Medical and Scientific Advisory Board members, a FCF grantee, and FCF's Chief Scientific Officer).

- *eLife* (2022): a collaborative study that identified that targeting protein kinase A effects on translation is a potential treatment strategy for FLC (funded by the FCF).

Key operational achievements

- Hired a new full-time CEO and Research Program Director, and a part-time biobank coordinator and development consultant.

- Developed a major donor campaign aimed at funding new clinical trials and translation research.

- Increased donations from 2021 to 2022 by 64%, including over $4M in major gifts.

Key community achievements

- Revamped grant review process to include community reviewers (patients and/or caregivers) in every review.

- Established a Patient and Caregiver Advisory Board to guide key programs.

After the Grant

- With the support of the Fibrolamellar Cancer Foundation, the FLC Research Network is advancing significant progress toward treatments. FCF-funded researchers at Johns Hopkins University concluded a clinical trial that demonstrated the capacity of immune therapies to save lives in this cancer. Researchers tested a fibrolamellar-specific peptide vaccine plus dual immune checkpoint inhibitor (ICI) treatment, and showed that a strong immune response can be elicited against the driver protein of FLC. 25% of patients experienced major regression of their tumors, and a majority of patients experienced disease stabilization. This response rate to treatment is unprecedented in systemic FLC therapies.

- In a separate study funded by FCF at St. Jude Children's Research Hospital and published in *Cell Reports Medicine* in March 2024, researchers identified and isolated the gene for a T cell receptor with a high affinity for a FLC driver-specific neoantigen. When this TCR gene was transferred into *naïve* T cells, it conferred the ability to respond to the target peptide. Most importantly, the engineered T cells recognized and killed cells expressing the intact FLC driver protein. These promising results could inform the development of a trial of immune cell-based therapies.

- The organization's reach and collaborative impact continue to grow:

  - FCF committed over $5.4 million in research grants in 2023, a significant increase over its typical $1.0-1.5 million annual research commitment before receiving the CZI grant.

  - In 2023, the FCF extended their *working group* model of collaboration to a broader set of researchers and institutions, launching a Working Group on Targeted Therapies to promote new collaborations and data-sharing. Several potential new network collaborations have already been identified.

  - Nearly 70 investigators from the US and Europe shared their recent findings (under a confidential disclosure agreement) at FCF's Fibrolamellar Scientific Summit in April 2023.

  - FCF launched a new initiative to implement a DNA-encoded library screen of the disease's driver mutation to identify potential small molecule inhibitors in partnership with researchers from three academic institutions and a commercial company.

  - FCF initiated a collaborative effort to create the first consensus guidelines for the disease.

  - A paper in *NPJ Precision Oncology* (2023) funded and co-authored by FCF demonstrated that FLC incidence is likely five to eight times higher than previous estimates.

  - FCF held its second Patient and Research Summit in June 2024.

"The Rare As One experience has been absolutely transformative for FCF. The funding, trainings, and interactions with similar foundations have driven self-assessment and a broad series of changes. We're a more effective organization today and are continuing to evolve."

Kurt Losert
CEO, Fibrolamellar Cancer Foundation

Glut1 Deficiency Foundation

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To increase awareness, improved education, advocacy for patients and families, and support and funding for research.

Glucose Transporter Type 1 (Glut1) Deficiency Syndrome is a rare genetic metabolic disorder characterized by a deficiency of a protein required for glucose to cross the blood-brain and other tissue barriers, with an estimated prevalence of at least 1 in 24,000. Symptoms include seizures, body movement disorders, developmental delays, cognitive impairment, migraines, hemiplegia, and speech and language disorders. The disorder has no treatment.

The Glut1 community gathers at the Glut1 Deficiency Foundation Family and Scientific Convening in July 2022.

During the Grant Period

Impact Spotlight
When asked about Glut1 Deficiency Foundation's biggest accomplishments during the CZI grant period, Executive Director Glenna Steele emphasized the organization's work to bring people together.

From introducing and encouraging researchers to form new collaborations, to engaging the NIH around the idea of a Glut1 Transporter research initiative, the organization has worked to play a key role in advancing scientific progress.

Across all its efforts, Glut1 Deficiency Foundation centers patients, from conducting a community-wide survey of patients and family members to better understand disease experience and priorities for future organizational directions, to helping patients around the world connect with others.

Key research and research infrastructure achievements

- Launched quarterly Research Roundtables, which have initiated more than 15 collaborations among researchers.
- Launched a natural history study in 2022, with 30 patients enrolled by the close of the grant.
- Organized and created a Research Compass, a tool to share key publications with members of the Glut1 Deficiency community.
- Leveraged funds generated through participation in the University of Pennsylvania Orphan Disease Center's Million Dollar Bike Ride program, most recently supporting the development of a gene therapy candidate and drug repurposing projects.
- Pitched and secured NIH interest in exploring a cross-institute and -disease Glut1 Transporter research convening (reflecting the protein's role in diseases like Alzheimer's and diabetes) with the expected project start date in 2025.

Key publications

- *Epilepsia Open* (2020): an international consensus statement to facilitate diagnosis and elevate the standard of care for Glut1 Deficiency Syndrome (acknowledges Executive Director Glenna Steele as a contributor).
- *Neuroscience Insights* (2021): a study elucidating mechanisms and treatments for the myriad conditions involving the Glut1 protein (funded by Glut1 Deficiency Foundation).

Key operational achievements

- Received a $250,000 grant from the Patient-Centered Outcomes Research Institute for research capacity building.
- Hired a Science Director, part-time communications, development and operations coordinators, and a social worker consultant.

Key community achievements

- Conducted the Collective in Glut1 Deficiency Project, surveying 260 patients and family members of the community to better understand disease experience and priorities.
- Actively supporting efforts by Glut1 Deficiency patients and families around the world to create formalized organizations, including in the United Kingdom and Australia.
- Held monthly virtual meetings for Spanish-speaking community members.
- Launched virtual support groups for teen and adult patients.

Glut1 Deficiency Foundation Executive Director Glenna Steele meets with dedicated researchers in the Juan Pascual Lab at UT Southwestern for a lab visit and updates in August 2023.

Glut1 Deficiency Foundation team members and key research collaborators gather at the Global Symposium on Ketogenic Therapies in September 2023.

After the Grant

- In 2023, Glut1 Deficiency Foundation partnered with the International Neurological Ketogenic Society to host the 8th Global Symposium on Ketogenic Therapies, with a special focus on Glut1 as a prototype disease to better understand brain glucose metabolism and ketogenic therapies.
- The foundation also hosted a Research Ready Series to provide research fundamentals training to patients and families so they can be better prepared to participate in the research process and ensure efforts are patient-centered.
- In 2024, *Therapeutic Advances in Rare Diseases* published an article highlighting the road to patient-led research progress, authored by Glut1 Deficiency Foundation staff.

"The level of hope is just growing and growing, and it's organized hope… It's not just 'throw your wishes out there.' It's tangible, and that's huge."

Glenna Steele, MA
Executive Director, Glut1 Deficiency Foundation

Hermansky-Pudlak Syndrome Network

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To provide education and vital support programs to individuals and families with Hermansky-Pudlak syndrome while striving for improved care and innovative research on our journey to cure.

Hermansky-Pudlak syndrome (HPS) is a genetic metabolic disorder characterized by albinism, visual impairment and platelet dysfunction that results in prolonged bleeding. The most common HPS gene type can lead to development of inflammatory bowel disease, kidney insufficiency, and fatal pulmonary fibrosis. It affects 1 in 1,800 people in Puerto Rico, compared to 1-9 in one million worldwide, due to a founder effect. Presently, there are no treatments.

Attendees gather at the 2024 HPS Network Conference.

During the Grant Period

Impact Spotlight
The FDA's Center for Drug Evaluation and Research facilitates Patient-Focused Drug Development (PFDD) meetings, toward ensuring the patient voice is included in these important processes. When the opportunity arose for the HPS Network to elevate the patient voice and perspective in discussion with the FDA, the organization made ensuring all patients could participate a priority.

Because of a founder effect of Hermansky-Pudlak syndrome among people of Puerto Rican descent, many members of the HPS Network's community are either located in Puerto Rico and/or are Spanish-speaking. The HPS Network centered inclusivity throughout their approach to the PFDD meeting. First, the organization ensured the meeting was simultaneously translated in both English and Spanish — which the HPS Network believes to be a first for a PFDD. Recognizing connectivity issues in Puerto Rico, the organization invested in strengthening its patients' internet connections, hosting participation events, and also pre-recorded content for the meeting. Following the meeting, the organization supported the medical translation and simultaneous publication of its Voice of the Patient Report in both English and Spanish.

Key research and research infrastructure achievements
- Supported multidisciplinary clinics in Puerto Rico, with subspecialists volunteering to see HPS patients every 3-4 months.
- Developed and led CME-accredited program for 200 physicians in Puerto Rico on the use of ICD codes for HPS.
- Partnered with the Broad Institute of MIT and Harvard's Rare Genomes Project to conduct a study of HPS prevalence.

Key publications
- *Clinical & Translational Medicine* (2021): research describing CB1R and iNOS as effective antifibrotic strategies for HPS pulmonary fibrosis (funded by the HPS Network).

- *Molecular Genetics and Metabolism* (2022): a review of recent advances and insights into gene therapy for HPS pulmonary fibrosis, including insight on current gene therapy challenges (funded by the HPS Network).

- *Frontiers in Medicine* (2021): research demonstrating that automated computerized imaging analysis, which had been shown to measure fibrosis in mice, could also be applied to human samples; the technique offers important advantages compared to conventional methods (funded by the HPS Network).

Key operational achievements

- Hired key staff, including a Database Onboarding Manager, Director of Development, and an Assistant to the Director of Puerto Rico Affairs.

- Professionalized finance and accounting systems and policies, enabling planning for continued growth and sustainability.

Key community achievements

- Co-founded the board of the inaugural Research Program for the National Organization for Albinism and Hypopigmentation.

- Executive Director served as Chairperson of the Public Advisory Roundtable of the American Thoracic Society (ATS) and as the only patient representative on the ATS Board of Directors.

The Hermansky-Pudlak Syndrome Network is an advocacy organization for individuals and families affected by Hermansky-Pudlak syndrome.

After the Grant

- The HPS Network's efforts to host an inclusive and informative PFDD meeting have yielded positive results. A pharmaceutical company developing a new personalized platelet transfusion tool learned about this rare disease, characterized in part by platelet dysfunction, for the first time after attending the meeting. As a result, the company is as of June 2024 collaborating with the HPS Network to plan a potential clinical trial involving patients in Puerto Rico. This collaboration represents a significant step towards scientific advancements that could benefit individuals with uncontrolled bleeding.

- As of June 2024, the HPS Network is launching the Albinism International Databank, a global resource capturing patient-reported data of individuals with albinism including HPS and Chediak-Higashi.

Ashley Appell (left), of the Hermansky-Pudlak Syndrome Network, connects with fellow Rare As One Network Cycle 1 patient leader, Michael Raymond (right), of the Snyder-Robinson Foundation, at the Rare As One Network 2022 Meeting.

"It's knowing that you're not by yourself working on [building capacity], because you feel like a failure all the time: you go to bed every night without a drug, without a treatment, without a cure. To have…access to colleagues who are struggling and doing the same things as you was more life-changing and more affirming and gave us a breath of fresh air.."

On her experience as part of the Rare As One Network.

Donna Appell
Executive Director, Hermansky-Pudlak Syndrome Network

INADcure Foundation

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To support the development of treatments, including a cure, for Infantile Neuroaxonal Dystrophy (INAD) and other forms of PLA2G6-related neurodegeneration (PLAN).

Infantile Neuroaxonal Dystrophy (INAD) is one of three types of PLA2G6-associated neurodegeneration (PLAN), a rare neurodegenerative disorder caused by a mutation in the PLA2G6 gene. It appears within the first three years of life, presenting symptoms such as rapid motor and intellectual regression, low muscle tone, vision and autonomic nervous system problems, seizures, sleep apnea, developmental delays, loss of speech, and scoliosis. Life expectancy is 8-10 years. According to a recent prevalence study, this condition affects an estimated 4,000 children worldwide. There is no known cure or disease-specific treatment for INAD. Care is currently focused on managing symptoms and supporting quality of life.

Leena Panwala, president and co-founder of the INADcure Foundation, holds her daughter Ariya, who has the rare disease infantile neuroaxonal dystrophy (INAD).

During the Grant Period

Impact Spotlight
For the INADcure Foundation, serving the 150 known children in 20 countries diagnosed with Infantile Neuroaxonal Dystrophy INAD has always been the guiding priority. After years of concerted effort, patient and scientific members of the organization's community are energized by progress they've helped to drive toward a potential gene therapy for children impacted by this devastating, currently untreatable disease. By the end of the grant period, the INADcure Foundation and its partners were preparing to submit a pre-IND meeting request for a gene therapy candidate.

Throughout application development, the foundation operated as a central stakeholder, serving as the voice of the patient community in weekly working group meetings with research and industry partners, and in discussions around expectations of families involved in trials, research directions and costs.

And while much of their focus has been honed on bringing a gene therapy to clinic for patients, INADcure has kept their lens trained broadly, working with research partners to monitor for new scientific innovations that could be beneficial to the community, and planning for the long-term.

Key research and research infrastructure achievements

- Partnered with the Rare Genomes Project at the Broad Institute of MIT and Harvard to perform a prevalence study on INAD/PLAN, marking a significant milestone in research. When published, the study will list the foundation as a co-author.

- Initiated a partnership with researchers at Oregon Health & Science University to create a set of best practices for the care and management of individuals with INAD/PLAN. These clinical care guidelines have been submitted for publication, with the foundation as a co-author.

Key publications

- *eLife* (2023): researchers identified neuropathological mechanisms evolutionarily conserved in fly models, and used these features as biomarkers, testing 20 drugs targeting these pathways; identified four potential drugs that alleviate neurodegenerative phenotypes in INAD flies and INAD patient-derived neural progenitor cells (co-authored by the INADcure Foundation).

Key operational achievements

- Hired an Executive Director, as well as a range of staff and consultants focused on operations, development, social media, digital fundraising, gene therapy efforts, and translation.

- Improved digital tools, including an updated website, CRM, and fundraising platforms.

Key community achievements

Organized and hosted the first International Scientific Conference on INAD and other forms of PLAN in 2021 with 185 participants from 25 countries.

Amanda Hope (left) and Leena Panwala (right), of the INADcure Foundation, connect with fellow attendees at the Rare As One Network 2022 Meeting.

After the Grant

The INADcure Foundation continues to advance its gene therapy program through preclinical studies, with the goal of securing FDA approval for a clinical trial in 2025. Central to this program, the foundation has formed crucial partnerships for production of vectors and gene therapy materials. As the program's sponsor, the foundation's ability to progress is directly linked to fundraising efforts, and they devote substantial time to cultivating relationships and supporting INAD community-driven fundraising activities.

"From the onset, we approached our participation in Rare As One with a profound sense of responsibility and gratitude. It was a 'once-in-a-foundation's-lifetime' opportunity to strategically invest in core operations, enabling us to lay the groundwork for long-term sustainability for continued impact. Now… we've shaped an organization that's not just a driving force for INAD research, but also an attractive partner for biotech and institutions looking for reliability and a track record of meaningful collaboration.."

Amanda Hope, MPA
Operations Consultant, INADcure Foundation

KAT6 Foundation

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To support individuals and their families who are living with KAT6A and KAT6B syndromes around the world.

KAT6 syndromes are ultra-rare diseases caused by mutations in the KAT6A and KAT6B gene, with common symptoms including global developmental and speech delays, feeding difficulties and hypotonia. For the approximately 500 people diagnosed with KAT6 gene variants, treatment is directed toward the specific symptoms that are apparent in each individual, but no specific medications for KAT6 syndromes exist.

Peter Najm, who has the rare disease KAT6A Syndrome, presented his poster about genes and DNA to school management alongside his siblings and parents.

During the Grant Period

Impact Spotlight
When the organization led by Emile Najm received funding to join the Rare As One Network in 2019, it was known as the KAT6A Foundation. Since its founding in 2017, the organization and its small, ultra-rare KAT6A community had struggled to attract industry interest or investment.

At an early patient-research convening organized by the foundation — for some scientists, their first opportunity to meet a patient with KAT6A syndrome — a researcher encouraged the organization to expand its remit to include KAT6B syndrome, a disease with many significant overlaps to KAT6A syndrome. Though an exciting chance to approximately double the patient community and expand the organization's impact, a broadening of scope was not without challenges, including financial costs and mission expansion requiring greater investment and expertise.

Nevertheless, over the next several years, the KAT6A Foundation would commit to making these investments, gradually building relationships and trust. By the end of the grant period in 2023, the officially-renamed KAT6 Foundation represented a combined registered patient community of 187, with KAT6B syndrome representation on its board, and a goal of ultimately achieving 50% representation from KAT6A and KAT6B leaders.

For the KAT6 Foundation, this value of inclusion has remained central throughout their work. Additionally, the organization has broadened its international scope by involving researchers in Europe, and also expanding its reach to include patients in Australia.

Key research and research infrastructure achievements

- Provided seed funding to support creation of an iPSC line that covers many variations of the KAT6A and KAT6B gene mutations.
- Created a sharing policy among members of the collaborative research network, to promote open science.
- Supported research that confirmed the effectiveness of a vitamin therapy, utilizing fibroblasts obtained from patients.

Key publications

- *Human Genetics and Genomics Advances* (2021): a cross-disorder study describing 19 novel episignature disorders and comparing findings alongside 38 previously established episignatures for a total of 57 episignatures associated with 65 genetic syndromes, providing insight into the molecular etiology of Mendelian conditions like KAT6 (co-authored by KAT6 Foundation co-founder Natacha Esber).
- *Genes* (2022): a study on the pathogenic variants of the KAT6A gene, and the therapeutic effectiveness of epigenetic modulators and mitochondrial boosting agents (funded by the KAT6 Foundation).

Key operational achievements

- Hired a Fundraising Manager, who helped increase funds raised from $75,000 in 2019 to close to $375,000 in 2022.
- Hired a research coordinator in Australia.

Key community achievements

Expanded patient and research communities, growing conference attendance from 19 families and three speakers in 2018 to 180 attendees and 17 researchers/speakers in 2023.

After the Grant

- In 2023, the KAT6 Foundation established a committee to study patient mortality, with a goal to guide parents in understanding how best to adjust to KAT6 disorders and prevent suffering among the most vulnerable members of the patient community.
- Additionally, the foundation expanded the availability of its KAT6 Handbook, a resource for parents, teachers, doctors and caregivers, to seven languages, including Arabic, French, Italian and Portuguese.
- The foundation continues its work to engage both KAT6A and KAT6B patients. In 2024, the KAT6A Patient Registry was expanded to include all KAT6 families, and renamed accordingly, to the KAT6A/KAT6B Patient Registry.
- In June 2024, the foundation convened its community for the 5th International KAT6A & KAT6B Conference, attended by more than 70 families and 18 researchers.

Angie Serrano (left) and Saylor Williams (right), of Boston University, attend the Science in Society 2023 Meeting as research partners of the KAT6 Foundation. Dr. Serrano leads a research program that uses iPSC-derived models and zebrafish to understand cardiovascular and neurodevelopmental manifestations in rare disorders.

"Families are close to my heart. Witnessing someone in pain reminds me of my son's struggles. I am determined to spare others from experiencing such hardships."

Emile Najm
Co-Founder and CEO, KAT6 Foundation

KIF1A.ORG

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To improve the quality of life of families affected by KIF1A Associated Neurological Disorder (KAND), and to relentlessly drive research initiatives leading to a cure.

KIF1A Associated Neurological Disorder (KAND) is a progressive, neurodegenerative disorder caused by mutations in the KIF1A gene. KAND's symptoms include severe epilepsy, brain and optic nerve atrophy, spastic paraplegia, intellectual disability and autism. There are 550 known patients, for whom there is no treatment or cure, only symptom management including for muscle pain and spasticity, peripheral neuropathy, and seizures.

KIF1A.ORG Founder Luke Rosen, his wife Sally and his daughter, who has the rare disease KIF1A Associated Neurological Disorder.

During the Grant Period

Impact Spotlight
KIF1A.ORG was founded in 2016 with a patient community of 10 and only a few interested researchers. Recognizing the need to create a more robust community, KIF1A.ORG set its sights on building an army of patients and scientists.

As of 2022, and as a result of targeted efforts to identify and connect other patients, the patient community had grown to more than 500 people. Simultaneously, KIF1A.ORG convened a collaborative research community of over 160 members from 60 academic institutions and industry partners, breaking down research silos, and serving as a convener, catalyst, and funder of global KAND research.

To support this collaborative research network, KIF1A.ORG created a robust toolkit that is openly available to the scientific community, including biotech and pharma. The tools include a patient registry, detailed natural history and genotype/phenotype studies, iPSC lines of mutations with diverse phenotypes, animal models, and more. In addition, KIF1A.ORG worked to bring together the collaborative research network in regular research roundtables where real-time info and data-sharing take place. By the end of the grant period, KIF1A.ORG's research roundtable model had been replicated by many other organizations in the Rare As One Network.

In spring 2022, the foundation launched the **K**IF1A **O**utcome measures, **A**ssessments, **L**ongitudinal **A**nd endpoints (KOALA) Study led by Dr. Wendy Chung of Boston Children's Hospital, which will build upon the KIF1A.ORG-supported natural history study and the data of its hundreds of enrolled patients toward development of KIF1A-appropriate clinical trial endpoints to enable future treatment approval.

Key research and research infrastructure achievements

- Invested and served as a catalyst in several parallel therapeutic development projects, including toward gene therapy, hypothesis-driven small molecule testing, and high-throughput screening.

Families, researchers, and clinicians at the 2023 KAND Family and Scientific Engagement Conference in New York.

- Founding family collaborated with the n-Lorem Foundation and Dr. Wendy Chung to develop and deliver an antisense oligonucleotide (ASO) therapy for their daughter.

Key publications

- *Science Advances* (2021): a study of a KAND-associated missense mutation revealed that an uncharacterized structural element in the kinesin motor domain is critical for motor function and human health (funded and supported by KIF1A.ORG).
- *Human Mutation* (2021): a study describing four patients, which expanded the phenotypic characteristics of individuals with KIF1A pathogenic variants to include clinical features commonly seen in individuals with classic Rett syndrome.

Key operational achievements

Hired a Science Director and a Research Engagement Director.

Key community achievements

- Provided a platform to exchange information and perspectives between patients and researchers.
- Created community resources, including a KAND Research Network interview series.
- Hosted the 2022 Virtual Family and Scientific Engagement Conference.

After the Grant

- KIF1A.ORG collaborated with Dr. Rebecca Shi of Stanford University to develop a research laboratory course for undergraduates in Stanford University's Department of Biology focused on KAND. Recognizing the importance of patient perspectives in the study of the disease, the course included a session led by parents of KAND patients. KIF1A.ORG also developed science communication projects with Masters' students in Dr. Lili Yamasaki's course in biotechnology at Columbia University, with a focus on disease associations and mutation heterogeneity.
- Enrollment in the ASCEND Natural History Study and KOALA endpoint-enabling study resulted in an updated natural history study publication in *Genetics in Medicine* in August 2024, and a report on vision led by Dr. Aliaa Abdelhakim in the *American Journal of Ophthalmology* in December 2023.
- KIF1A.ORG's 2023 conference convened patient families, researchers, and clinicians to discuss key symptom areas for KAND patients. Key outputs were expanded preclinical vision research at MCRI led by Drs. Simran Kaur and Wendy Gold, and a multilingual speech and communication study led by Dr. Angela Morgan, with over 50 participants to date.
- A research group led by Dr. Wendy Chung of Boston Children's Hospital published a Brief Communication in *Nature Medicine* in August 2024, reporting on the use of an antisense oligonucleotide therapy in a KAND patient for the first time. The early findings indicated the ASO was safe and well-tolerated over the 9-month treatment, with demonstrated improvement in most outcome measures.
- KIF1A.ORG was highlighted in news coverage related to the ASO treatment and how the approach could be applicable to other patients and diseases, in publications including *USA Today*. A second KAND patient received her first ASO treatment in May 2024.
- KIF1A.ORG Research Network members secured funding to expand KIF1A projects in key areas including KIF1A protein structure, patient-centered model development, and gene-based therapy research.
- KIF1A.ORG formalized its International Ambassador program to identify and support KAND patients across the globe, with representatives in Canada, the UK, Spain, France, Germany, Italy, Poland, Romania, Australia, and China.

"The thing to work on isn't to silo [advocacy and science], but to really have the strongest bridge ever, so anybody can walk across… our scientific community members can walk across that bridge and be fully engulfed in the community, and our community members can walk across the bridge and be completely aware of what's going on with the science."

Luke Rosen
Co-Founder, KIF1A.ORG

Lennox-Gastaut Syndrome Foundation

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To improve the lives of individuals impacted by Lennox-Gastaut Syndrome (LGS) through advancing research, awareness, education, and family support.

Lennox-Gastaut Syndrome is a severe form of epilepsy that typically becomes apparent during infancy or early childhood, impacting approximately 50,000 people in the United States. Symptoms include seizures, cognitive dysfunction, delays in reaching developmental milestones, behavioral problems, and premature mortality. Approximately 70% of cases have a known cause, which can include trauma before or during birth, abnormal brain formation, and genetic factors. There is no cure, and current treatment options focus on controlling seizures.

Lennox-Gastaut Syndrome (LGS) Foundation staff joined members of its professional advisory board, scientists, and clinicians for a quick photo op in front of the American Epilepsy Society backdrop at AES 2018.

During the Grant Period

Impact Spotlight

Since its founding in 2008, the Lennox-Gastaut Syndrome Foundation's priority has been to improve the lives of individuals impacted by LGS. Initially, this meant a focus on supporting projects that could alleviate LGS' characteristic, devastating seizures. But, based on deep engagement with the patient community, the organization's leaders recognized that true impact for patients would require far more, including addressing the disease's communication, behavioral and socialization manifestations. Doing this would require going beyond symptom management, to identify disease-modifying therapies that targeted LGS' underlying biology.

With this goal in mind, in 2021, the LGS Foundation convened a two-day Meeting of the Minds, bringing together more than 200 researchers and patient families. There, these stakeholders aligned on priority next steps, including to advance research focused on understanding the epileptic network of the disease based on an EEG biomarker, and expand the availability of a learning health system for LGS.

Though much work remains to advance these priorities, the foundation has observed a meaningful shift in the research community, toward recognition of the insufficiency of current treatments, and expanded study of the EEG biomarker. And throughout, the LGS Foundation has remained at the center, working to lay the groundwork for future clinical trials grounded in meaningful, patient-identified endpoints.

Key research and research infrastructure achievements

- Supported research, including by providing patient data, leading to the identification of a previously unknown EEG biomarker.
- Funded the first-ever LGS mouse models, which are being leveraged in research to explore potential treatments that target the LGS large-scale neural network.

Key publications

- *Annals of Neurology* (2021): a double-blind, randomized study of continuous centromedian thalamic nucleus deep brain stimulation (DBS) in patients with LGS, to assess efficacy and safety; 50% of participants recorded seizures reduced by half at the study exit, evidence of the treatment effect (funded by the LGS Foundation).
- *Seizure* (2022): a follow-on publication on DBS, evaluating cognition, adaptive skills and epilepsy disability/severity in patients with LGS undergoing treatment (funded by the LGS Foundation).
- *Epilepsy & Behavior* (2020): a paper on the psychosocial family impact of epilepsies (co-authored by Executive Director Tracy Dixon-Salazar; survey design and distribution supported by the LGS Foundation).

Key operational achievements

- Doubled internal capacity, growing staff size from four to eight.
- Implemented a matching donation tool, which led to an 85% increase in donation matching by corporations.

Key community achievements

- Expanded Patient Advisory Council membership.
- Grew the LGS Community of Support to reach 11,000 members.

After the Grant

- In the fall of 2023, the LGS Foundation hosted its second Meeting of the Minds event, where more than 150 stakeholders discussed advancements in clinical research for LGS.
- As of June 2024, the Foundation is collaborating with researchers on a new comparative treatment study that examines two primary approaches: medication and surgery.
- The foundation continues to work to spread awareness of LGS, including through participation in a *Lifetime TV* special airing in 2023, and a follow-up article published by *Today* in 2024.
- The foundation plans to launch a natural history study in 2024.

Tracy Dixon Salazar (center), Executive Director of the LGS Foundation, connects with a fellow attendee at the Chan Zuckerberg Initiative Rare As One Network 2022 Meeting.

"We believe that rising tides lift all our boats, that many hands make lighter work for us all, and that we will find the cures faster if we share our learnings and our tools with each other."

On the value of learning with a network of similar organizations.

Tracy Dixon Salazar, PhD
Executive Director, LGS Foundation

Lymphangiomatosis & Gorham's Disease Alliance

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To connect patients and families to peers and networks of care, partner to advance new research, and educate the medical community to help all people navigating complex lymphatic anomalies have hope for a healthier tomorrow.

Complex lymphatic anomalies (CLA), are a group of rare diseases characterized by abnormal growth of lymphatic vessels. Prevalence of CLAs vary, but all are life-threatening diseases with highly variable clinical and biological characteristics, making diagnosis, treatment, and research extremely challenging. There is no standard approach for treatment for CLAs, with a range of medications prescribed aimed at reducing symptom burden.

Louise Murgia, Director of Operations of the LGDA, listens to presentations from fellow patient leaders at the Rare As One Network 2022 Meeting. Louise was hired during the Rare As One Network Cycle 1 grant period.

During the Grant Period

Impact Spotlight

In 2019, the LGDA joined the Rare As One Network as a small organization managing its community and donor base via hard copy documents. Today, the LGDA's efforts include working to grow and refine its international patient registry, making the database more relevant to the organization's patient and scientific communities.

Moreover, the LGDA has become a leading player in international collaborations focused on advancing global scientific progress for complex lymphatic anomalies (CLA). Through international partnerships with LGDA-Europe and the Lymphatic Malformation Institute (LMI), the LGDA has expanded its global footprint, a collaborative approach that has led to efficiency and opportunity, including through shared advisory councils, joint meetings, and infrastructure.

Key research and research infrastructure achievements

- Tripled the size of its research network to include 200+ individuals from a range of disciplines and more than 25 countries.
- Partnered with AllStripes, Inc. to perform natural history studies for the four diseases under the CLA umbrella.
- Supported research leading to the identification of Angiopoietin 2 (ANG2) as the first CLIA-certified biomarker for Kaposiform Lymphangiomatosis, a CLA.

Key publications

- *Frontiers of Cell and Developmental Biology* (2021): evaluation of alterations of immune cells in Gorham-Stout disease, a CLA (funded by LGDA).
- *Lymphatic Research and Biology* (2022): a study of how dietary fatty acid composition impacts the potential for lymphatic dysfunction and chyle accumulation in CLA (funded by LGDA).

Key operational achievements

- Made key hires to expand organizational capacity, including an Executive Director, a Director of Operations, and a Director of Development.
- Built a professional CRM.

Key community achievements

- Increased patient involvement in research by featuring patient perspectives at the 2021 LGDA-LMI International Conference on Complex Lymphatic Anomalies, holding meet-and-greets with scientists and patients, and providing lay summaries of all key scientific developments to the patient community.
- Created a patient guide available in nine languages.

After the Grant

- In 2024, The Lymphangiomatosis & Gorham's Disease Alliance (LGDA) joined the National Commission on Lymphatic Diseases (NCLD), working alongside a diverse group of researchers, doctors, and other stakeholders who treat and study CLA.
- As of June 2024, the alliance has further expanded its engagement with the patient and family community, growing registry participation to over 500 patients.

"[This collaboration] is something that's going to help us sustain this progress over time. We're better together. If we can get together, set priorities and set a structure… we'll be much better servants for our global communities as we move forward."

On the partnership between LGDA, LGDA-Europe and LMI.

Mike Kelly, MD, PhD
Executive Director, Lymphangiomatosis & Gorham's Disease Alliance

Li-Fraumeni Syndrome Association

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To provide information, advocacy, and support services for individuals and families with Li-Fraumeni Syndrome, and support a consortium of researchers, medical providers, and caregivers to further research and promote optimal care for the LFS community.

Li-Fraumeni Syndrome (LFS) is an inherited condition characterized by increased risk for certain types of cancer, caused by pathogenic TP53 germline variants. Symptoms ultimately include a range of cancer types such as breast, brain, sarcoma, leukemia and adrenocortical carcinoma. There is no treatment or cure.

Li-Fraumeni Syndrome Association hosts its 2nd LFSA Youth Workshop. The group represents youth from six countries who spent an afternoon touring Boston, MA, and learning at Dana Farber Cancer Institute.

During the Grant Period

Impact Spotlight

Since its founding in 2010, the Li-Fraumeni Syndrome Association has centered patient concerns in all of its work. For female patients, who have a risk as high as 90% of developing cancer in their lifetime, this particular concern is paramount.

In 2022, the association convened a scientific symposium, which included breakout sessions focused on connecting clinicians and researchers with small groups of patients. In these discussions, Dr. Judy Garber, a member of the LFSA Medical Advisory Board, heard again and again concerns from patients about the recurrence of breast cancer. Recognizing this patient-identified need, Dr. Garber partnered with Dr. Maria Isabel Achatz, Co-Chair of the LFSA's Scientific Advisory Board, to launch a research project focused on more deeply understanding breast cancer recurrence in LFS patients, with the hope of identifying predictive factors and advancing progress toward treatment for these patients.

Key research and research infrastructure achievements

- Jointly convened Scientific and Medical Advisory Boards for an in-person meeting of 12 experts from around the world focused on aligning on current and future research priorities.

- Secured the NIH National Cancer Institute (NCI) as a core partner, leading NCI to host the 6th International LFS Scientific Symposium.

Key publications

The Lancet Regional Health: Americas (2022): a study led by Maria Isabel Achatz, Co-Chair of the LFSA's Scientific Advisory Board, explored the cost-effectiveness of cancer surveillance for patients with LFS in Brazil, where there is a higher prevalence of the disease due to a founder mutation; the LFSA is leveraging the results as a foundation for engaging patients in the region.

Key operational achievements

Onboarded a Communications Director, additional development volunteers, and a professional grant writer.

Key community achievements

- Collaborated with the EveryLife Foundation to create a policy pitch for biotech companies to sponsor an ICD-10 code for LFS.

- Supported 11 international chapters, including by creating social media accounts for chapters, recruiting new patients, translating materials, and hosting international chair meetings.

Li-Fraumeni Syndrome Association hosts its 2nd LFSA Youth Workshop. The group represents youth from six countries who spent an afternoon touring Boston, MA, and learning at Dana Farber Cancer Institute.

After the Grant

- The foundation is collaborating to establish a TP53 biobank to study LFS through the Abramson Cancer Center at Penn Medicine.

- In 2023, the foundation continued to expand their International Youth Workshop program and brought together 23 young people and their families at the prestigious Memorial Sloan Kettering Cancer Center in New York City for a two-day event of fun, education and friendship.

- LFSA's robust network of international chapters continue to work to reach and provide support to those with LFS in their communities.

"Our purpose remains powerful. I know you, like me, are determined to put an end to our kids and our family members being diagnosed with cancer. My most fervent desire is that one day LFS will be treated as a chronic condition."

From the LFSA's 2023 Annual Impact Report.

Jenn Perry
President and Co-Founder, Li-Fraumeni Syndrome Association

NEC Society

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Dedicated to building a world without necrotizing enterocolitis (NEC) through research, advocacy, and education.

Necrotizing enterocolitis (NEC) is an intestinal disease primarily affecting premature and medically fragile infants by causing an inflammatory process that can lead to severe damage or death of the baby's intestinal tissue. Every year in the US, thousands of infants are diagnosed with NEC, and hundreds tragically die from the disease. Many of the infants who survive NEC struggle with lifelong neurological and nutritional complications.

Two hundred participants from nine countries and 35 U.S. states gather at the NEC Symposium in 2023, which focused on advancing research and quality care.

During the Grant Period

Impact Spotlight
Though necrotizing enterocolitis is a leading cause of infant mortality in the United States, major research questions remain, and few people have heard of NEC.

The NEC Society is working to change this, assembling the research and care community, and developing critical research infrastructure. In 2019, the organization partnered with Dr. Misty Good of the University of North Carolina Children's to launch the NEC Biorepository. The NEC Biorepository includes many of the leading research institutions in the US: University of North Carolina, Texas Children's, Indiana University, Medical University of South Carolina, Oregon Health & Sciences University, Oklahoma Children's Hospital, UC Davis Children's Hospital, and Cornell Medicine. The primary aim of the NEC Biorepository is to support the discovery of a biomarker for NEC and efforts to uncover how to prevent the disease.

As the NEC Society has worked to enable sustained research progress in NEC, the organization has also addressed immediate needs in the community. Based on early evidence that probiotic supplements might lower NEC risk in premature infants, the organization convened researchers to develop and publish a statement and toolkit providing guidance on the use of probiotic supplements in the NICU to prevent NEC. The toolkit, the first of its kind for the disease, is available to anyone providing NICU care for NEC.

Key research and research infrastructure achievements

- Launched the Research Incubator, a closed space for the NEC community to discuss key questions and collaborate on research projects; includes more than 100 active members and a young investigator mentorship program; modeled after an approach developed by another RAO Network grantee.
- Developed a community-informed research agenda, focusing on 20 prioritized topics (from 150).
- Secured additional CZI funding through the Patient-Partnered Collaborations for Single-Cell Analysis of Rare Inflammatory Pediatric Disease grant program to apply single-cell methodology to understand the cellular and molecular pathophysiology of neonatal NEC.

Key publications

JAMA Network Open (2021): an analysis of trends and racial and geographic disparities in NEC-IMR from 1999 to 2020 (co-authored by Executive Director Jennifer Canvasser).

Key operational achievements

Hired five paid employees, including a Research Director and a Development Director.

Key community achievements

- Launched a Nurse Ambassador program, engaging 100+ nurses dedicated to bringing NEC awareness and resources to their unit and patient-families.
- Launched the NEC Society Champions program, an industry/nonprofit roundtable and corporate giving program that unites companies and organizations that support and share the NEC Society's vision of a world without NEC.

After the Grant

- The NEC Society launched a patient registry in 2023, enabling the capture and use of patient data for research. The NEC Registry was developed by Co-PI's Erin Pryor (NEC Society) and Allison Rose (Emory University). Despite a major setback of the organization's selected registry company going out of business in January 2024, the NEC Society, with feedback and encouragement from others in the RAO Network, selected a new host platform, with plans to relaunch to the NEC community in early 2025.
- NEC Society leadership were among co-authors on two patient-centered publications, one on long-term outcomes and life-impacts of necrotizing enterocolitis (*Seminars in Perinatology*, 2023), and another on contemporary use of prophylactic probiotics in NICUs in the United States (*Journal of Perinatology*, 2024).
- With work underway to educate their patient community about opportunities to contribute to the organization's biorepository and participate in research, the NEC Society continues to work toward establishing standards of care for the disease and inspiring more early career clinicians and scientists to join the international movement of building a world without NEC.
- NEC Society is part of the University of Arizona College of Nursing-led research team awarded $1.9 million by the Department of Health and Human Services in October 2024. The award will fund the distribution of NEC-Zero, a tool to support neonatal ICUs to prevent, diagnose and treat NEC.
- NEC Society Founder and Executive Director, Jennifer Canvasser, was one of seven Patient Advocacy Honorees named to the *Fierce Pharma* 'Fierce 50 of 2024', a list of people and companies advancing change in healthcare, pharma and biotech.

Members of the NEC Society community gather at the NEC Symposium in 2023. Jennifer Canvasser (center left), Founder and Executive Director of the NEC Society, holds a photo of her son, Micah, who died due to complications of NEC in December 2012.

"As we work to prevent this absolutely devastating disease, it fills my heart when I hear families saying, 'I'm so glad I'm not alone'... because I felt so alone when Micah was diagnosed and died. Now, families and clinicians have a community and a place that they never had before, and they belong to something that's bigger than their individual experience, trauma, or work; they're part of a movement."

Jennifer Canvasser, MSW
Founder and Executive Director, NEC Society

Project 8p Foundation, *of the* Commission on Novel Technologies for Neurodevelopmental Copy Number Variants

Project 8p Foundation
project8p.org

Ring14 USA
ring14usa.com

Dup15q Alliance
dup15q.org

To empower a unified community for chromosome 8p heroes for a meaningful life today while accelerating treatments for tomorrow.

Chromosome 8p disorders affect approximately 550 patients around the world, with most cases de novo. Symptoms are wide-ranging and vary in severity, and include intellectual disability, congenital heart defects, epilepsy, autism, GI dysfunction, orthopedic and muscular conditions, agenesis of corpus callosum, and sensory processing disorders. There are no current treatments.

The leaders of the Commission for Neurodevelopmental Copy Number Variants (CNVs), left to right: Yssa DeWoody, Bina Maniar, Vanessa Vogel-Farley -attend the Chan Zuckerberg Initiative Rare As One Network 2022 Meeting.

During the Grant Period

Impact Spotlight
When Project 8p Foundation Founder Bina Maniar considered applying for Rare as One Cycle 1, she saw the opportunity as a chance to make progress not just for those with chromosome 8p disorders, but for the broader neurodevelopmental copy number variants (CNVs) community, and ultimately, beyond.

Maniar joined forces with Yssa DeWoody of Ring14 USA, and Vanessa Vogel-Farley of the Dup15q Alliance, and approached CZI's grant to the Project 8p Foundation with a shared question and goal: could first-of-its-kind collaboration drive progress for these complex disorders?

Toward generating proof positive, the three leaders launched the Commission for Neurodevelopmental Copy Number Variants (CNVs), with the hypothesis that, though their respective brain development diseases affected different chromosomes, collaborative study would reveal converging biology, and in turn, opportunities for common research progress toward treatments and cures.

By the end of the grant, the Commission's work had begun to bear fruit. What would have been disparate, disease-specific data streams have been consolidated into one centralized repository, a wide-ranging resource that has attracted interest from industry and other disease efforts, alike, and all with patient interest and need at the center.

Key research and research infrastructure achievements

- Built the collaborative Copy Number Variants (CNVs) Data Portal, a workspace where approved investigators can access biospecimens, clinician- and patient-reported data and sequenced genomes.
- Launched a collaborative partnership with Global Genes/RARE-X to host the CNVs Data Portal for longitudinal data collection and support regulatory and operational needs.
- Advanced open science partnership with Illumina to provide long read sequencing, RNA seq, DNA methylation and analysis to support molecular characterization of variants and the identification of potential therapeutic targets associated with neurodevelopmental chromosome disorders.

Key publications

American Journal of Human Genetics (2022): a roadmap to improving outcomes for patients with neurodevelopmental copy-number variants (authored by the Commission on Novel Technologies for Neurodevelopmental Copy Number Variants).

Key operational achievements

- Developed a fundraising model for support of the Commission for Neurodevelopmental CNVs.
- Executed a Charter among all Commission members, aimed at supporting a Team Science approach for effective collaboration.

Key community achievements

Hosted two conferences: a virtual conference and a joint in-person Family & Science conference, bringing together Project 8p, Ring14 USA and Dup15q Alliance families and stakeholders.

After the Grant

The Commission and its leaders are working to identify additional research opportunities and approaches, all in the close patient-centered partnership that has been so central to their progress thus far. The Commission will be co-hosting the "Uniting Chromosomal Disorders for Translational Breakthroughs in Rare Disease THINK TANK" in 2025 aimed at advancing its foundational goals.

In summer 2021, Project 8p, Ring14 USA, and Dup15q Alliance hosted the Moving Mountains joint conference, the first time the three nonprofits collaborated to reflect similar clinical phenotypes and goals. The CNV Commission brought together scientists actively co-authoring a roadmap published in the American Journal of Human Genetics*, doctors, patients, and their families to mix and mingle, share sorrows, and collect data for the database.*

"When you truly collaborate in an open science format and leveraging team science, it's powerful for innovative breakthroughs."

Bina Maniar, MBA
Founder and CEO, Project 8p Foundation

PSC Partners Seeking a Cure

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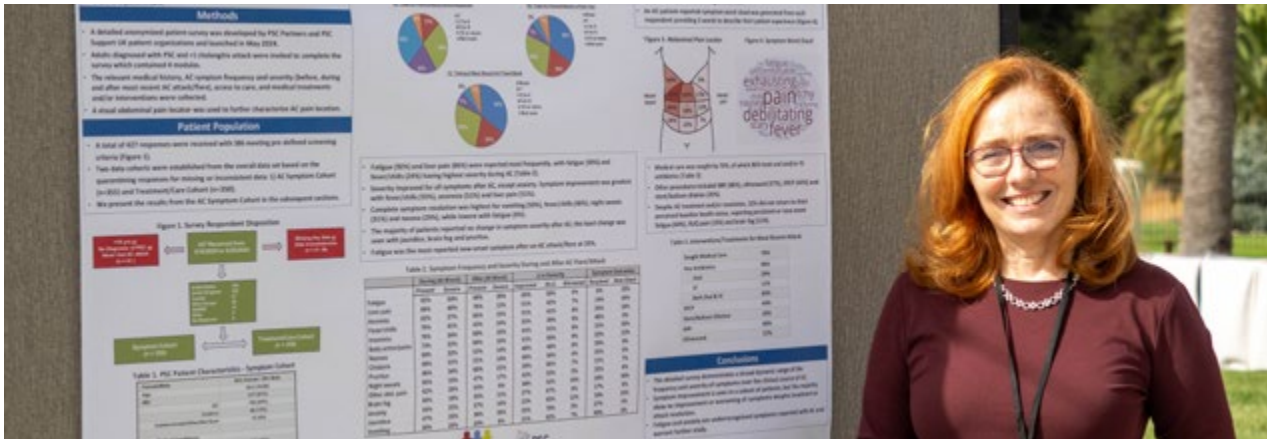
To drive research to identify treatments and a cure for primary sclerosing cholangitis (PSC), while providing education and support for those impacted by this rare disease.

Primary Sclerosing Cholangitis (PSC) is a rare disease that has no known cause and that damages the bile ducts inside and outside the liver, resulting in fibrosis and cirrhosis of the liver and possibly liver failure, with some patients requiring a liver transplant. Over 30,000 patients in the United States are estimated to have PSC. Though some medications and procedures can relieve symptoms, there is no approved treatment to slow down disease progression and there is no cure.



Mary Vyas, PSC Partners' Vice President of Strategic Initiatives, presents the results of a multinational patient survey during a poster session at the Chan Zuckerberg Initiative Science in Society 2024 Meeting.

During the Grant Period

Impact Spotlight
For PSC Partners Seeking a Cure, advancing progress toward treatments and cures for all PSC patients begins with leaving no patient behind. At the center of the organization's efforts is a commitment to break down barriers, transcend borders, and engage in non-traditional research partnerships and collaborations, while maintaining the growing patient community at its center.

In 2022, PSC Partners was named a Patient Organization Primary Investigator in a $2 million, 4-year grant from CZI (Patient-Partnered Collaborations for Single-Cell Analysis of Rare Inflammatory Pediatric Disease). Together with Canadian researchers and clinicians from the University Health Network, Hospital for Sick Children and the University of Toronto, PSC Partners is leveraging international collaboration to help understand the cellular dynamics of PSC and to identify potential cellular targets for effective therapies. Specifically, the international research team will explore the connection between PSC and comorbid inflammatory bowel disease (IBD), an important patient research priority.

One of the organization's key initiatives has been convening patients, researchers, psychologists and social scientists for the PSC Partners Symptom Assessment Project to develop three PSC-specific, symptom-focused, regulatory-grade Patient-Reported Outcome Measures for use in clinical trials and research studies.

PSC Partners launched an International Collaborative Research Network (ICRN), broadening its research community to draw international scientific expertise and develop patient-prioritized research.

Key research and research infrastructure achievements

- Hosted a Patient-Focused Drug Development Forum with the FDA in October 2020, developing a Voice of the Patient Report as a summary of the input shared by patients and their caregivers during the meeting and presenting a poster of findings from the meeting at the 2021 American Association for the Study of Liver Diseases (AASLD) Liver Meeting.

- Hosted 10 webinars focused on patient education and engagement in research, with focus groups to capture needs, questions and priorities voiced by the patient community, leading to the development of a Strategic Research Plan.

PSC Partners Seeking a Cure staff attend the 2024 American Association for the Study of Liver Diseases (AASLD) Liver Meeting in San Diego, CA.

- Designed WIND-PSC, a global, multi-center longitudinal observational cohort study and database aiming to enable the development of an appropriate real-world data comparator cohort to serve as an external control for interventional clinical trials in PSC.

Key publications

- *Hepatology Communications* (2020): a systematic review of patient-reported outcomes in Primary Biliary Cholangitis and PSC, and the instruments used to measure them (co-authored by Founder and CEO Ricky Safer and Registry Director Rachel Gomel).
- *Hepatology Communications* (2022): a study demonstrating that spatial transcriptomes combined with additional RNA sequencing can refine the localization of gene content and cell lineages in the search for antifibrotic targets (funded by PSC Partners Seeking a Cure).

Key operational achievements

- Strengthened development efforts, including creating a development assessment and plan, and hiring a Development Director.
- Expanded to two full-time research staff: Chief Scientific Officer and Manager of Research Programs.

Key community achievements

- In response to patient-identified needs, raised $4M+ in support from the PSC community for the launch of the WIND-PSC study and the Symptom Assessment Project.
- Hosted series on Embracing Diversity in PSC, and joined The Rare Disease Diversity Coalition's Patient and Caregiver Committee and Clinical Trials Committee.

After the Grant

- In September 2023, PSC Partners hosted the first of two in-person scientific convening of the PSC Partners International Collaborative Research Network (ICRN). The gathering featured in-depth presentations and discussions between 56 interdisciplinary experts from North America and Europe.
- In June 2024, PSC Partners launched the WIND-PSC study, a research effort aimed at accelerating the development and approval of treatments for PSC.
- In July 2024, PSC Partners hired an Executive Director with extensive nonprofit experience.
- PSC Partners staff, community members and research partners continued to contribute to research progress, including:
  - *Journal of Hepatology* (2024): a single-cell, single-nucleus and spatial transcriptomics study supported with PSC Partners patient funding and patient collaboration, to describe interactions between the tissue microenvironment, cellular identity, and immunological function underlying PSC and developing a framework for investigating the drivers of PSC and uncovering precision medicine targets for possible therapies.
  - *Hepatology Communications* (2024): collaborative publication generated from PSC Partners Registry and PFDD survey data and co-authored by PSC Partners team and external investigators on insights on patient priorities and involvement in clinical trials.
  - PSC Partners co-authored abstracts and posters at annual hepatology meetings, including The AASLD Liver Meeting and the European Association for the Study of the Liver (EASL) Congress in 2023 and 2024.
- PSC Partners expanded their efforts to advance health equity: launched a community-wide survey aimed at identifying barriers to PSC care in diverse populations; formed a health equity steering committee and working group; initiated a scholarship fund to cover the cost of attending the three-day annual patient conference for underserved people living with PSC.

"Twenty years ago, I started PSC Partners so that no one living with PSC would have to feel alone. Today, our growing, tiny, mighty community has learned to think big, reaching out to create impactful collaborations, leading and driving research, and believing that a PSC diagnosis can come with a cure."

Ricky Safer, MA
Chief Executive Officer, PSC Partners Seeking a Cure

Systemic JIA Foundation

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To accelerate research and treatment for Systemic JIA (Systemic Juvenile Idiopathic Arthritis), also known as Still's Disease, and associated complications such as Macrophage Activation Syndrome (MAS).

Systemic Juvenile Idiopathic Arthritis (JIA) , also known as Still's Disease, is a rare, life-threatening disorder of the innate immune system, with symptoms including the variable occurrence of chronic arthritis, fever, rash and organ involvement. Some patients can achieve remission through use of existing biologics and immunosuppressive medications, but others' disease is refractory, controlled only with systemic steroids. With an estimated prevalence of more than 10,000, the disease's causal mechanism remains unknown.

During the Grant Period

Impact Spotlight
When Rashmi Sinha's son was diagnosed with a rare phenotype not typical of Systemic Juvenile Idiopathic Arthritis, she founded the Systemic JIA Foundation, but was quickly left with more questions than answers, and many decisions to make. Should the foundation focus exclusively on her son's ultra-rare phenotype? Would the foundation achieve more impact with a focus on a single disease, or by aligning with other autoinflammatory disease organizations?

The foundation decided to start by finding patients and building community. Creating an online community, the foundation brought together 50 patients virtually, and ultimately, in-person for the first SJIA Family Conference, where patients participated in research and gave samples, and researchers in turn could learn more about the disease and patient needs.

Today, several such conferences and multiple research projects later, the foundation's efforts and convening power have led to a better understanding of SJIA, as well as its "refractory" subtypes. With each new finding, the potential benefit for the broader field of autoinflammatory diseases — both rare and more common — grows.

Key research and research infrastructure achievements

- Developed an Open Science Policy, outlining open and free distribution of research as a key goal, and encouraging open sharing of publications and research outputs by funded researchers.

- Added 10 academic centers to the research network.

Rashmi Sinha, PhD, founder of Systemic JIA Foundation, speaks to patients, scientists, clinicians, pharmaceutical companies, and FDA representatives at the NextGen Research in SJIA & MAS Conference, Systemic JIA Foundation's annual research conference.

Key publications

- *Arthritis Rheumatology* (2022): a study in which authors identified biomarkers in SJIA, co-occurrent MAS, and SJIA-LD (a disease form with increased incidence of high-mortality interstitial lung disease) (funded by the SJIA Foundation).
- *Pediatric Rheumatology* (2020): describes the proceedings and conclusions of two international scientific meetings convened by the SJIA Foundation, which brought together patient families, researchers, clinicians and FDA/EMA representatives (co-authored and funded by the SJIA Foundation).
- *Nature Immunology* (2021): describes the repression of H3ΔN, which is reduced in monocytes from patients with SJIA, in monocyte-to-macrophage development during immune cell differentiation (funded by the SJIA Foundation).

Key operational achievements

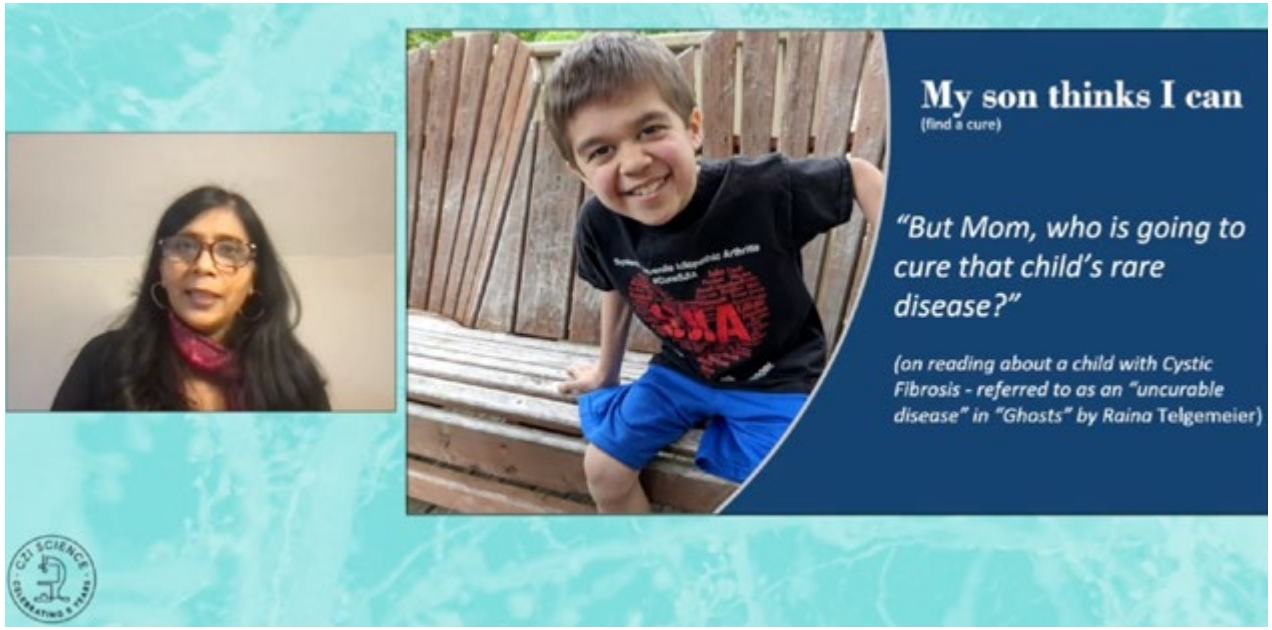
Expanded staff capacity to include bioinformatics, database coordination, events management and data analysis.

Key community achievements

Expanded Patient Board to include representatives from Europe and South America.

After the Grant

- The foundation developed and distributed a patient-reported survey to gather patient feedback for a MAS clinical trial.
- In 2024, the foundation hosted a virtual Social Hour for SJIA and Still's Patients and Caregivers with different breakout groups with different topics (Newly Diagnosed, Transitioning Care for Young Adults, Managing MAS/ Lung Disease, Older Teens and Young adults, Still's Patients, etc.) where patients, parents and caregivers had the opportunity to share their stories and experiences.
- In November 2024, the foundation organized its 5th NextGen Therapies for SJIA & MAS conference in Washington, DC with the goal of bringing together all stakeholders for the disease, including patients, researchers, clinicians, pharma and regulators. Five representatives from the FDA participated in the conference and several EMA representatives attended via Zoom. The conference was productive, with the foundation following up on concrete next steps.



Rashmi Sinha speaks during a session on patient communities as essential drivers of research at the CZI Science 5-Year Anniversary Symposium in 2021.

"Patient groups can be the quarterbacks that rare diseases need."

Rashmi Sinha, PhD
Founder, Systemic JIA Foundation

The Snyder-Robinson Foundation

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To advance medical and scientific research relating to Snyder-Robinson Syndrome and related disorders, in order to find a cure or treatments that will improve the lives of the boys and men affected by this rare disease.

Snyder-Robinson Syndrome (SRS) is an ultra-rare, genetic, X-linked intellectual disability affecting only males, with varying prognoses and unknown prevalence. SRS, which is associated with changes in the Spermine Synthase (SMS) gene on the X-chromosome, is characterized by muscle and bone abnormalities, and developmental delays affecting speech, mobility, and cognition. Treatment options are currently limited to symptom management.

At the Science in Society 2023 Meeting, Oakey Daskas (left) and Anna Chu (center) of We The Action, connect during a poster session with Michael Raymond (right), Co-Founder of the Snyder-Robinson Foundation. We The Action, a program of Civic Nation, supports the legal needs of Rare As One Network grantees, as one of CZI's capacity building partners.

During the Grant Period

Impact Spotlight

Over the course of its Rare As One grant, the Snyder-Robinson Foundation (SRF) focused its work on collaboration, from identifying and engaging six new researchers, clinicians with diverse expertise, and family members of 46 new patients from around the world, to creatively convening its patient and research communities in in-person and virtual formats.

In 2023, the value of these incremental investments became clear, when SRF leadership and key research partners connected with a researcher/clinician previously unknown to the organization, who had expertise with a drug — DFMO — identified as a potential treatment for Snyder-Robinson Syndrome (SRS). In just a few short days, the SRF and its research network identified additional partners from a range of institutions, and connected them with the researcher: plans for the first collaborative drug repurposing trial for SRS, leveraging the drug DFMO, were underway.

Enabling this and any future trial will be the SRF's knowledge of and connections with the patient and research community, pre-clinical data generated through SRF-funded research, a mouse model developed as a result of SRF investments, and patient data sourced and collected by the SRF through a biobank and natural history study.

Key research and research infrastructure achievements

- Funded mouse model phenotyping at the Jackson Laboratory, with researchers now able to order these mice for further study.

- Expanded research network — "the Polyamigos" — to include additional researchers studying polyamines and other areas relevant to SRS.

Key publications

- *Journal of Medicinal Chemistry* (2021): describes the development and outcomes of a prodrug for spermine, which releases free spermine inside human SRS fibroblast cells and SMS mutant male flies, and was found to be relatively nontoxic (funded by the SRF).

- *JCI Insight* (2022): explores a potential therapy in which the repurposed FDA-approved drug phenylbutyrate (PBA) is used to treat SRS using an in vivo Drosophila model and patient fibroblast cell models (acknowledges SRF support).

Key operational achievements

- Developed medically translated website content in all 13 languages spoken by known SRS patient families, including detailed resources for providers.

- Hired a Director of Research and Director of Membership.

Key community achievements

Launched collaboration with the International Center for Polyamine Disorders, including for use of a shared natural history study and biobank platform, enabling study of SRS and related disorders.

Connor Raymond (center) and family visit with Cat Lutz, Ph.D. at The Jackson Laboratory in Bar Harbor, ME. When Raymond was 5, he was one of only a handful in the country diagnosed with Snyder-Robinson Syndrome.

After the Grant

- The Snyder-Robinson Syndrome Foundation continues to support important research progress against SRS. While they were disappointed that the use of DFMO in the mouse model failed safety tests in the lab, they continue to seek other opportunities.

- A 2024 publication in the journal *Rare*, co-authored by SRF Director of Research Teri Koerner, explores bone manifestations in Snyder-Robinson Syndrome along with considerations for healthcare providers.

"If we hadn't had the opportunity to build up the research network like this, I don't think that this would have been possible."

On the organization's progress toward treatment of a Snyder-Robinson patient with a repurposed drug.

Michael Raymond
Co-Founder and Member of the Board of Directors

TANGO2 Research Foundation

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To lead the way in finding a cure for TANGO2 deficiency disorder.

TANGO2 deficiency disorder (TDD) is a genetic disorder estimated to affect more than 8,000 patients worldwide, characterized by intellectual disability, seizures, hypothyroidism, and recurrent episodes of rhabdomyolysis with metabolic crises. TANGO2 deficiency disorder presents by age three with muscle breakdown, metabolic crises and life-threatening cardiac arrhythmias brought on by illness or other stressful event. If the child survives acute presentation, they experience significant cognitive and physical regression, with some never returning to baseline.

The TANGO2 community gathers at the TANGO2 Research Foundation's Family Conference in 2022.

During the Grant Period

Impact Spotlight
Since the identification of TANGO2 gene mutations as the cause of TDD in 2016, patient families have observed anecdotal evidence suggesting that over-the-counter vitamins alleviate symptoms and reduce metabolic crisis occurrences. In 2019, the TANGO2 Research Foundation, in collaboration with Baylor College of Medicine, initiated a natural history study (NHS) to investigate this possible association and to better characterize TDD.

By 2022, data from the NHS and two independent foundation-funded studies indicated that components of the B vitamin complex may mitigate risks of metabolic crises and arrhythmias in TDD patients. Notably, patients taking B-vitamins in the NHS experienced no TANGO2-deficiency-related metabolic crisis fatalities. These findings prompted rapid updates to TDD nutritional guidelines.

Additionally, the foundation convened a clinical advisory board comprising 10 clinicians to develop and publish updated care recommendations in GeneReviews® incorporating these insights.

Key research and research infrastructure achievements
Funded twelve researchers to advance seven research projects in four countries, focused on patient-prioritized topics including pathogenic mechanisms in hiPSCs-derived neurons, effects of mitochondrial stabilizing compounds on TANGO2 deficient cells, assessment of abnormal movements in TDD, exploration of novel TANGO2 interacting partners as a new mechanism for the role of TDD, potential TDD treatments through TANGO2 patient-derived iPSCs cardiomyocytes and in vivo modeling, and deciphering the mechanisms of TANGO2-deficiency induced cardiac arrhythmogenesis.

Key publications
- Pre-print (2022): a study demonstrating that use of B-vitamins is effective in mitigating cardiac crisis in TANGO2 patients (funded by the TANGO2 Research Foundation).

- *Genetics in Medicine* (2022): the first natural history study of TANGO2 deficiency disorder (funded by the TANGO2 Research Foundation, leverages foundation natural history study data).

- *European Journal of Human Genetics* (2022): a study examining the health-related quality of life, illness perceptions, and lived experience of children with TANGO2 and their parents (TANGO2 Research Foundation provided funding and supported enrollment).

Key operational achievements
Hired two full time staff members, an Executive Director and Research Engagement Director, retained strategic planning and social media consultants, and implemented an Early Detection and Diagnostic Committee.

Key community achievements
Partnered with the Broad Institute's Rare Genomes Project to develop a disease prevalence estimate, which indicated higher expected prevalence in Mexico, and led the foundation to engage with clinicians and researchers in Mexico City toward support for patient diagnosis.

Members of the TANGO2 team attend the Science in Society 2023 Meeting. Left to right: Co-Founder and President Mike Morris, Research Engagement Director Deena Chisholm, Executive Director Ann Geffen, and Co-Founder Kasha Morris. Deena and Ann were hired during the Rare As One Network grant period.

After the Grant

- The TANGO2 Research Foundation continues to grow and convene its patient and researcher community. As of June 2024, the foundation's Early Detection and Diagnostic Committee is working to develop an ICD-10 code application for TDD.

- With support from Amgen, the foundation launched a series of mental health podcasts in 2023, aimed at supporting their community by addressing the gaps in education and emotional support for TDD caregivers.

- In partnership with the foundation, a multi-institutional research team prepared and submitted an FDA grant to conduct a prospective natural history study to support TDD clinical trial readiness.

- Based on community feedback and self-reporting, B-vitamins continue to enhance the daily lives of individuals with TANGO2 deficiency disorder, notably improving energy levels, mobility, and overall well-being.

"Our unwavering dedication persists, propelling us forward in the relentless pursuit of progress. Together, we stand alongside our families, fostering a collective spirit that drives us to overcome challenges and embrace the possibilities of a brighter tomorrow."

Ann Geffen, JD, MA
Executive Director, TANGO2 Research Foundation

TESS Research Foundation

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To improve the lives of those affected by SLC13A5 Epilepsy by driving cutting-edge research, supporting children with SLC13A5 Epilepsy and their families, and increasing awareness about this severe neurological disorder.

SLC13A5 Epilepsy (aka SLC13A5 Deficiency or Citrate Transporter Disorder) is an autosomal recessive epileptic encephalopathy. Affected children have intractable seizures from birth, a debilitating movement disorder, and can understand language, but speak only a few words. They are trapped in their bodies and require lifelong 24-hour care. SLC13A5 Epilepsy affects entire families. No specific treatments exist to cure the disease.

In person attendees — including patients, families, researchers, clinicians, and industry partners — from the TESS Research Foundation 2022 Clinical Research Conference.

During the Grant Period

Impact Spotlight
TESS Research Foundation's investments with a line of sight to translation have helped progress SLC13A5 Epilepsy from gene discovery to gene therapy in less than a decade.

Building on initial work to identify patients, fund basic research, and fund the development of a candidate gene therapy, the foundation partnered in 2020 with a biotech company to advance development of the gene therapy toward clinical trials.

Throughout the grant period, TESS Research Foundation served as a key partner to the biotech's efforts. The Foundation shared data from its natural history study and registry (by the end of the grant period, the foundation had fully enrolled more than 130 patients from 25 countries) to inform the company's proposed trial protocol and outcomes, introduced industry and academic research partners, and published data that further supported the development project, including a natural history study-based pre-print publication with proposed clinical trial endpoints.

Key research and research infrastructure achievements

- Held inaugural Clinical Research Conference in 2022 in conjunction with the University of Texas Southwestern and supported by an NIH R13 grant, convening 100 key stakeholders with a focus on young and minority investigators.

- Expanded a preclinical toolkit openly accessible to the research community, which includes patient samples, foundation-funded tools including nanobodies, patient-derived iPSCs, and openly available resources like biobanks and repositories.

- Since 2015, funded $2M in research to more than 20 different labs around the world.

Key publications

Metabolites (2021): a publication characterizing the non-neurologic health of 15 SLC13A5 patients using medical records uploaded to Citizen Health (funded by TESS Research Foundation; co-authored and led TESS Scientific Director, Tanya Brown, PhD, and Founder and Executive Director Kim Nye).

Key operational achievements

- Developed a strategic and operational plan.

- Hired a full-time Scientific Director and part-time Development Director.

Key community achievements

- Executive Director appointed as a co-lead of the Epilepsy Leadership Council Research Task Force, and served as a member of American Society of Gene and Cell Therapy committees.

- Scientific Director convened meetings with the CDC, the American Academies of Neurology and Pediatrics, and other key decision makers to discuss challenges in the ICD system.

- Individual giving increased by 21.6%; Development Director also spearheaded annual fundraising event.

Ellie (SLC13A5 Epilepsy Patient; center) with her family, Tanya Brown, PhD (TESS Scientific Director; back right), and Naomi Dirckx, PhD (front right), in 2022.

After the Grant

- TESS Research Foundation continues to advance efforts aimed at treatments for SLC13A5 Epilepsy, to develop comprehensive treatment guidelines, and to expand the SLC13A5 research community.

- The biotech company previously advancing the SLC13A5 gene therapy deprioritized the program due to budget constraints. TESS now plans to fund the trial themselves, and partner with an academic sponsor to run the trial.

- In addition, TESS continues to invest in other research initiatives, including additional model creation (zebrafish and humanized mouse models), rational drug design, and drug repurposing studies.

- In March 2023, *Frontiers in Genetics* published an article describing the results of TESS Research Foundation's partnership with Citizen Health to develop a Digital Natural History of SLC13A5 Epilepsy. The study was co-authored and led by TESS Scientific Director Tanya Brown, PhD and Executive Director Kim Nye.

Abhi (SLC13A5 Epilepsy Patient) and Kim Nye (TESS Founder and Executive Director) at the 2022 Clinical Research Conference.

"It would be impossible for a family like mine to go from disease discovery to potential disease modifying therapy in a few years without the urgency of the patient voice and the philanthropic investments of our community."

Kim Nye
Founder and Executive Director,
TESS Research Foundation

Usher 1F Collaborative

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To fund medical research to find an effective treatment to save or restore the vision of those with Usher Syndrome type 1F.

Usher Syndrome is a pathogenic mutation and the leading cause of inherited deaf-blindness. Children with Usher 1 — the most severe subtype — are born profoundly deaf and progressively lose their sight. With newborn hearing testing, babies' deafness is identified at birth, and, with early cochlear implants, they can learn to hear and speak similarly to peers. Currently, there is no treatment or cure for Usher 1F's progressive blindness.

The Root family of New Jersey, Rachel, Emily, Jared, and Zachary, who has Usher 1F, at a Sight.Sound.Cycle fundraising event for Usher 1F research. Multi-city Sight.Sound.Cycle events, founded by the Roots, raised $300,000 for Usher 1F research over three years.

During the Grant Period

Impact Spotlight

Early in 2023, researchers funded in part by the Usher 1F Collaborative announced positive results from a study in mice that used a "mini gene" to replace the mutated gene in Usher 1F and that in turn restored hearing. Later in the year, they also announced that the mini gene restores vision in a zebrafish model. The results are a significant step toward development of a gene therapy for the disease, a longstanding goal of the collaborative.

Alongside these promising results, the Usher 1F Collaborative is advancing a range of other efforts to move forward research progress, including by forging a relationship with researchers at the Salk Institute. Researchers there are leveraging an approach called RNA end-joining to develop alternate gene therapy delivery vectors, which they hope could serve as a workaround for delivery of a gene therapy for the disease's large causal gene.

Usher 1F Collaborative also funded researchers in Oregon exploring a magnolia-based potent antioxidant compound as a potential treatment that could restore partial vision. The Usher 1F Collaborative and its partners are looking forward to engaging the FDA and moving ever-closer to a treatment or cure.

Key research and research infrastructure achievements

- Partnered with Foundation Fighting Blindness (FFB) to launch and recruit for a natural history study, RUSH1F, leveraging FFB's platform.
- Held a large two-day international scientific research conference focusing on Usher 1F and other types of Usher syndrome caused by mutations in large genes.
- Partnering with Usher Syndrome Coalition to develop a joint registry leveraging the RARE-X platform.

Key publications

- *Nature Communications* (2023): a study reporting the development of a "mini-gene" therapy which rescued hearing in a mouse model (funded by the Usher 1F Collaborative).
- *eLife* (2021): research leveraging a Pcdh15-deficient mouse into a potential therapy for progressive loss of vision (funded by the Usher 1F Collaborative).

Key operational achievements

- Hired a Development Director and expanded the Board.
- Established Usher 1F Collaborative Canada.
- Implemented fundraising platforms and policies and procedures.

Key community achievements

- Recognizing the increasing number of identified rare mutations and the broadened understanding of the affected population, to maximize inclusivity, the organization, rebranded and focused research on gene therapies to address all known mutations.
- Held two virtual family meetings, including an ASL interpreter to ensure all could participate.
- Created a 50-minute film describing research progress and future directions and leveraged the film in fundraising efforts around the organization's 10th anniversary in October 2023.

After the Grant

- The foundation's close research collaborator at Harvard received a 3-year, $1.2 million Translational Research Acceleration Program grant from Foundation Fighting Blindness (FFB) for preclinical testing of the Usher 1F mini gene.

  As of May 2024, Usher 1F Collaborative has directly funded approximately $5 million in research, with researchers supported by the foundation leveraging that support to raise an additional approximately $9 million. Of the FFB support he received, and how the Usher 1F Collaborative played a role in enabling it to be secured, the Harvard researcher commented, "this grant is a great example of how seed funds from individual donors can support pilot projects that generate much larger funding from foundations and NIH. Donors should appreciate that their contribution can be leveraged in this way."

- In addition to expanding their patient network, including engaging families in France and Germany, Usher 1F Collaborative continues to support other research efforts, including partnering with the Usher Syndrome Society on a targeted drug screen at the University of Oregon Institute of Neuroscience using all of that lab's Usher syndrome zebrafish models.

The three children of Usher 1F Collaborative Founder and Board President, Melissa Chaikof. Melissa's daughters, Rachel (left) and Jessica (right), have Usher Syndrome type 1F. Jessica is accompanied by her service dog.

"As we've learned that the [disease] impacts those outside of the Jewish community, too — almost 40% — there are certain therapies that we could fund that would only work on the Ashkenazi Jewish mutation. [Board President Melissa Chaikof] is really steadfast on… fund[ing] research that is going to impact all of the individuals with Usher 1F, not just this specific mutation."

Sarah Gauch
Development Manager, Usher 1F Collaborative

The Yaya Foundation for 4H Leukodystrophy

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To provide hope for children and families affected by 4H Leukodystrophy by accelerating the discovery of therapies through research, and providing education and emotional support for families.

4H Leukodystrophy (4HL) is a rare disease of the central nervous system, caused by mutations in one of four genes. Like other leukodystrophies, 4HL affects the white matter of the brain and damages the myelin sheath. Symptoms are managed with supportive care, but there are no targeted treatments or cures. Symptoms vary, and can include motor, movement and learning problems. There are approximately 300-600 known patients, but total prevalence is unknown.

Kurt Triptow (parent and Member of the Board) gives remarks to supporters at the Yaya Foundation 2nd annual event in Minneapolis, MN, which was attended by sponsors, donors, supporters and industry leaders.

On October 17, 2024, Yaya Foundation supporters gathered in Minneapolis, MN to launch a $1 Million Yaya IMPACT Campaign. Left to right: Executive Director Ben Smith, Ron Garber (Board Chair), Kurt Triptow (parent and Member of the Board).

During the Grant Period

Impact Spotlight
When Ron Garber, one of the co-founders of the Yaya Foundation for 4H Leukodystrophy, submitted the organization's application to be part of the Rare As One Network Cycle 1 in late 2019, he described developing a data strategy and international patient database as a central goal for the foundation.

With few known patients at the time, Ron, who co-founded the organization following the passing of his daughter, Yaya, from 4HL, just weeks after her first birthday, knew success in this effort would require working from the ground up, from securing buy-in from the research community to share data, to identifying and engaging additional patients, and establishing data use agreements and collection protocols.

By the close of the three-year grant period in early 2023, with these pieces methodically put into place, the Yaya Foundation's Data Collection Program, in partnership with RARE-X, has registered and enrolled more than 70 families. The foundation intends to leverage the registry as the basis for a future natural history study, as well as to one day enable more effective and efficient clinical trials.

Already, the Data Collection Program is bearing fruit. Later in 2023, the Yaya Foundation continued to promote data collection as an important tool to help inform researchers about 4HL and its progression, and to establish a data foundation to help with data and design for use in clinical trials. Additionally, the foundation combined patient-entered data collected through their Data Collection Program, with clinician-entered data collected by academic centers, making the previously-siloed academic center data available to researchers, clinicians, and drug developers via the RARE-X platform.

Key research and research infrastructure achievements

- Partnered with researchers to develop a mouse model to inform Phase 1 of a gene therapy development project, with a next phase focused on generating proof of concept underway.

- Partnered with the Broad Institute's Rare Genomes Project on a study to better understand the prevalence of relevant genes, indicating underdiagnosis of 4H Leukodystrophy.

Key publications

American Journal of Medical Genetics (2021): a correspondence on distinguishing severe phenotypes associated with pathogenic variants in POLR3A, one of the genes associated with 4HL, co-authored by Geneviève Bernard, a member of the foundation's Scientific Advisory Board.

Key operational achievements

- Exceeded 2022 Giving Tuesday goal by 180%.

- Hired two Executive Directors and an Advancement Advisor.

Key community achievements

- Initiated a Family Needs Assessment survey to better understand community needs and priorities.

- Collaborated with the United Leukodystrophy Foundation to sponsor and host a 4HL-specific conference agenda within the broader ULF 2022 Conference's agenda, engaging additional researchers and families.

After the Grant

- In May 2023, the Yaya Foundation awarded a grant of nearly $50,000 to researchers at the Children's Hospital of Philadelphia, to investigate the use of non-coding RNA as a biomarker for 4HL. Of the grant, co-founder Ron Garber said, "one of the challenges of 4HL is early detection and diagnosis, and there is not yet any known treatment or cure for the disease. Having specific, unique biomarkers for 4HL will enable researchers at CHOP and around the world to diagnose people more effectively and to develop therapies that will enable people affected by 4HL to live longer, more healthy lives."

- In September 2023, *Brain* (2023) published results of work led by Yaya Foundation Scientific Advisory Board member Geneviève Bernard of McGill University and funded by the Yaya Foundation, to create the first representative animal model of 4HL. Dr. Bernard's lab will use the mouse model in continued exploration of gene therapy as a potential treatment option for 4HL, including by leveraging a $994,500 grant from the Canadian Institutes of Health Research for further study and testing of therapeutic approaches using the animal models.

- In 2024, the Yaya Foundation continued to expand its organizational capacity and scientific goals, developing a 3-year research project forecast to begin in 2025. The organization also hired a Community Engagement Coordinator, and launched three new Board committees and external engagement initiatives.

Executive Director Ben Smith (right), and Jill Triptow (left), a 4HL patient, at the annual Fore for 4H golf scramble outside of Cleveland, Ohio, hosted by Debbie and Kurt Triptow, two of the Yaya Foundation's co-founders. The event has raised over $200,000 since it began.

"Our community is strong and we gather in hope and action — we journey together on this road to support our patients and the lifegiving science."

Ben Smith, MBA
Executive Director, The Yaya Foundation for 4H Leukodystrophy

Closing Call to Action

Science in Society grantees, including members of the Rare As One Network, and other key stakeholders in the rare disease ecosystem, gather at the Science in Society 2022 Meeting.

Making meaningful progress in rare disease requires not only more research funding, but also requires identifying and connecting rare disease patients, bridging siloed research efforts, collecting and integrating fragmented patient data across borders and disparate record systems, creating research-enabling assets, addressing tremendous diversity, equity and inclusion challenges and more. We have seen throughout this report and beyond how patient-led rare disease organizations are addressing these and many other challenges head-on, actively de-risking investment in their diseases by building strong and inclusive patient and research communities, aligning them along shared research priorities, and developing critical research-enabling infrastructure. These organizations are setting the table for research and enabling sustained progress toward the development of treatments and cures.

The lack of funding for patient-driven rare disease organizations remains a significant challenge, however, severely limiting their capacity to make progress towards their mission. Optimizing the power of these organizations to drive scientific discoveries and accelerate the development of treatments and cures requires that we fully embrace patients as central stakeholders. Patient-led rare disease organizations are essential to advancing meaningful, sustainable progress against rare diseases. We hope you will join us in supporting their work and bringing hope to the 400 million rare disease patients worldwide.

Chan
Zuckerberg
Initiative

Building a Better Future for Everyone

chanzuckerberg.com