ALLIANCE TO CURE CAVERNOUS MALFORMATION NEWSLETTER

Expanding Our Vision

Since our inception in 2002, the Alliance to Cure Cavernous Malformation (originally called Angioma Alliance) has embraced a single vision: a permanent cure for cavernous malformation (CCM). In recent years, with advances in technology like gene therapy and focused ultrasound and with increased understanding of the biology of CCM, this vision is within reach.

However, just because a treatment or cure exists doesn't mean that everyone needing it can access it. For example, we recently heard about a $4.25 million gene therapy treatment for another rare disease, certainly out of reach for the average family. We have no way to predict or control pricing for upcoming CCM treatments. We don't want our patients or parents left in the tragic situation of seeing privileged patients saved while watching their own or their child's condition worsen.

> We envision a world with a permanent cure for cavernous malformation: available, accessible, and affordable for all.

We support and celebrate the possibility of CCM becoming curable with gene therapy or other expensive interventions. Just like surgery can be curative for many people with sporadic disease, a cure for anyone is worth fighting for.

However, Alliance to Cure's job is not done until there is a cure for *everyone*. We don't exist simply for research success; we exist to bring care, cure, and resources to people affected by cavernous malformation. To reflect this, the Alliance to Cure Cavernous Malformation has updated our vision statement, which you can see in the box at the center of this page.

This vision of equity drives our mission. This vision statement brings us full circle to our reason for being: you.

We will evaluate everything we do through this lens. To us, achieving our vision of a cure means facilitating available, accessible, affordable information, support, care, research participation, and opportunities to bring our voices together for change.

In this issue, you will read about a survey we're conducting to better understand our members' accessibility barriers. We hope you'll participate if you are a patient or caregiver. This information will directly feed into enhancements in our programming to better serve you now and in the future.

This issue also contains a breakthrough clinical drug trial announcement from Recursion and information about research and patient activities: the highlights of our scientific meeting, the christening and progress of our CureDriver Lab™, and the latest on a focused ultrasound trial. You'll read about ways we've brought together our families, through our family weekend, and through past and future patient conferences and awareness events.

United, we can improve lives now and in a future with a cure. There is no time to waste.

A message of thanks from Chris Gibson, CEO of Recursion, to our patient community

Dear Alliance to Cure Friends,

This week Recursion announced the topline data from the Symptomatic Cerebral Cavernous Malformation Trial of REC-994 or "SYCAMORE" trial (see page 2 of this newsletter). Over the coming months we will be preparing presentations and publications to communicate the specific findings of the trial.

Today, I wanted to recognize the tremendous partnership and support of the Alliance to Cure and all of you in the success of recruiting into this trial. Without your enthusiasm and courage, advancements in the science around CCM would never be possible. So many of you helped in spreading the word about the trial and participated, and for that we are eternally grateful. We thank you for your time, your passion, and your commitment to your community.

Recursion looks forward to sharing the data about the trial and continued partnership with Alliance to Cure.

Thank you!

Recursion Press Release: CCM Drug Trial Breakthrough

Recursion Announces Phase 2 Data of REC-994, a First-in-Disease Investigational Treatment for Symptomatic Cerebral Cavernous Malformation (CCM), has Met its Primary Endpoint of Safety and Demonstrates Encouraging Trends in Objective MRI-Based Exploratory Efficacy Measures

Recursion plans to advance development of REC-994 for the potential treatment of symptomatic CCM in subsequent studies and will seek a meeting with the FDA in early 2025 to discuss study design.

SALT LAKE CITY, Sep. 3, 2024 (GLOBE NEWSWIRE) – Recursion today announced top-line results of the SYCAMORE trial, a 12-month Phase 2 randomized double-blind, placebo-controlled safety, tolerability and exploratory efficacy study for REC-994 in symptomatic CCM patients. REC-994 is an orally bioavailable, superoxide scavenger small molecule drug.

REC-994 met its primary endpoint of safety and tolerability, demonstrating a similar profile across placebo and both 200mg and 400mg dosage-arms with regard to the frequency and severity of treatment emergent adverse events after 12 months of treatment. Magnetic resonance imaging-based secondary efficacy endpoints showed a trend in patients at the highest dose (400mg) as having a reduction in lesion volume and hemosiderin ring size as compared to placebo. Time-dependent improvement in these trends at the 400mg dose was also observed in this signal-finding study. Improvements in either patient or physician-reported outcomes were not yet seen at the 12-month time point. A meeting with the FDA is anticipated in early 2025 to discuss plans for an additional clinical study. Recursion plans to present data from this trial at a forthcoming medical conference and intends to submit these data for publication in a peer-reviewed scientific journal.

"I speak for the patients who have participated in the trial and those who have been cheering from the sidelines while waiting for news. This promising start is a critical step forward and will bring hope to thousands of families who currently have no options but brain or spinal cord surgery," said Connie Lee, CEO of the Alliance to Cure Cavernous Malformation. "The Alliance to Cure Cavernous Malformation looks forward to partnering with Recursion as they move to the next stage of the REC-994 program."

"These studies are making significant strides in the development of therapeutics for CCM. The data from this readout is an impressive start and will provide a valuable contribution to the existing CCM literature and strongly support the need for a future study, with a longer duration and a larger patient cohort" added Dr. Jan-Karl Burkhardt, MD, Division Head, Cerebrovascular Surgery, University of Pennsylvania.

"We are encouraged by the recent data from our signal-finding Phase 2 study in CCM, where the trial successfully met its primary safety endpoint and became the first investigational therapy to demonstrate preliminary safety alongside some promising trends in efficacy endpoints," said Najat Khan, Ph.D., Chief R&D Officer and Chief Commercial Officer of Recursion. "We are deeply grateful to the patients and investigators for their dedication to addressing this significant unmet need, and we are energized and committed to advancing potential transformational therapies for CCM and beyond."

"This is an important step in our efforts in CCM, our first program in patients at Recursion," said David Mauro, M.D., Ph.D., Chief Medical Officer of Recursion. "The safety profile from this study is comparable to what was seen in our previous study in healthy volunteers where REC-994 was dosed up to 800 mg. Subsequent larger studies will allow us to deepen our understanding of these encouraging signs of activity across a potentially higher range of doses. We are enthusiastic about a meeting with the FDA to advance this program further."

Recursion has sought and received Orphan Drug Designations in the US and Europe.

The Alliance to Cure is waiting to hear from Recursion about their process and timing for moving all patients in the Long Term Extension Part 2 of the study to the 400 mg dose level. We'll let you know once we have additional information that can be shared.

Research News

20th Anniversary International CCM Scientific Meeting

In late June, the Alliance to Cure Cavernous Malformation hosted our 20th-anniversary scientific meeting. Convening at the Peter Gilgan Research Centre associated with Sickkids Hospital in Toronto, researchers from academic institutions and pharmaceutical companies met to share their latest findings and plan solo and joint efforts to move cures forward.

A 20th Anniversary is notable. Our first meeting, in Durham North Carolina, in 2005, was attended by 17 scientists; this year, we hosted 105. Happily, of the 17 original Durham attendees, 5 were in attendance in Toronto, including Dr. Brent Derry, who presented the 20th anniversary keynote. He discussed the history of our understanding of CCM from a scientific perspective, through the lens of the animal model that is the focus of his lab, *c. elegans*, a mighty nematode.

We also discussed advances in:

- Blood biomarkers that could be used to diagnose, monitor, or predict disease course.
- Nuances in the outcomes of low-dose rapamycin testing, with some mouse models receiving more benefit than others.
- A potential new way of using standard MRI technology to identify who may be at risk for re-hemorrhage.
- The economic, family, and social impact of pediatric cerebrovascular surgery.
- An update on using focused ultrasound to deliver treatments to the brain.

Some talks were presented at the concurrent patient conference, including the progress at the University of Pennsylvania on nanoparticle delivery of medicines directly to cavernous malformation lesions, and the progress of gene therapy at the University of Rochester. Your donations to the Alliance to Cure have provided funding for both projects.

Attendees at the 20th anniversary International CCM Scientific Meeting

The patient conference clinical sessions featured an all-star line-up of CCM experts including Drs. Ed Smith, Leslie Morrison, Ionela Iacobus, Peter Dirks, Kelly Flemming, Atif Zafar, and Issam Awad. All patient conference sessions are available for viewing on our YouTube channel.

A group of patients and caregivers in Toronto for the CCM Patient Conference.

Alliance to Cure Cavernous Malformations CureDriver™ Lab

At the CCM Scientific Meeting, researchers were most excited by the Alliance to Cure's new pre-clinical treatment testing program, which we have named CureDriver™. The researchers were captivated by the promise of CureDriver to rapidly and systematically test medicines in CCM disease models, because we are filling a critical gap. While there are many potential treatments or even a cure, sitting on shelves, academics are unable to test them at scale and pharmaceutical companies will only test their own products.

With your support, we will have the capacity to test 50 medicines a year in cell line models and up to 8 good candidates in mice. As of this writing, in collaboration with Miguel Lopez-Ramirez's lab at UCSD, we are already testing 16 drugs in CCM cell lines, alone or in combination. If any look promising, we can test them in our CCM1, CCM2, and CCM3 mouse models at a scientific research institute.

We have also been asked by researchers to test or validate medicines they have identified as potential treatments. These are compounds they can't test because of limitations on space, staff, or funding. You can only imagine how relieved the scientific community, frustrated by their capacity limitations, is to have this resource. Our lab will also be able to serve pharmaceutical companies looking to assess the efficacy of their new drugs. CureDriver will propel us forward at a speed previously thought impossible.

NIH Science Funding and a Research Roadmap

One sobering thing we learned from our scientific meeting was that government funding for CCM research – both natural history research and research conducted in laboratories – has been declining in the US and Europe, and is on a trajectory to be reduced 75% relative to what government funding agencies spent in 2017-2018. The loss of US National Institutes of Health (NIH) and EU funding is an enormous barrier, and we expect to see many of our academic research labs forced to leave CCM to pursue opportunities in other research areas.

Why is this happening? We don't have all the answers, but there are three drivers at NIH that we can identify. The first two affect research funding in general.

First, especially in basic biological research, research funding has been down overall. NIH has been shifting to funding tools and technology, as in the NIH BRAIN Initiative. The National Institute of Neurological Disorders and Stroke has been particularly hard hit and is now funding only 11% of the grant applications it receives.

Second, along similar lines, the largest grants that were used to fund multi-institute consortia are no being offered for individual diseases, at least not rare diseases. The latest large basic research collaborative grant opportunities ask researchers to study biological mechanisms that are shared by many diseases.

Finally, CCM research has been generously funded for the last 10-15 years, as we received both a natural history research consortium grant that will end this year and a 10-year basic research consortium grant that will end next year. We can imagine that NIH expects us to have achieved a level of knowledge from their investment that will allow us to focus on treatments, rather than understanding disease mechanisms. Other diseases that have been less fortunate deserve their turn.

The Alliance to Cure Cavernous Malformation is taking an active role at this turning point. Our first task is to determine whether NIH might be right: how much basic research or natural history gathering do we need at this point? Where are the knowledge gaps that hold us back and how might we address those? We will have a Research Roadmap completed this year that synthesizes everything we know now and creates a vision of the path forward. It will be a living document, updated with new discoveries and conditions. If there are areas where seed funding or new programs could make a difference, we will ask for your support. We have an outsized role to play now, and we are confident, knowing that you are behind us 100%.

Focused Ultrasound Trial

The Alliance to Cure Cavernous Malformation is working with the University of Virginia (UVA) and NaviFUS, a focused ultrasound machine manufacturer to bring the first trial of focused ultrasound to CCM patients. Focused ultrasound (FUS), in its potential application for CCM patients, uses sound waves directed at CCM lesions to gently and temporarily open the blood brain barrier. While the original experiments with mice were designed to determine whether FUS could be used to deliver medicines, researchers at UVA discovered that opening the blood brain barrier with FUS was enough to precipitate a healing response in existing lesions and to prevent the development of new lesions.

We are now ready to move a clinical trial with our CCM patients forward. We are working with UVA and NaviFUS to begin the first tests to determine whether FUS is safe for patients and whether there is, indeed, some sign of a response.

The trial protocol is currently being written. Once complete, it will be sent to the Food and Drug Administration (FDA) to receive approval. If FDA approves the protocol quickly and funding is secured, we will see the first patients treated with focused ultrasound in 2025. The details of the protocol, including which patients will be treated, are still in flux and not available publicly. As soon as they are, we will share these with our community.

Focused ultrasound has the potential to be a critical treatment tool and, if the mouse evidence extends to humans, to be a non-invasive cure for some. Your support will help to make this a reality.

Our Patient Registry Drives Trials

As our research moves from bench to bedside, understanding and communicating with patients becomes critical. Our patient registry is a resources we use to assist every clinical trial, both in planning and support.

It takes 20 minutes for you to become part of the solution. If you are a patient or parent, please take the time to participate at ccmregistry.org. There can be no cure without you.

Alliance to Cure Neurology Resident and Summer Research Awards

Congratulations to the recipients of our first Alliance to Cure Cavernous Malformation Neurology Awards, Dr. Vanesha Waiters and Dr. Minnie Mitchell of the Morehouse School of Medicine's Class of 2024.

Dr. Waiters (left) will be a surgery resident at Emory University, with plans to enter neurosurgery, and Dr. Mitchell (right) will be a neurology resident at the Morehouse School of Medicine. Our Board Member Kandance Weems Norris (center) recognized

the doctors at a ceremony earlier this summer.

Additionally, the Alliance to Cure sponsored Mideny Bell, a Morehouse School of Medicine rising second-year medical student, who completed an 8-week summer research experience at CCM Center of Excellence Boston Children's Hospital.

Mideny offered his thanks. "Working alongside Dr. Alfred See and having the chance to observe the intricate processes involved in pediatric neurosurgery and neurology was both educational and motivating. The insights and skills I've gained over the past few months have profoundly enriched my understanding of the field and have further solidified my commitment to learn more about cerebral cavernous malformation."

The Alliance to Cure Neurology Awards support more equitable access to neurological clinical care. Our thanks go to Justworks' Spring Forward Fund for their commitment to our vision of a permanent cure for cavernous malformation: available, affordable, and accessible to all.

Understanding Access Barriers: In 15 Minutes, You Can Help Shape the Future

People with cavernous malformations, no matter their background, face access challenges. For some, it's access to information or support resources. For others, it's access to quality care or opportunities to participate in studies. Living with CCM is inherently difficult – disability and anxiety about the future can reduce quality of life dramatically. Access challenges add yet another layer of stress and frustration to the lives of our families. While we may not have a cure yet, access challenges are addressable.

The Alliance to Cure intends to move the needle to increase access to information, support, care, and research for our families. No two patients or families have identical challenges. For example, higher-income rural patients have different access gaps than lower-income rural patients. Caregivers of children face challenges that are not the same as caregivers of spouses. Some patients face systemic barriers because of gender, race, or ethnicity.

We hope to understand the broader landscape and use this to design programs that are individualized to the greatest extent possible – to help you and those you love. We have already increased our use of technology to make patient information accessible, and we plan to expand this. Additionally, we are developing medical education programs. We know there are many easy and not-so-easy ways we can make a difference.

First, we need to understand the community's needs. We've created a survey for patients and will follow this with a separate survey for caregivers of spouses and children. Individuals who are both a caregiver and a patient are welcome to complete both.

Our 15-minute patient survey is available at rebrand.ly/ACCM-AccessSurvey and will close on September 30th. Our caregiver survey will be available by the end of September, and we will send out alerts through our registry and social media.

We are grateful for your participation as we achieve our vision.

Community Health Worker Clinical Trial Education: Educating Educators

Clinical trials are the path to treatments and a cure for cavernous malformation. Most people are not familiar with what happens during a clinical trial, primarily because trials are not on their radar. Community Health Workers, the front-line personnel in many areas for educating patients and families, are not offered information about the clinical trial process in their training.

Nowhere is this information more urgent than in New Mexico, where a founder mutation makes the disease more prevalent than anywhere in the world. In New Mexico, CCM is not a rare disease – it's a public health issue. We anticipate that clinical trials will begin in New Mexico by the end of 2025, if not sooner.

With generous funding from the Rare Disease Diversity Coalition, the Alliance to Cure is tackling this lack of information by creating a training program covering both CCM and clinical trials for Community Health Workers (CHWs). The goal is for CHWs to become certified in CCM and clinical trial education so they may convey information and opportunities to community members. They should be able to dispel misconceptions about clinical trials and explain in simple terms the process of moving a treatment from bench to bedside. We have created a 12-hour online course and a mobile progressive web app and are working with the New Mexico Department of Health to pilot and distribute it.

Once approved, the course will be translated into Spanish and should become available in New Mexico, El Paso, and other areas where the CCM1 Common Hispanic founder mutation regularly occurs. The course will also be available to all Alliance to Cure members. The Rare Disease Diversity Coalition intends to adapt our course so that it may be used by other rare disease organizations.

The Alliance to Cure is excited to bring this information to our CCM families and serve as a model for other rare diseases.

Spotlight

The Inspiration for CCM Fundraising Powerhouse Elle's Angels Atlanta

A special person

Fifteen-year-old Elleanor lives in Atlanta, Georgia with her parents, Mindi and Mike Wilson. She is in the 10th grade at a small public charter school and enjoys spending time with her family and friends.

"Elle is special," Mindi says. "She's been through more in her short life than most of us encounter in a lifetime. But she never complains, and she never gives up."

A life-changing neurological event

Eleven years ago, 4-year-old Elle was about to build a sand castle on the shores of Tampa Bay, Florida when she suffered a sudden stroke that left her temporarily unconscious and unable to walk. Emergency CT and MRI scans revealed multiple cavernous malformations, including one in her brainstem that had caused the bleed. The lesion was at a high risk of re-bleeding.

Elle underwent a successful surgical resection by Dr. Daniel Barrow of Emory University in Atlanta. Elle would have deficits from the bleed, but she was out of immediate danger. Mindi and Mike moved their family from Florida to Atlanta to support Elle's recovery and manage her condition.

Mindi and Mike found patient and caregiver support through Alliance to Cure by connecting with CEO and Founder Connie Lee.

"Philanthropy creates speed."

Years later, when Elle's CCM3 diagnosis was revealed by genetic testing provided by Alliance to Cure, Mindi and Mike decided to establish their own public charity, Elle's Angels Atlanta, to raise funds for brain health research.

"There is nothing we can do to better Elle's prognosis," Mindi says, but "the research Connie Lee has spearheaded promises hope and a cure. Elle needs that."

Since 2022, Elle's Angels has held the annual "Holy Smokin' Bar-B-Que Bash" in Atlanta benefiting Alliance to Cure and, since 2023, Emory's Brain Health Center. Elle's Angels has raised more than $175,000 to support Alliance to Cure's mission.

"Research takes TIME," Mindi says, but "philanthropy creates SPEED!" Elle's Angels' contributions have enabled Alliance to Cure's recent efforts to drive research for a cure including the preclinical treatment testing lab, focused ultrasound bridge grant to UVA, and gene therapy grant to the University of Rochester.

"We are doing what we can to support Connie and accelerate a cure," Mindi says. "[Elle] is amazing, and her gifts, passions and strengths can be supported and protected. It is our job and our joy to help her carve out a meaningful life."

To learn more, visit ellesangelsatlanta.org

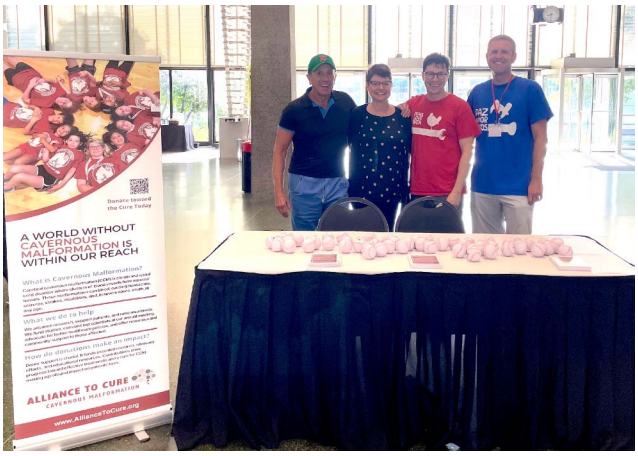
Events and Fundraising

Thank you, CCM Cure Champions!

Our community fundraisers together have raised over $150,000 this year to drive research for a CCM cure. Check out alliancetocure.org/events to join an event near you. If you'd like to hold your own fundraiser, email Lindsay at lindsay@alliancetocure.org.

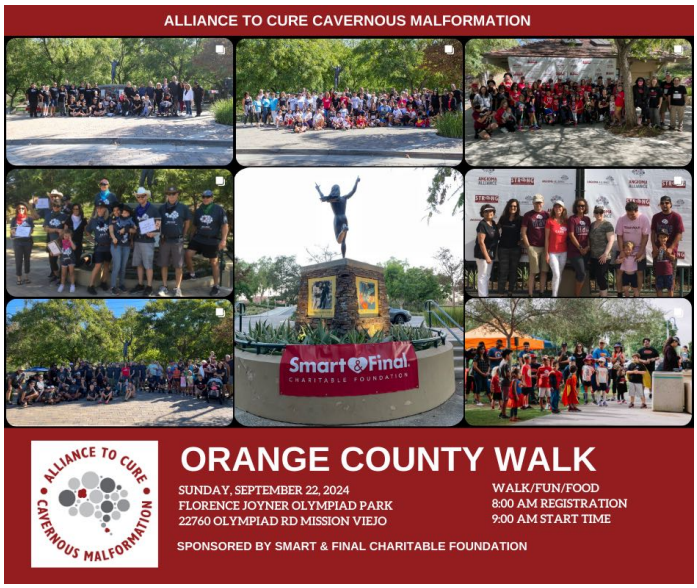
- Holy Smokin' Bar-B-Que Bash, GA
- Strides to Cure CCM - 30 for 30 Challenge
- Chip-in for a Cure Golf Scramble, MD
- Swinging for a Cure Golf Tournament, CA
- Rocking for a Cure Fundraiser Concert, MD
- Esperanza's Step for a Cure, NM
- Kody's Summer Bash, MN
- Alliance to Cure Cavernous Malformation Charity Golf Tournament, CO
- Saberseminar, IL

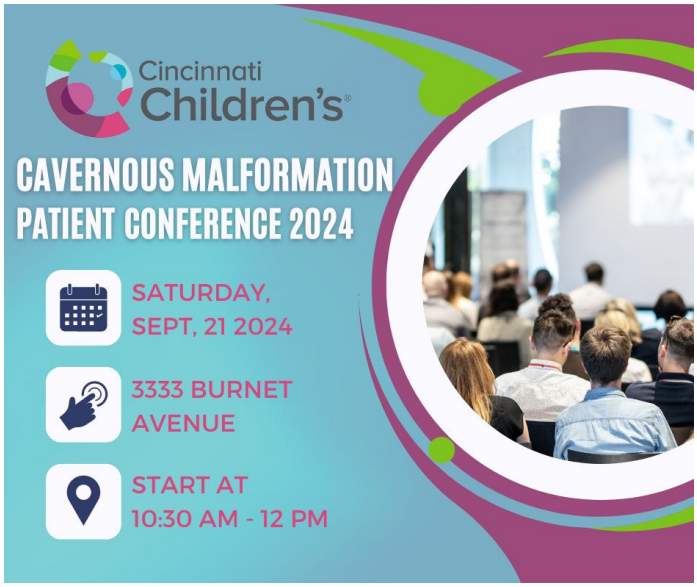
Thank you to our community members who held events or fundraised through Strides to Cure CCM: the Baron Delgado Family, Kelly Bowles, Dan Brooks, Chad Cavallaro, Nicole Clayton, Yasemin Cole, Kristyne Cole, Evan Compton, K.C. Eames, Julia Echenique, Elle's Angels Atlanta, Kristen Fowler, Angela Johnson, Chuck Korb, Bailey Krueger, Brett Margolis, Esperanza Martinez, Marco Merced, David Meyer, Allison Mintz, Diana Montenegro, Lisa Schesso, Debby Stickney, Grace Topp, Ron Weaver

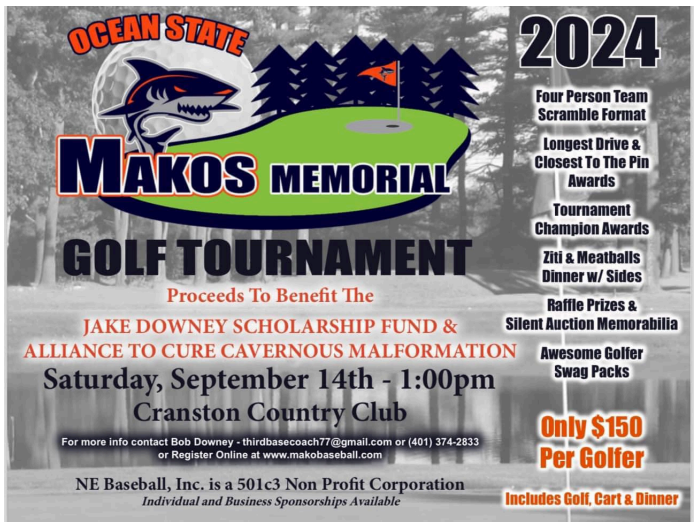


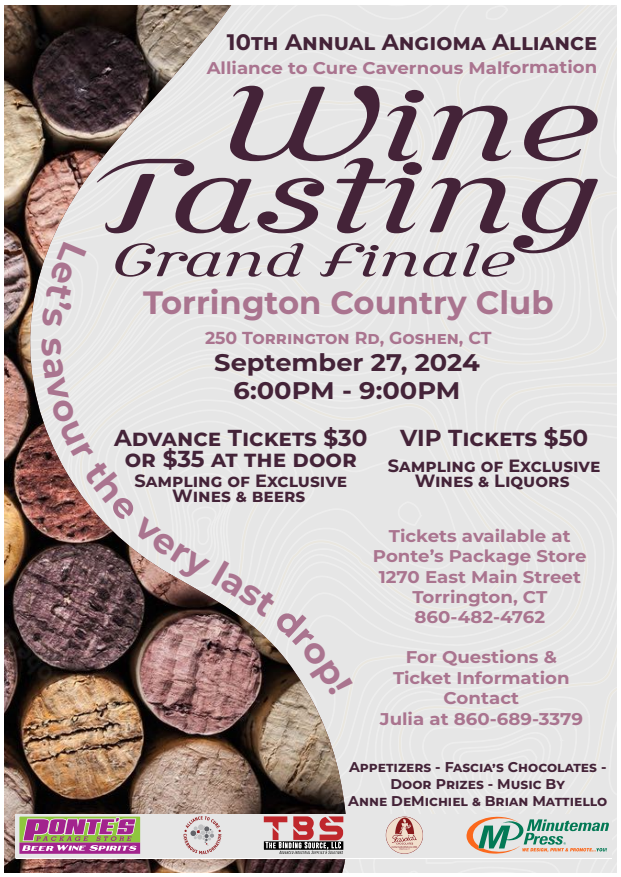
Sabreseminar 2024

Esperanzas Step for a Cure 2024; photo Nicholas Peña









Upcoming Events

This newsletter will hit mailboxes after our national Rhythms of Hope event. We hope you were able to catch it live or at one of our 6 in-person locations. Rhythms of Hope captures the spirit of the Alliance to Cure – we come together to strengthen our community, improve care, and make research possible.

The fun isn't over yet! Pictured on this page are events through September 27th, with locations around the country. We hope to see you!

Also in the works with more info to come on our website and social media:

- September 30th – Heine Strong Golf Tournament, MO
- October 25th – Courts for a Cure, TN
- October 26th – 10th Anniversary Malibu Walk for a Cure, CA

If you're interested in organizing an event, we can help! Please contact Lindsay Ramirez at lindsay@alliancetocure.org for information.

First CCM Family Weekend Brings Joy to Community

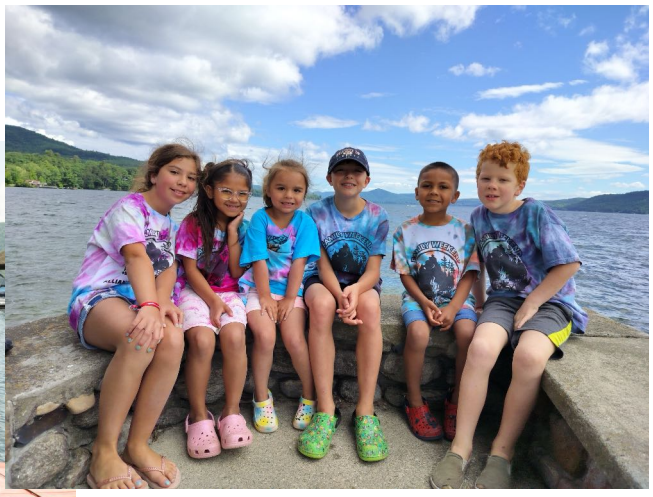
Our first-ever CCM Family Weekend was a heartwarming and unforgettable experience! At the end of June, we welcomed more than 70 patients and their families from across the U.S. to a weekend of fun and relaxation at the Silver Bay YMCA in Lake George, New York.

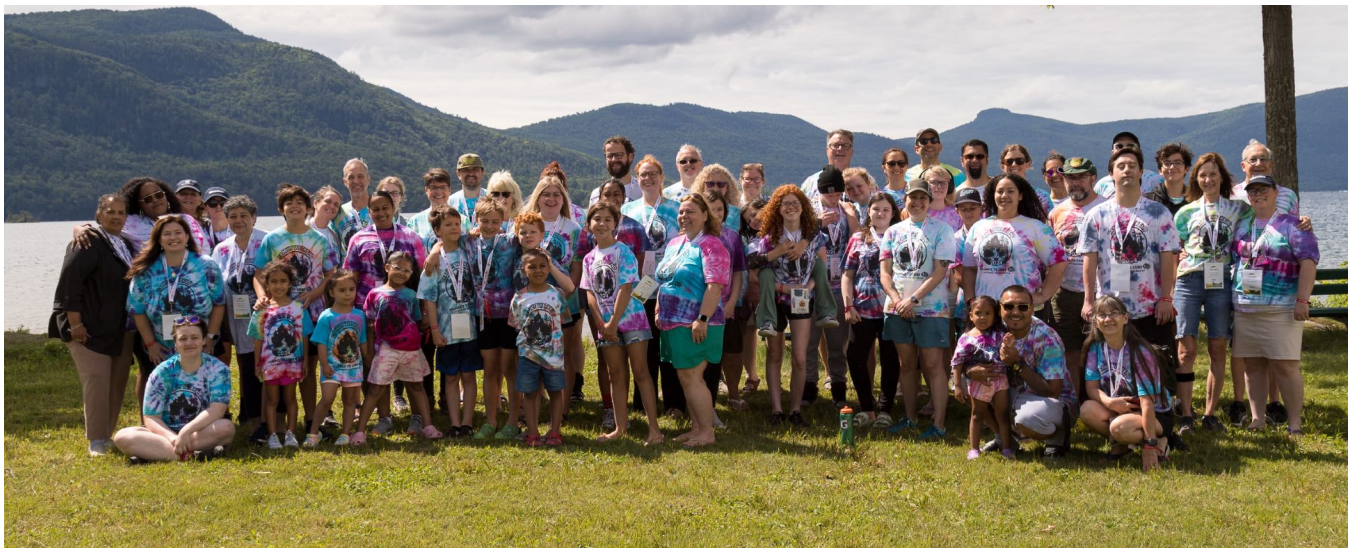
The three-day event allowed our community members to share their stories and build lasting connections as they took part in a wide range of activities, from painting and relaxing in rocking chairs on the porch to rock climbing and archery.

"I truly enjoyed family weekend and hanging out with people who understood my situation," said one participant. "It made me feel empowered and happy to be alive."

The weekend was made possible through the generous gift of one of our community members as well as our industry partners Recursion, Ovid, and Graviton.

We look forward to many more gatherings like this in the future!





How You Can Help

Volunteer: Share your talent and time in any number of ways including Community Alliances, peer support, events, legislative advocacy, and much more: www. alliancetocure.org/care-community/community/volunteer/.

Donate: Your contributions help fund our research initiatives toward a cure and our patient support programs. To donate, please send a check or money order in the enclosed envelope or visit our website at www.alliancetocure.org to donate with a credit card.

Sponsor: Sponsorships can maintain essential programs or help us expand our support for the patient and research community. Sponsors are acknowledged with logo placement, naming opportunities, or appropriate other recognition. Contact us at info@alliancetocure.org to learn more about these opportunities and valuable benefits for your company.

Our Mission and Goals

It is our mission to inform, support, and mobilize those affected by cavernous angioma and drive research for better treatments and a cure. We do this by developing and executing strategic, creative, high-return interventions as a model for rare diseases:

1) **Facilitate and participate in cavernous malformation research to achieve a complete understanding of the disease** and facilitate clinical drug trials and other treatment improvements. We do this through our Accelerating Cures program, Scientific Meetings, patient registry and biobank, genetic testing program, research collaborations, and outreach to special populations.

2) **Provide disease and resource information** to educate and improve the lives of people affected by cavernous malformation, caregivers, health professionals, researchers, policymakers, the media, and the general public. We achieve this through our website, publications, webinars, conferences, and media appearances.

3) **Foster and promote a caring community to provide support**. We offer live and online support opportunities and broad international outreach.

4) **Get people involved in advocacy and active participation toward a cure**. Involvement can include activities like research participation, Community Alliances, our upcoming Patient-Expert Certification, legislative advocacy, and public events.

5) **Build and sustain a broad base of funding sources to support our mission and goals**. We count on you!

About Alliance to Cure Cavernous Malformation

Alliance to Cure Cavernous Malformation is a non-profit, international, patient-directed health organization created by people affected by cerebral cavernous malformations (also known as cavernous angiomas or CCM). Our mission is to inform, support, and empower individuals affected by cavernous malformation and drive research for treatments and a cure. We are monitored closely in our educational efforts by a Scientific Advisory Board comprised of leading cerebrovascular neurosurgeons, neurogeneticists, and neurologists.

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