

ANGIOMA ALLIANCE NEWSLETTER

because brains shouldn't bleed

Clinical Care Consensus Guidelines are Published

We are proud to announce, after a three-year major effort, the Angioma Alliance Clinical Care Consensus Guidelines have been published in the peer-reviewed journal *Neurosurgery*.

Until now, there has never been a single published document providing expert, comprehensive disease and treatment information to the medical community. Medical treatment has been inconsistent, very much depending on chance factors like where a physician trained. Our guidelines, available to all medical providers, recommend a standard of care and a framework for clinical decision-making that can be used to inform treatment and save lives. This is ground-breaking.

Led by Chief Scientific Officer Dr. Amy Akers, Angioma Alliance assembled the authors of the Clinical Care Consensus Guidelines, including clinician members of the Angioma Alliance Scientific Advisory Board and invited experts, in 2014. The group engaged in an extensive process of reviewing, compiling, and scoring decades worth of medical literature to develop guidelines based on the best evidence available. They also identified gaps where more research is needed – for example, on the effect of blood thinning agents on lesion bleeding. Once each section of the document was created, the expert group engaged in rounds of discussion and voting to achieve consensus. Finally, the article was submitted to a

medical journal where an outside group of experts reviewed and approved the findings. These guidelines represent the best information available.

We urge you to share these consensus guidelines with your doctors, to improve your own care and also to impact the care of patients to come. By disseminating the guidelines, we hope to increase treatment consistency: you should be able to receive quality care no matter where you live. A synopsis of the guidelines is available to you online in *Neurosurgery* (doi.org/10.1093/neuros/nyx091). The full-length consensus guidelines, similarly peer-reviewed, are available on our website: www.angioma.org/CCMGuidelines.

We have written a version of the guidelines for patients in our new booklet, *Cerebral Cavernous Angioma: A Patient's Guide*, available on our website. These booklets will be available at our Centers of Excellence (see our article on the University of New Mexico Center of Excellence on page 8) and printed copies can be requested as a patient resource by any doctor in the world who would like to use them. The booklet already has been translated to Portuguese; a Spanish version is in process. We hope these new resources will improve the lives of cavernous angioma patients everywhere.

Connie Lee

The Clinical Care Consensus Guidelines address what is known about the following topics:

Epidemiology And Untreated Clinical Course

- Prevalence of the illness and number of people who develop symptoms,
- Discussions of the hereditary and the sporadic forms of the illness,
- The untreated course of the illness, including risk factors for hemorrhage, information specific to spinal cord cavernous malformations, seizures, and the impact of the illness on functioning.

Genetic Testing And Counseling

- Recommended genetic tests and criteria for testing, including testing of additional family members,
- Differences in disease severity between the three mutations.

Imaging CCMs And Reporting Standards

- Recommended MRI sequences, specific information to include in an MRI report, and timing of follow-up MRIs,
- Use of additional imaging techniques like CT Scan and angiography.

Neurosurgical Considerations

- Decision-making for surgery of CCMs depending on location, and special considerations for surgery of CCMs associated with seizures,
- Use of stereotactic radiosurgery.

Neurological Considerations

- Management of symptoms, including in children and during pregnancy,
- Physical activity recommendations,
- Potential risk and benefit of medications.

News

June is Cavernous Angioma Awareness Month!

Cavernous Angioma Awareness Month is an international effort by Angioma Alliance and its sister organizations around the globe to raise awareness among the public and decision-makers about CCM and its impact on patients' lives. In June, we ask everyone affected to stand up and show their support in the following ways!

1 - Participate on social media

★ Thunderclap it!

Go to www.tinyurl.com/junethunderclap and sign up before June 15 to show your support on social media. We need 250 supporters so our message is shared!

★ Add an awareness ribbon to your Facebook profile picture

Click on your profile picture and select "add frame" then search for "cavernous angioma."

★ Post a short video or picture on social media

Share your story about why you are involved. Use the hashtags #careforccm #brainsshouldntbleed and share with us @angiomaalliance.

2 - Support or plan an event in June

★ Art for Angioma Alliance

Throughout June, amateur and professional artists will be auctioning off their artwork to benefit Angioma Alliance. Get involved as an artist or bid on some of the amazing artwork. Go to www.facebook.com/artforangiomaalliance for more info! Thank you to Jana Bergholtz for hosting.

★ Mets Game

Join us on June 4 as Angioma Alliance holds an inaugural fundraiser at a New York Mets game! The Mets will play the Pirates during this family-friendly 1:05 game at Citi-field! \$10 of every ticket sold will benefit Angioma Alliance. A Curtis Dickerson autographed baseball will be raffled off and kids in attendance can take part in the Mr. Mets Dash, an exclusive opportunity where kids can run the bases after the game! Purchase your tickets at



www.tinyurl.com/2017metsgame or make a donation if you can't attend! This is a great way to connect with other families who are affected. Special thanks to Kristina and Joseph Jankowski for hosting the event. Your dedication is so important to our mission.

★ Chili Cook-Off

On Saturday, June 3, at Okeena Park in Dyersburg, TN, Sommer Lynn Nowlin and her family are hosting a Chili Cook-Off to benefit Angioma Alliance! Entry to compete in the Cook-Off is \$25, and \$10 will provide you with an all you can eat ticket. To buy tickets: tinyurl.com/chiliforangioma. Thank you Sommer and family for hosting.

★ Meet and Greet and Chocolate

Please join us on June 24th from 4-6 pm at Fascia's Chocolates, 44 Chase River Rd, Waterbury, CT for a chance to meet others affected by cavernous angioma, while enjoying chocolate. Check our Facebook page for more information.

3 - Reach out to local media

Share your story on TV, radio, and in print. Contact salband@angioma.org for more details on pitching a story.

4 - Make a donation

Help us find a cure by donating at angioma.org/donate or mail to Angioma Alliance, 161 Jefferson Drive, Palmyra, VA 22963.

3rd Annual Cincinnati Reds Cavernous Angioma Night Held on May 8

The Cincinnati Reds and Angioma Alliance held its third annual Cavernous Angioma Night on May 8 as the Redlegs played the Yankees, in this rare interleague game. The event was the largest yet, with over 450 Angioma Alliance supporters and sponsors in the stands. More than \$9,000 was raised to benefit our mission, and the event served as an amazing awareness opportunity, with over 25,000 fans in attendance and millions more watching from home. The pre-game ceremony included one lucky winner, Tim Wolf, who won the on-field opportunity to catch the first pitch thrown by Joe Price, retired Reds Pitcher, and Jim Leyritz, retired Yankees catcher. Our video played on the Jumbotron and we received media coverage from Fox 19 and Fox Sports. Way to knock it out of the park!

\$6 of every ticket sold benefited Angioma Alliance. A very special thank you to Tony & Cari Mayer who hosted the event and to the sponsors who supported us. In 2012, the Mayer's 1-year-old son suffered a seizure which led to his diagnosis of cavernous angioma, two subsequent surgeries, and the possibility of future surgeries. Your dedication to our mission is so important. If you are interested in getting more involved in next year's event, please reach out to Tony Mayer at mayeraj44@yahoo.com.

15 for 15

In 2002, Angioma Alliance began with a mother, an infant, and a need. On May 15, 2017, Angioma Alliance celebrated its 15th Anniversary.

Connie Lee, founder of Angioma Alliance and parent of a child with CCM states, "fifteen years have allowed us to create a national and international community where there was none, to drive research to the cusp of better treatments, and to provide real hope to the thousands of families living with cavernous angioma. I am profoundly grateful."

A two-week long giving and awareness campaign was held to highlight the accomplishments made by Angioma Alliance with the help of the CCM community. Over \$1,000 was donated to support the campaign and many long-time members shared how the organization has been an important part of their CCM experience.

In a video, Connie reflects on the past fifteen years with a poignant and hopeful message about her family's experience and how the Angioma Alliance community has grown. You can read a transcript of Connie's reflections on page 9 of this newsletter, or watch the video on YouTube: youtu.be/3eLGo_TnQBk.

You can still donate at www.crowdrise.com/15-for-15. Here's to another successful 15 years and to fulfilling our vision of a permanent cure for CCM.



Tony Mayer, Angioma Alliance Board member and organizer of the event; Tim Wolf, winner of the "catch the first pitch" raffle; Jim Leyritz, retired Yankee catcher; Joe Price, retired Reds pitcher.

Events

Baca Family Historical Project

The Baca Family Historical Project has taken off with several events scheduled over the summer. We are looking forward to our first presentation on May 23, at Las Vegas, New Mexico where we will share information about Baca Family genealogy and cerebral cavernous angioma. Las Vegas is rich in Spanish history and an extension of the Camino Real de Tierra Adentro trail that continued up to Taos, NM and southern Colorado.

As we know, traveling with the Spanish families and explorers was the cerebral cavernous angioma genetic mutation. Because of geography, the people of Las Vegas lived in isolation, containing the gene within Spanish families. We believe the town to be home to many undiagnosed patients whom we hope to find with our initiative.

Please join us! Our visit in Las Vegas will begin with an interview at KFUN radio, followed by a special presentation at 10 am to the Las Vegas Public Health Office Council Meeting, and then a community wide presentation at 2 pm at Highlands University, Lora Shields Lecture Hall 1.

Other scheduled events can be found on our website: www.bacafamily.org. In the coming months, we will be making presentations at multiple Albuquerque and Santa Fe area senior citizen centers. Still pending is a special historical presentation in Los Lunas later this summer.

6th Annual Angioma Alliance Canada Conference

Angioma Alliance Canada will be holding its 6th annual conference on June 10, from 8:30 am to 5 pm at the Peter Gilgan Centre for Research and Learning, at the Toronto Hospital for Sick Children. The event will also include a meet and greet on the evening of Friday, June 9.

Speakers at the conference include neurosurgeon Dr. Christopher Wallace, of the Kingston General Hospital; Dr. Benjamin Lant, a researcher studying CCM genetics in the laboratory of Dr. Brent Derry; and psychologist Shannon Mossip.

In addition to providing opportunities to learn from experts, the conference allows time to meet other families affected by cavernous angioma. Because the illness is rare, many patients have never met another person with the illness. The conference provides the opportunity to share your experiences and to become more involved in the work of Angioma Alliance Canada.

For more information, visit the Angioma Alliance Canada website at www.angioma.ca.

Orange County Walk

Angioma Alliance is proud to announce its inaugural Angioma Alliance Walk and 5K honoring Florence Griffith Joyner to be held on Sunday, September 24, 2017 at Flo Jo Park in Mission Viejo, CA. Flo Jo, still the fastest female athlete of all time, passed away from complications related to cavernous angioma.

Her daughter, Mary Joyner, a former contestant on America's Got Talent, will sing the National Anthem. The Walk and 5K will take place around the beautiful Lake Mission Viejo in Orange County, California. Highlights include lots of family-friendly activities, refreshments, raffle and more!

We are currently recruiting participants, committee members, sponsors and in-kind donors. Please go to tinyurl.com/flojowalk to get more information or reach out to salband@angioma.org. Thank you Linda Fuchser and Kristen Lewis for hosting.

Paint Nite Fundraiser

Paint Nites are held across the country, most likely there is a location near you! To invite your friends and family, go to paintnite.com and enter code VF-CUREFORCCM. Angioma Alliance will receive \$15 per ticket sold! Go anytime through the end of July. Thank you to Mary Collier for hosting.

Don't see any events in your area? Reach out to Stephanie, salband@angioma.org, to plan something in your community.

Angioma Alliance leading the way at the FDA

During the first week of May, Angioma Alliance had the opportunity to lead a meeting about CCM clinical research and drug development at the Food & Drug Administration (FDA).

In attendance were more than a dozen FDA scientists, as well as key leaders from our Scientific Advisory Board, the pharmaceutical industry, and academic research.

Who attended this meeting?

Angioma Alliance

Drs. Amy Akers and Connie Lee.

Academic Researchers & Scientific Advisory Board Members

Dr. Issam Awad's team is working to develop imaging biomarkers and planning for a trial to assess the effects of Lipitor (a cholesterol medication) on hemorrhage in CCM patients.

Dr. Yashar Kalani's research interests focus on the effects of propranolol on CCM. His team is also planning a trial to study the ability of propranolol to control hemorrhage in CCM patients.

Dr. Helen Kim's lab studies the genetic variability of CCM patients and is working to better understand the factors related to risk of experiencing a severe disease course.

Dr. Leslie Morrison led the first small simvastatin trial and shared her clinical expertise related to variability of related patients carrying the Common Hispanic mutation.

Industry Researchers

Tim Considine, Senior Vice President, Strategic Development at Recursion Pharmaceuticals, a company focused on rare disease treatments, is a member of a team working to repurpose the drug Tempol as a therapy for CCM.

Dr. Lisa McKerracher, CEO of BioAxone BioSciences, leads a team interested in Rho Kinase inhibitor drugs. BioAxone is working to develop a new drug currently called BA-1049 as a CCM-specific therapeutic.

What was discussed?

The meeting focused on challenges and opportunities for CCM drug development.

Endpoints are what a clinical trial measures to assess efficacy of a drug. Given that CCM is such a variable illness, what is best to measure? For example, there is much interest in reducing hemorrhage rates, but hemorrhage is an infrequent event, and one not experienced by all patients. Angioma Alliance aims to develop an instrument, the CCM Health Index, that can measure the total patient reported disease burden and provide an endpoint that can be used in future trials.

Biomarkers are tools that measure something related to disease, but not a direct clinical symptom. For example, Dr. Awad's team is developing MRI tools that can measure iron deposits caused by cavernous angioma hemorrhage as well as permeability. These measures are related to bleeding and vessel leakiness and will be used to screen study participants to determine eligibility, and to provide outcome data related to drug effectiveness.

Clinical trial design must be considered carefully, particularly with rare diseases when patient numbers are limited. Much of our discussion focused on strategies for optimizing trial design and how best to study adult and pediatric CCM.

Preparing for Clinical Trials

With at least 8 different drugs or druggable targets currently under investigation in animal models, we are excited to see studies moving to humans soon. Angioma Alliance will be involved at a variety of levels, including regulatory meetings, protocol and trial designs, and recruitment. As is the case with other disease areas, recruitment will be among the most challenging parts of running a successful clinical trial.

This is where we need your help: if you are interested in learning about future trials and possibly participating, please sign up for the patient registry. The more people we have registered, the more likely we'll be to fill trials quickly. You can create your profile online: www.angioma.org/registry. See the article on the next page for more on participating in clinical trials.

Amy Akers

Can the Community of Bacteria Living in our Gut Change the Course of CCM Disease?

New data from mouse studies at the University of Pennsylvania suggest that modulating the type of naturally-occurring bacteria in our gut can block development of CCM lesions.

The team at U Penn has worked for several years with genetic models of CCM1 and CCM2 diseased mice. This is an early-onset model that uses a genetic trick to turn off both copies of a CCM gene specifically within endothelial (blood vessel) cells, just after the mouse is born. In this model, mice develop many CCM lesions within a week after birth. To turn the gene off, an injection of the drug tamoxifen is given, which works with engineered sequences in the mouse DNA to selectively turn off genes.

This story of discovering the gut connection to CCM began after moving the mouse colony to a new animal facility on campus. The research team noticed a subset of the mice suddenly stopped developing lesions. These resistant mice continued to breed and no CCMs were seen for generations. Mostly.

A few mice in this new CCM-resistant group did develop an aggressive course of CCM. Interestingly, these mice with CCM lesions also had developed bacterial infections at the tamoxifen injection site. This observation of bacterial infections being associated with lesion formation led the team to further investigate the natural bacteria living in the mice, their microbiome.

The team hypothesized that a specific type of bacteria, gram-negative bacteria, accelerates lesion formation. Several experiments provided evidence toward this hypothesis:

Bacterial infection: Using resistant mice (those from the portion of the colony that have the genetic mutations and should develop lesions, but do not), the team injected gram-negative bacteria to cause the mice to develop an infection. Indeed, 9 out of 16 previously-resistant mice developed CCM lesions. This experiment showed that the bacterial signal traveled through the blood to stimulate lesion development in the brain.

Sterile C-Sections: To assess the impact of germs in the environment, the team aimed to raise mice from the original colony (that develop CCM lesions) in sterile, germ-free environments. Mice were delivered by sterile C-section and raised by mothers in a standard or germ-free environment. Amazingly, 7 of 8 mice that were raised germ-free had no lesions!

Fecal analysis: As a last step, the team analyzed fecal matter and found one specific type of bacterial especially prevalent in the mice that develop lesions and absent from those lesion-free mice.

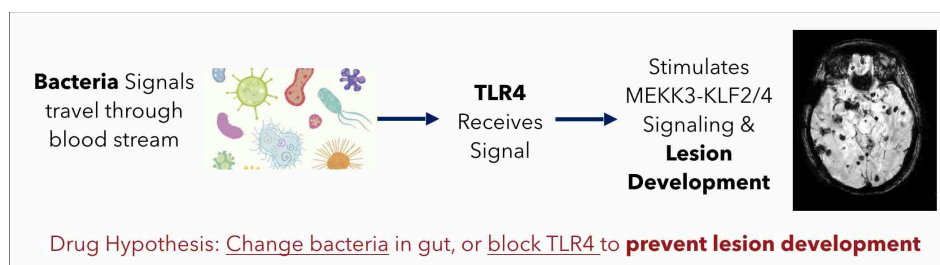
How can these findings translate to therapies for human CCM patients? In associated studies of the signaling molecules, the team identified the molecule TLR4 as that which receives signal from the gram-negative bacteria and stimulates downstream events to cause lesion development. The details of the chemical signal are described in more detail in the paper: tinyurl.com/CCMmicrobiome. The UPenn Study team identified two potential drug targets: TLR4 (the signal receiver) and gut bacteria (which sends signals through the blood), both of which were tested in mice with exciting results.

The model below illustrates how bacteria trigger TLR4 to stimulate further signaling and eventually CCM lesion development. Disrupting the signaling pathway at either the point of the bacteria or the TLR4 receptor has shown to inhibit lesion development in mice.

Blocking TLR4 with a small molecule inhibitor (drug) decreases lesion volume in mice by 80%. Also, treating parent mice with antibiotics specific for the gram-negative bacteria resulted in mouse offspring with a 95-100% reduction in lesions.

These results show us that targeting either the bacteria themselves or the TLR4 molecule that receives the bacterial signal can have profound effects on lesion development. The next step in the research process is to determine whether these findings translate to the human condition. Investigation of human CCM patient microbiome is underway, and Angioma Alliance will begin enrolling participants with a known genetic mutation shortly.

Amy Akers



Opportunities to participate in CCM research

Are you interested in learning more about studies and participating in CCM research? Join the patient registry today.

The *Susan Sukalich* Angioma Alliance INTERNATIONAL PATIENT REGISTRY

Angioma Alliance's patient registry is designed to connect the patient and research communities by providing a platform for communication about CCM research. If you are interested in learning more about opportunities to participate in current or future research studies, please visit www.angioma.org/registry and create your profile today. We do not share your information with researchers, but instead inform you about research studies that need participants.

Recruiting Now!

The Brain Vascular Malformations Consortium (BVMC) is investigating three rare diseases that cause brain vascular malformations: Hereditary Hemorrhagic Telangiectasia (HHT), Sturge-Weber Syndrome (SWS), and Cerebral Cavernous Malformations (CCM).

We are currently recruiting participants for a study called, "Brain Vascular Malformation Consortium: Predictors of clinical course. Project 1: Modifiers of Disease Severity and Progression in Cerebral Cavernous Malformations (CCM)."

The goal of this study is to investigate the genetic factors that contribute to CCM disease severity and progression. To address this question, researchers are looking specifically at the genetic variations in individuals with familial CCM.

If you are interested in learning more about this study, please join the patient registry and contact Amy Akers at amy.akers@angioma.org.

Coming Soon!

Angioma Alliance will soon be a recruitment site (in addition to UCSF and UNM, which are currently recruiting) for a study investigating the relationship between gut microbiome and cerebrovascular malformations.

The goal of this study is to investigate the bacteria that lives in our gut and helps to break down food (called the "gut microbiome"). Mouse studies strongly suggest that

the gut microbiome influences CCM lesion development. This study aims to understand the relationship in human CCM patients and determine whether the gut microbiome may predict clinical course of CCM disease. (See the article above for more on this hypothesis.)

If you are interested in learning more about this study, please join the patient registry and contact Amy Akers at amy.akers@angioma.org.

Free Genetic Testing Initiative – Two Year Anniversary

Angioma Alliance has been offering free genetic testing to our members in the United States and Canada who have multiple lesions and cannot get coverage for testing through their insurance. At the two-year mark, we've had over 200 requests through our international patient registry.

Who Can Be Tested?

Anyone in the US and Canada with multiple cavernous angioma lesions that are not clustered around a DVA or developed as a result of radiation treatment for brain cancer is eligible to participate. We also offer testing to other family members once a known affected individual has had their specific genetic mutation identified.

Why Should You Receive Genetic Testing?

Research studies, like the microbiome study discussed on page 6, have a preference for enrolling individuals who already know their genetic mutation. Clinical drug trials, once they begin, will also require individuals to know their genetic mutation. In both instances, this helps researchers determine if there are differences in the clinical effects of the different mutations. These may need to be taken into account as data is collected and treatments are developed.

Genetic testing is also important in making current treatment decisions. For example, individuals with a mutation of the CCM3 gene are also at risk for scoliosis and other benign brain tumors. They should be monitored for these conditions. Even asymptomatic individuals may benefit from testing as they are planning to have their own families or thinking about common sense restrictions like contact sports or using blood thinners.

How Can I Get Involved?

To express your interest in genetic testing, register at www.angioma.org/registry. Learn more about the program on our website at www.angioma.org/testing.

UNM Named Cavernous Angioma Center Of Excellence: Joins University of Chicago as One of Only Two Centers Nationally

The University of New Mexico has been recognized by Angioma Alliance as a Clinical Center of Excellence in treating cavernous angioma – only the second such designation in the country. The designation is awarded to clinical centers that provide high-quality interdisciplinary care for both sporadic and familial cerebral cavernous malformation patients and have an ongoing research program.

“We’re very proud of our long-standing work in cerebral cavernous malformation and are excited about our recent designation by the Angioma Alliance,” says Leslie Morrison, MD, professor in the Department of Neurology who has directed a major research effort for familial Cerebral Cavernous Malformations at UNM. “Together, we will continue our vital support of patients and families in New Mexico and elsewhere affected by this condition.”

For at least 20 percent of those diagnosed with cavernous angioma, the illness is hereditary. Familial cavernous angioma occurs at a higher rate among Hispanic-American families who trace their heritage to New Mexico. This prevalence in Southwestern Hispanic-American families is due to a specific genetic mutation that has been passed through as many as 16 generations.

According to Angioma Alliance, designated clinical centers of excellence are ranked as either Clinical Center or as a Center of Excellence, reflecting the number of clinical disciplines with expertise and the level of involvement in clinical research and in professional and patient education.

Co-directors of the UNM Center of Excellence are Dr. Leslie Morrison and Dr. Atif Zafar. Other key personnel include neurosurgeons Drs. Chohan, Yonas, and Carlson, geneticist Dr. Heidenreich and genetic counselor Joanne Drautz. To make an appointment with the clinic, please call (505) 272-3160.

To achieve the Alliance’s Center of Excellence status, a facility must exceed the Standard of Care designation, and,

- Have at least two additional specialty physicians with cerebral cavernous malformation expertise in any of the following disciplines: pediatric neurology, pediatric neurosurgery, dermatology, or neuro-ophthalmology. Children’s Hospitals may qualify with one additional specialty;
- Maintain an active clinical research program with a history of publications that can include natural history studies, comparative treatment outcomes research, genetics/genomics research, and/or clinical drug trials. The Clinical Center of Excellence must have one active IRB-approved CCM research project;
- See at least 50 CCM patients per year;
- Host at least one Grand Rounds per year; and
- Organize at least one patient education event annually either independently or in collaboration with the Angioma Alliance.

For more information on cerebral cavernous malformation research, visit information the Brain Vascular Malformations Consortium at www.rarediseasesnetwork.org/cms/bvmc, or the Rare Diseases Consortium Clinical Research Network at www.clinicaltrials.gov, or call (505) 272-3194 to speak with a UNM CCM research coordinator.



Dr. Connie Lee, Dr. Leslie Morrison, and Dr. Atif Zafar.

Reflections on 15 Years of Angioma Alliance

In 2002, I felt alone. I had a 2-year-old daughter who had already been through 3 brain surgeries to remove hemorrhaging cavernous angiomas. She was spunky and happy and doing well, but a cloud hung over my enjoyment of her: will there be another hemorrhage? Will today be the day? I didn't know anyone else—either child or adult—with the illness. I worried that Julia, my daughter, would grow up never knowing anyone who was like her. That was the simple idea behind Angioma Alliance: let's make a space for affected families to share stories and to learn from each other.

In 15 years, the Angioma Alliance community has given Julia and me more than we could have ever imagined. About a year after Angioma Alliance formed, Julia had another hemorrhage, deep in her cerebellum. This time, the Angioma Alliance community was there for us; sharing experiences and walking with us through the surgery and rehabilitation that followed. A researcher who was herself a mom sent Julia a small stuffed unicorn that arrived on surgery day. Julia held that gift close for years and felt its comfort. We weren't alone, and I remain grateful to you for holding us in your care.

As she grew older, Julia wanted to join the neighborhood children riding their bicycles around our cul-de-sac. Almost every sunny day would find Julia, me, and a purple bike, struggling to stay upright.

"Let's do this!" I would encourage.

"Okay, mommy, I'm ready."

Under my breath I would whisper, "Please stay up this time. I'm getting too old for this."

I held her up on the bike and ran. I let go and watched momentum carry her. It was her turn to pedal. One rotation, two rotations, three; it was working! Until it didn't. Like every other attempt, she listed to the right as her weaker right leg tried to push the pedal down. Her handlebars turned 45 degrees, and she toppled, with a scream for good measure.

"Julia, that was wonderful. I think you went farther than ever. Do you want to try it again?" And try she would, and try, and try... As Dr. Awad put it, "we are asking Julia to climb Mt Everest without oxygen."

When she was 11, just before Angioma Alliance's 10th anniversary, Julia underwent a spinal fusion to treat scoliosis, the result of her specific genetic mutation, CCM3. Because of complications, the surgery almost took her life. Julia was in the hospital for weeks, and even after discharge, her recovery was long and painful.

As horrific as the surgery was, it taught us that nothing is promised. And, it led to one of the highlights of our lives so far: our choice to take a 5-month drive around the United States during which

we visited Angioma Alliance families in every city we could. Julia had the opportunity to meet you, those of you who have few visible effects of the illness, and those of you who are severely affected: unable to walk or see or speak.

She saw the way your family conducts your life: with dignity, with purpose, with a spirit of generosity. You model everyday courage, a

lesson we both took to heart.

After our trip around the country, it was time to buy Julia a bigger bike that she still couldn't ride and try again. This time, when we visited the bike shop, we found it. Just inside the front door; big and blue with three wheels and a seat as wide as a house. An adult tricycle, the kind older ladies in Florida ride on their way to canasta.

"Are you sure?" I asked her. I worried riding a tricycle as a teenager might cause her to be teased and rejected by the kids on the block.

Julia didn't blink. We shooed away a pre-schooler who was using it as a jungle gym and asked the saleslady for a test drive. In the parking lot behind the cycling shop, as my 13-year-old daughter took off without me for the first time in her life, I held my breath and let the tears fall. Julia's face beamed, with pride. She had arrived.



When we unloaded the bike from the car at home, her best friend ran over and drooled over the big white wire basket on the back and the old-fashioned bell. When Julia rode in the cul-de-sac, the adult neighbors lined the street, cheering, raising their glasses, and expressing appropriate amounts of envy. The third wheel was metaphor, and we all glimpsed her future. Her invisible struggles and potentially stigmatizing solutions had a tangible representation—the tricycle—and we were humbled by her courage. The courage she had learned from Angioma Alliance families.

My goal with Julia is not necessarily to prepare her to live an independent life; she may not have that luxury. My goal is to encourage her to develop the skills and flexibility to figure out how to make the best of any life the cards deal her; to accept the third wheel with grace, to give back when she's able, and to never let an opportunity for community pass her by.

At the 15-year mark, Angioma Alliance is still giving back to me. Now, it's teaching me to run marathons. I've always been a sprinter, overcoming obstacles as needed. A juggernaut, I'm told. I've let out some frustration over the years about the pace of CCM science. However, our dedicated researchers have taught me the value of building a solid foundation of basic science on which to launch treatments. They have welcomed me into their labs and let me look in their microscopes. They have trusted me with secrets. They place faith in the power of Angioma Alliance to

accelerate progress with our approach of building shared resources.

In 2002, when we began, there was only one gene identified, a disjointed research community, and little understanding. In 2017, we have 8 treatments preparing for trials with more on the way. We have a growing research community that now collaborates, to bring each lab's strengths to bear. Angioma Alliance is central to this progress, and we're humbled to receive your support of our often-unconventional efforts; I promise you they are working.

I'm excited about the next 15 years. We will all be asked to participate. I feel up to the challenge, and I hope you do, too. Where there once was no one, there are now thousands and thousands of connected families around the globe. We can nurture each other, and we can find a cure.

I still have much to learn from you, and I would love to spend more face-to-face time meeting you in coffee shops or at events. Your story inspires me and motivates everything that Angioma Alliance strives to accomplish. Brains shouldn't bleed. I feel confident that in 15 years (or less), they won't.

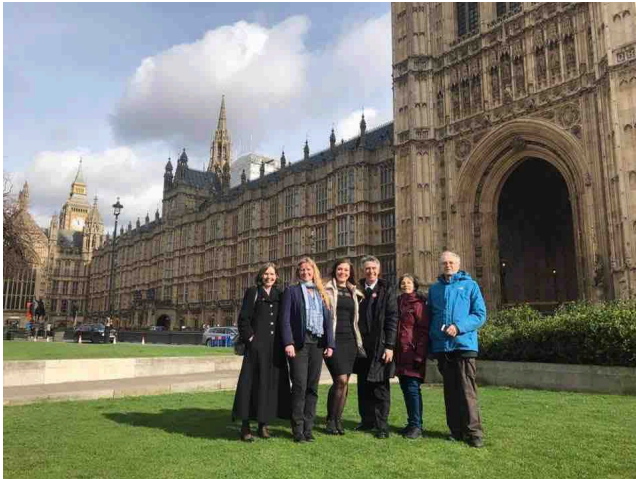
Watch Connie Lee's video on the Angioma Alliance YouTube channel.

JUST A FEW OF THE MANY ACCOMPLISHMENTS MADE IN HELPING PEOPLE WITH CCM:

- 1 Hosted 12 Annual CCM Scientific Meetings
- 2 Hosted 50+ Family Regional Conferences
- 3 Counseled 200+ on genetic testing and offered testing to 100 individuals
- 4 Introduced and passed legislation to increase awareness, improve care for people with CCM and encourage CCM research
- 5 DNA/Tissue Bank provides samples/data to 15 laboratories around the world
- 6 Enrolled 1,270 people in International Patient Registry
- 7 Provided peer support to over 5,000 people
- 8 Created CCM Clinical Care Guidelines
- 9 Established 2 Clinical Centers of Excellence
- 10 Launched New Mexico Engagement Project
- 11 Serves as a model for 11 international Cavernous Angioma organizations
- 12 Currently, there are 8 drugs in the pipeline as potential treatment for CCM.
- 13 Provided resources and information to 1.25 million+ visitors to website
- 14 Invested over \$3,000,000 in advancing research and providing resources.
- 15 Provided almost 100 website pages of resources and information.

Cavernoma Alliance UK

Rare Disease Day in February was marked at the Palace of Westminster with a group of six of us travelling to London to represent over 1,500 members.



Sarah Bird, Debbs Urch, Simona Stankovska, Ian Stuart, Pat Spallone and David White.

Now in its 22nd year, Brain Awareness Week has been an integral part of CAUK's calendar since 2010. During the week, five regional events took place around the country, culminating in a fascinating talk by Professor David Werring on a neurologist's perspective of cavernous malformations to a packed room of CAUK members at the National Hospital for Neurology and Neurosurgery in London.

At our second Brighton CaverCentre, members discussed the importance of meeting face to face as opposed to discussing concerns virtually, with future gatherings planned concentrating on entitlements and benefits for those with cavernoma, alternative therapies, or possibly a more formal meeting with a medical professional.

Our CaverFamilies had its first meeting of 2017 in Windsor, where both children and parents had workshops on cavernoma before spending the evening together. The second day was spent at Legoland, thanks to tickets donated by Merlin's Magic Wand.

The five-year Big Lottery award (2013-18) tapers in the last two years of the grant, so our members' extraordinary fundraising activities are even more vital to the charity's existence. One brilliant example was a Masquerade Ball held at the end of March for Ffion.

Diagnosed with multiple brain cavernomas at eleven months following pneumococcal meningitis, Ffion is relatively well despite having three more haemorrhages over the last twelve months, in addition to the six bleeds she had since birth. And so her parents, Dean and Ellie Davies, threw a ball to benefit CAUK. A masked David White, CAUK's chair, and his wife, were in attendance at a superb evening.



Dean Evans, Ellie Evans, Pat Spallone and David White.

In addition, CAUK are grateful to other fundraisers, such as Kristen Macintosh who has raised substantial funds and awareness of CAUK by pounding the sidewalks of northern Scotland distributing our leaflets, giving a talk, and appearing in the local press. And also and to Katy Baple, who has run in two events raising funds for CAUK following a bleed from "Clive the Cavernoma." Katy's story is especially interesting as she is a British doctor on a year's leave to work in an Australian hospital, where she was on the day of her cavernoma bleed. "I was suddenly the 'stroke call,' which is the alarm that goes out on doctors' pagers, telling them that there's a patient with a potential stroke that needs an urgent review. This alarm always causes my heart to race, but this time my heart was racing even faster as I was the patient." (Katy's full story can be read here: www.cavernoma.org.uk/katy-surrey/)

Our Forum at the University of York is on 24 June to which you are all invited.

Ian Stuart

How You Can Help

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.angioma.org to donate with a credit card.

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. Sponsorships are available for the following:

Scientific Meeting - \$35,000 to \$1,000

Our scientific meeting offers a variety of opportunities to support and reach the research community, including travel awards and sponsored speakers, breaks, and meals.

Newsletter - \$10,000 to \$5,000/year

This newsletter reaches thousands of patients and donors both in print and online. It is the only patient-directed source of information for the cavernous angioma community. If you would like to reach this community and support our efforts, please contact us.

Website - \$10,000 to \$1,000/year

Our website has a global reach, and is always in the top three search results for cavernous angioma. It is the first place newly diagnosed patients look for information and support. In addition to being a patient resource, the website provides information to medical support staff, researchers and the general public.

Events - Range of opportunities

Angioma Alliance members host multiple events throughout the year, from Cavernous Angioma Awareness Night at major league sporting events to smaller Fun Runs and tournaments. Sponsorship opportunities are always available with varying levels of public exposure depending on the event.

DNA and Tissue Bank - \$20,000/year

The DNA and Tissue Bank is the major source of cavernous angioma biological samples for labs around the world, and we have provided the raw materials for several major published studies.

Contact Stephanie Alband at salband@angioma.org to learn more about these opportunities and valuable benefits for your company.



**ANGIOMA
ALLIANCE**

About Angioma Alliance

Angioma Alliance is a non-profit, international, patient-directed health organization created by people affected by cerebral cavernous angiomas (also known as cavernous malformations or CCM). Our mission is to inform, support, and empower individuals affected by cavernous angioma 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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A copy of the latest financial report, registration filed by this organization and a description of our programs and activities may be obtained by contacting us at: Angioma Alliance, 520 W 21st St STE G2-411, Norfolk, VA 23517, info@angioma.org. If you are a resident of one of the following states, you may obtain financial information directly from the state agency.

- Florida – A COPY OF THE OFFICIAL REGISTRATION AND FINANCIAL INFORMATION MAY BE OBTAINED FROM THE DIVISION OF CONSUMER SERVICES BY CALLING TOLL-FREE, WITHIN THE STATES, 800-435-7352 (800-HELP-FLA) OR BY VISITING www.800helpfla.com. REGISTRATION DOES NOT IMPLY ENDORSEMENT, APPROVAL OR RECOMMENDATION BY THE STATE. Florida Registration CH20096
- Georgia – A full and fair description of our programs and our financial statement summary is available upon request at our office and email indicated above.
- Colorado – Colorado residents may obtain copies of registration and financial documents from the office of the Secretary of State, 303-894-2860, www.sos.state.co.us/ Reg. No. 20063003635.
- Maryland – For the cost of copies and postage, from the Office of the Secretary of State, State House, Annapolis, MD 21401.
- Michigan – MICS # 35000
- New Jersey – INFORMATION FILED WITH THE ATTORNEY GENERAL CONCERNING THIS CHARITABLE SOLICITATION AND THE PERCENTAGE OF CONTRIBUTIONS RECEIVED BY THE CHARITY DURING THE LAST REPORTING PERIOD THAT WERE DEDICATED TO THE CHARITABLE PURPOSE MAY BE OBTAINED FOR THE ATTORNEY GENERAL OF THE STATE OF NEW JERSEY BY CALLING 973-504-6215 AND IS AVAILABLE ON THE INTERNET AT: <http://www.state.nj.us/lps/ca/charfrm.htm>. REGISTRATION WITH THE ATTORNEY GENERAL DOES NOT IMPLY ENDORSEMENT.
- New York – Upon Request, Attorney General Charities Bureau, 102 Broadway, New York, NY 10271
- North Carolina – Financial information about this organization and a copy of its license are available for the State Solicitation Licensing Branch at 919-807-2214. This is not an endorsement by the state.
- Pennsylvania – The official registration and financial information of Angioma Alliance may be obtained from the Pennsylvania Department of State by calling toll-free within Pennsylvania 800-732-0999. Registration does not imply endorsement.
- Virginia – State Division of Consumer Affairs, Department of Agriculture and Consumer Services, PO Box 1163, Richmond, VA 23218.
- Washington – Secretary of State at 800-332-4483 or <http://www.sos.wa.gov/charities/>. REGISTRATION WITH A STATE AGENCY DOES NOT CONSTITUTE OR IMPLY ENDORSEMENT, APPROVAL OR RECOMMENDATION BY THAT STATE.