ANGIOMA ALLIANCE NEWSLETTER
because brains shouldn't bleed

Angioma Alliance: 20 Breathtaking Years

When Angioma Alliance started, my daughter Julia was a young toddler, enjoying Barney and baby dolls between brain surgeries. She had no genetic diagnosis because, well, CCM3 hadn't been discovered yet. She received care from our local specialists who were wonderful people, but not experts. We lived in the isolation of not knowing another child with the illness.

What a difference twenty years can make.

Now, Julia is 22 and planning to enroll in her first clinical drug trial.

Now, we can go online or travel almost anywhere and find a community of wonderful families who share our challenges.

Now, we have our choice of expert medical centers.

Now, there is deep scientific understanding and the promise of a cure.

Thinking about this progress takes my breath away.

Twenty years is both a long time and the blink of an eye. Many people were part of building the original Angioma Alliance, from our earliest scientific advisors Dr. Issam Awad and Dr. Doug Marchuk and our first Board members, to the friends and families whose faith in our purpose was expressed through their financial support. There are thousands of heroes since 2002 who have given time or treasure to build our community and push us toward a cure. This newsletter issue is packed with news of research advances and collaborations, gatherings, and achievements. Please know that there are many more activities happening behind the scenes that we can't yet announce publicly. Because of your work and support, there is incredible momentum that we are harnessing to make advances on all fronts.

One specific piece of news has been long-awaited. We will see the release of ICD-11 in 2022, the latest update of the international classification system for diseases, and it finally includes a diagnostic code for us! H00534 is the code specifically for Cerebral Cavernous Malformation and will allow us to get a better sense of how many patients we truly represent. It will also bring some resolution to the issue of the name of the illness. We will be sharing more about this in May.

Also in May, to celebrate our 20th Anniversary on May 15, we ask that you consider participating in Strides to Cure CCM (see page 8) in whatever way you are able. It is a celebration event but also an event of remembrance and honor. We have lost too many in our community to CCM and even more have been left with life-changing disability. We hold them close in our hearts and keep space for them in all we do, including on May 15th. Please participate to honor someone you love and to recognize everyone who lives daily with the challenge of cavernous malformations.

Thank you for our first 20 years. We could not have come so far without you. We look forward to the promise of the next 20 year, with your partnership in this journey.

Connie Lee

Discovering Angioma Alliance

I've been editing the Angioma Alliance newsletter since 2007, and here's how I got where I am today.

It was a hot summer day in late July, 2005. I had been working hard, juggling three projects, one with a tight deadline, and my stress level was high. I'd also had a lot of back pain, which had led me to take aspirin for a week, something I rarely did.

At the end of the day on Thursday, I suddenly felt very tired. I went to bed in the early evening, thinking I'd just sleep it off. The next day, Friday, I felt nauseous and had a headache; I decided to spend the day in bed.

Over the weekend, I started having funny numb feelings in my right leg, but thought little of it. Friends were visiting, and we ate and drank merrily, enjoying the late summer weather. I lived in a village in the French Alps at the time, and, while the days were hot in this season, the nights were cool and relaxing.

I started having headaches, and on Monday, suddenly much of the right side of my body was numb. I went to see my GP, who thought I had multiple sclerosis, and scheduled an MRI. The headaches and numbness persisted, and when I had the MRI a few days later, it showed a cavernous malformation in my brainstem. But given the fact that it was a very low-power MRI machine, it didn't give much more information, and the radiologist's report was vague.

When I returned home—I had had to travel a few hours to get the MRI—I looked up cavernous malformation, or cavernoma as it is called in Europe, and found very little information. I did, however, find the Angioma Alliance website, which, I quickly learned, was to be my support for the coming years. Connie Lee was helpful when I contacted her, and when I saw a neurologist a few days later, and told him about the site, he was happy to know about it. He only had one other patient with cavernous malformation, and that person had multiple lesions, none in the brainstem.

It took many years for the symptoms I had to dissipate; it was a slow process, and I was quite fortunate, compared to some other people. The headaches, numbness, and dizziness were an annoying constellation of symptoms, and some dizziness still remains from time to time. I occasionally get other, minor symptoms, and have had a few micro-bleeds over the years, and get fatigued more easily than before, but now, more than 16 years later, my lesion is stable.

In 2007, I volunteered to help Angioma Alliance by editing this newsletter, and this is the 46th issue I have produced. I'm very happy to help Angioma Alliance, and the cavernous angioma community, and I owe a great deal to Connie Lee, both for the help she gave me, and everything she has done over the past 20 years, to strive for a cure.

Let's hope that, in the coming years, we make the progress that Connie has worked so hard for, and find a cure for this disease.

Kirk McElhearn

CCM Health Index Longitudinal Study Update

We would like to thank this community for stepping up in such an enormous way to participate in the first round of the CCM Health Index longitudinal study, our collaboration with the University of Rochester. Recruitment ended on February 28. In the end, 616 of you enrolled and completed the survey! Our original target was 400; you are superstars, and we are grateful. Additionally, 29% of participants identified as being a member of a racial or ethnic minority, which is huge. Representation is critical for many, many reasons. It's important that the in index reflect everyone's experience so that it useful and is taken seriously by regulatory agencies.

Six months after initial enrollment, enrollees will receive an email asking them to complete the survey again; we are measuring how our members' symptoms change over time. If you are in the study, please be sure to respond to the email you receive. The CCM Health Index is critical to clinical drug trials and clinical research – it is the only tool specifically for our illness. Thank you for helping to make it a reality.

Angioma Alliance Patients Break New Ground with Research

Our patient community is powerful and never more so than when we work together for research. In January, *Atlantic* magazine published an article, reprinted below, with the story of the genetic CCM2 exon 2-10 deletion founder mutation. Our Angioma Alliance patients working together in a Facebook group—the Bowlin family and many more—made this research and this article possible, putting CCM on a national stage and helping us to find even more affected families.

How a Rare Brain Mutation Spread Across America

The Bowlin family knew they had a history of malformations in the brain. But they had no idea how far back it went.

Of the three Bowlin sisters, Margaret, the middle one, was the first to show signs. She began having seizures as a toddler. Then the eldest, Bettina, had a brief and mysterious episode of weakness in her right hand. In 1986, as an adult, she had a two-week migraine that got so bad, she couldn't hold food in her mouth or money in her right hand. The youngest, Susan, felt fine, but her parents still took her for an exam in 1989, when she was 19. A brain scan found abnormal clusters of blood vessels that, as it turned out, were in her sisters' brains too. These malformations in the brain can be silent. But they can also leak or, worse, burst without warning, causing the seizures, migraines, and stroke-like symptoms Bettina and Margaret experienced. If the bleeding in the brain gets bad enough, it can be deadly.

At the time, doctors could not tell the Bowlins exactly what was wrong, only that they suspected it ran in the family. The girls' father, Jerry Bowlin, had the same malformations in his brain (though he had no symptoms), and he knew of an uncle with epilepsy. To understand his daughters' afflictions, he began mapping out a family tree. Jerry asked around his family and, later, reconnected with long-lost cousins through Facebook, and he kept hearing more stories of seizures and strokelike illnesses. But even as the family tree filled out, the exact cause of these malformations remained elusive.

Then, in 2004, Bettina began having seizures multiple times a day. Her face would go numb, and she couldn't speak. A scan showed a malformation in her brain and one in her spinal cord that needed to be removed immediately in two surgeries. Around the same time, Susan also began feeling a tingling in her cheek. It got worse and worse over the course of a day, until she started slurring. She couldn't read. She couldn't hold a pencil. She was rushed to the hospital, where doctors eventually found a massive bleed in her brain; one of her malformations had burst. "At one time, we had one daughter in ICU in New Orleans, and one daughter in ICU in Biloxi," their mother, Charlene Bowlin, told me. Both of them recovered, but Susan has permanent numbness on her right side and Bettina still experiences nerve pain and can't feel hot or cold on her right side.

The family found a silver lining during this terrible period. Through a patient advocacy group called the Angioma Alliance, Bettina learned she could donate tissue from her second surgery to a lab that studies the genetics of unusual blood vessels in the brain, known formally as cerebral cavernous malformations, or CCMs. (An angioma is another term for vascular abnormalities; CCMs are a type of angioma.) Her tissue donation led to a major breakthrough in understanding her family's brain malformations, the cause of which was then traced all the way back to the 1760s.

Bettina's tissue ended up in the lab of Douglas Marchuk, a Duke geneticist who has studied CCM mutations that run in families, including one in Ashkenazi Jews and another in Hispanics in New Mexico that can be traced to descendants of 16th-century Spanish colonists. These mutations usually happen in one of three genes individually named CCM1, CCM2, and CCM3. Any of them can make the walls of certain blood vessels unusually weak. In the brain, these weakened blood vessels can grow into mulberry-shaped malformations full of blood. CCMs are rare, but they do sometimes form in people with no family history of them; patients with an inherited CCM mutation, however, can have multiple malformations at once. Any single CCM may stay

silent, but having so many increases the odds of at least one leaking or bursting. And they tend to start doing so when people are between the ages of 20 and 50.

The Bowlin family's malformation can indeed be explained by a mutation—a newly discovered one. Theirs is a deletion in the gene CCM2, and this mutation is dominant, meaning the trait does not skip generations and has a 50 percent chance of being passed on. Marchuk's lab didn't just find it in Bettina's donated tissue, though; the scientists also found it in seven other unrelated patients all at the same time in 2007. How odd, Marchuk remembers thinking, to see the identical deletion eight times in a row. But, he says, "we couldn't see any common ethnic heritage, and those eight families, we couldn't connect them in any way ourselves." The deletion happens to occur in a natural recombination hot spot —where DNA gets cut and pasted back together—so he figured it might just have happened independently in those families.

Then things got stranger. More families with the exact same deletion started showing up after the Angioma Alliance began a genetic-testing program for people with suspected CCM mutations. In the first year alone, a quarter of participants tested had the same CCM2 deletion. The affected families lived across the U.S., with the exception of the Northeast, but they were concentrated in the South and Midwest. (The Bowlins are from Mississippi.) "About two years in, I could say that if you live in Oklahoma, and I'm about to test you, I can pretty much predict which mutation you're going to have. Or if you live in Mississippi, Alabama, Louisiana—same thing," says Connie Lee, Angioma Alliance's president. The distribution clearly wasn't random, which suggested the deletion wasn't showing up by chance. The families probably were related. They just didn't yet know how.

In search of a connection, the families and Lee created a Facebook group to share stories and names. They scoured census, birth, marriage, death, and other public records. They took AncestryDNA tests. A professional genealogist even came on board and looked for records in person at the Family History Library, in Salt Lake City. In late 2018, a new family joined whose ancestry allowed the group to link up two family trees. That was a crucial clue.

Over the next few months, the families managed to trace their rare mutation back 250 years to a single North Carolina couple born in the 1760s: Matthew Malachi Rushing and Sarah Mae Harrell. Group members couldn't test the long-dead couple's DNA directly, of course, but they could infer from the pattern of inheritance in living descendants. Bettina, Margaret, and Susan are the couple's great-great-great-great-grandchildren. Their migraines, their seizures, their tingling and weakness in the limbs—it all goes back to the DNA of this one couple in colonial America.

The Duke researchers have now studied 27 families with this CCM2 deletion. Whenever Carol Gallione, a researcher in Marchuk's lab, analyzed the CCM2 gene from a patient in one of these families, she found the same sequence. "They were all interchangeable," she says, which is what you would expect if they all came from the same ancestor. A recent preprint, which has not yet been peer-reviewed, describes how scientists and patients together traced the history of this mutation.

The precise origin of the mutation likely goes back further than Rushing or Harrell, as not all of the families today with the CCM2 deletion are directly descended from the couple. A few have also found common ancestors in 1600s Virginia. But the mutation can't have gone back too much further, because it seems to have originated in America. Geneticists in the U.K., Europe, and Brazil have looked for but not found the deletion. "It certainly looks like it's American-specific," says Jonathan Berg, a geneticist at the University of Dundee, in Scotland, who was not involved with this study but has worked with Marchuk in the past. As the mutation spread across the U.S., it followed the migrations that shaped larger American history. It began on the East Coast, before spreading south to the Gulf Coast and west to Oklahoma and then California. The families saw in the mutation's dispersal the imprint of old family stories passed down over the years. "Yes, this is when the Mississippi land grants happened," Lee remembers hearing the families say. "And yes, my father was one of the people who was following

where the lumber harvests were happening … going back and forth along the coast of the Gulf." The gene's history is the families' history is America's history.

Evolution has not selected out the CCM2 deletion over the years because its consequences tend to manifest only in adulthood, when patients have already had children. So the mutation has persisted for centuries. Some of the family members with the CCM2 deletion were so distantly related, Marchuk says, that they shared little DNA beyond the mutation. This sliver of DNA connected them all, its consequences lurking in their brains.

When Bettina learned she needed brain surgery in 2004, she sat in her car and prayed for some kind of purpose. The ensuing research from the tissue she donated after that surgery has been exactly that, she says: "the answer to my prayers." With genetic testing, patients can find out if they're at risk for these brain malformations and get them monitored. Multiple medications are now in clinical trials for controlling the condition.

But mysteries about these mutations remain too. A CCM mutation does not necessarily guarantee a lifetime of brain bleeds. Different families might have inherited the same mutation, "yet we see striking differences," says Helen Kim, the director of the UC San Francisco Center for Cerebrovascular Research, who studies the CCM mutation predominant in New Mexico. (Kim was not involved with Marchuk's study, but she is on the Angioma Alliance's scientific board.) Genes may not be enough; environmental factors might also play some role.

This pattern is clear even in the Bowlin family. Jerry, the father, is now 82 years old. A recent MRI for an unrelated issue found malformations in his brain. But, he says, "to my knowledge, I've never had one symptom." He's had headaches, of course, like everyone, but nothing like the migraines, seizures, or brain bleeds experienced by his daughters. The story of this CCM2 deletion is a story about the power of genes, but also their limits.

Sarah Zhang
Atlantic Magazine, January 24, 2022

International CCM Mouse Model Consortium

CCM mouse models are mice engineered to have cavernous malformations, that can be used to understand the illness and to test possible treatments. Examples of ways that mice can be manipulated:

- A regular mouse can be bred to have any of the three mutations: CCM1, CCM2, or CCM3.
- A mouse can be manipulated to have lesions in the brain only or they can have a CCM mutation throughout their entire body. This simulates the sporadic versus familial forms of the illness.
- A mouse can develop lesions when very young or lesion development can be held off until later.
- Some mice can only be evaluated after death. Other mice can be monitored serially over time using MRI or other techniques.

Thinking about all the possible combinations, you can imagine how many different CCM mouse models are in labs around the world. Experimental results from one mouse model sometimes can't be replicated in other models, and it can be hard to draw conclusions.

Following November's International CCM Scientific Meeting, Angioma Alliance initiated the creation of a global CCM Mouse Model Consortium that now includes 13 labs. Initially, the group will comprehensively catalog all the CCM mouse models and the treatments that have been tested in each. To facilitate this, Angioma Alliance has created and is hosting a database where researchers have begun to enter and pool their mouse model information.

Next, we will prioritize models to use for treatment testing and create a multi-site experiment design and proposal. Any treatments will need to be tested head-to-head in multiple models, and we need to be smart about how we do this. We will fund or seek funding on behalf of the consortium because such head-to-head treatment testing is not a project that NIH or other government agency will support. This project will reduce wasted effort by coordinating the treatment testing activities of 13 labs rather than having each lab create and try to fund one-off experiments that may or may be replicable. It will save years and lives.

Research Update

The February issue of the academic journal *Vessel Plus* included an article by Angioma Alliance CEO Connie Lee sharing information about the role of our patient advocacy organization in advancing CCM awareness and research. The article, *Unique contribution of Angioma Alliance in Advancing Cerebral Cavernous Malformation Awareness and Research*, describes in detail three of the outreach programs we have sponsored and their impact. The programs include our work with CCM3 patients, our Baca Family Historical Project addressing those with the Common Hispanic Mutation, and our Breaking Barriers for Black Health Empowerment initiative. You can find the article here: vpjournal.net/article/view/4617.

Leading German researchers in Essen performed an extensive retrospective natural history study of 238 patients with multiple cavernous malformations to identify hemorrhage rates for this group. The researchers found that the cumulative 5-year risk of hemorrhage was 21.6% for the entire group. In the group that presented with hemorrhage at diagnosis, the 5-year cumulative risk of hemorrhage rose to 30.7%.

Santos AN, et. al. Medication intake and hemorrhage risk in patients with familial cerebral cavernous malformations. J Neurosurg. 2022 Feb 25.

A large Chinese study explored hemorrhage risk for those with spinal cord cavernous malformations in a retrospective study of 306 patients. In this cohort, the 5-year cumulative hemorrhage risk was 35.1%. Patients who had previous hemorrhage and pediatric patients were at the highest risk of hemorrhage.

Ren J. Natural History of Spinal Cord Cavernous Malformations: A Multicenter Cohort Study. Neurosurgery. 2022 Jan 24.

In a companion study to the German research above, the same authors looked to see whether statin or anti-thrombotic use made a difference in hemorrhage rates. They did not find a statistically significant difference between those who had been taking statins or anti-thrombotics, but there appeared to be a tendency toward decreased bleeding among these patients. There was no difference between those taking propranolol and those who took no medicine. Dosage levels were not considered. Dosages of atorvastatin and propranolol being testing for treatment of CCM are higher than dosages most people who are using these medicines to treat other conditions receive.

Santos AN, et. al. Multiple Cerebral Cavernous Malformations – Clinical Course of Confirmed, Assumed and Non-Familial Disease. Eur J Neurol. 2022 Jan 20.

Researchers at Mayo also explored medication use in spinal and cerebral cavernous malformation patients in a prospective study focusing the use of common headache and migraine medications. 329 patients were followed over a 5-year period. The authors concluded that, while 92 hemorrhages were observed during this time, use of NSAIDs, triptans, and/or Botox were not associated with an increased risk of hemorrhage.

Flemming KD, et. al. Safety of select headache medications in patients with cerebral and spinal cavernous malformations. Cephalalgia Reports. 2021 Nov 30.

New Faces at Angioma Alliance

Clinical Programs Director

With our first industry-sponsored trial opening and plans for other trials underway, we have an urgent need to build out our CCM Clinical Center network. To do this as well as launch a number of other medical care-related initiatives, we have created the position of Clinical Programs Director and have hired **Michelle Crook** to join our team. Michelle is a seasoned registered nurse with specialities in program development, case management, and patient advocacy.

National Community Development Specialist

We welcome **Linda Fuchser** to Angioma Alliance as our new National Community Development Specialist. Linda's role will be to facilitate member events around the country. Linda has been involved with Angioma Alliance for ~15 years since her diagnosis with the Common Hispanic Mutation, organizing walks and other events in multiple locations. Linda is at linda@angioma.org.

Baptist Health and Wolfson Children's Hospital designated as CCM Clinical Center

Baptist Health and Wolfson Children's Hospital in Jacksonville, Florida, were recognized as designated Clinical Centers for the treatment of CCM in both adults and children.

Wolfson Children's is the first children's hospital in Florida to receive this designation and the only pediatric hospital in the southeast. Baptist Health is the only designated CCM Clinical Center in the Northeast Florida region.

"It's an honor to be the first children's hospital in Florida to receive this designation," said Philipp Aldana, MD, co-medical director of the Walter and Michelle Stys Neuroscience Institute at Wolfson Children's and pediatric neurosurgeon at the UF College of Medicine – Jacksonville. "Our team has worked closely with the Angioma Alliance to move this program forward as we are committed to providing outstanding care closer to home for children and families affected by CCMs. We look forward to raising visibility for this complex disease and helping patients get faster access to optimized treatments."

The designated, multidisciplinary team at Baptist Health consists of:

- Ricardo Hanel, PhD, MD, neurosurgeon at Baptist Health; director of Baptist Neurological Institute; co-medical director of the CCM program at Baptist Health
- Philipp Aldana, MD, co-medical director of the Stys Neuroscience Institute at Wolfson Children's and pediatric neurosurgeon with the UF College of Medicine – Jacksonville; co-medical director of the CCM program at Baptist Health
- Harry Abram, MD, pediatric neurologist with Wolfson Children's and Nemours Children's Health, Jacksonville
- Noemi Cintron, RN, nurse coordinator, CCM Program at Baptist Health and Wolfson Children's Hospital
- Scott Dellorso, MD, vascular neurologist at Baptist Health
- Benjamin Ludwig, MD, diagnostic radiologist with Radiology Partners
- Chetan Shah, MD, pediatric diagnostic neuroradiologist, Wolfson Children's and Nemours Children's Health, Jacksonville
- Pamela Trapane, MD, pediatric geneticist, medical director for the Duran Genetics Center at Wolfson Children's and UF College of Medicine, Jacksonville

"Only one in 500 people have a cerebrovascular cavernous malformation. While most people will have no symptoms, the condition can be devastating," explained Ricardo Hanel, MD, PhD, neurosurgeon at Baptist Health. "Patients and families facing this diagnosis search for a team with expansive expertise that will create an individualized care and treatment plan. We're honored to provide this coordinated, compassionate care at Baptist Health and Wolfson Children's Hospital and to be recognized by the Angioma Alliance for our CCM program." Baptist Health is an enrollment site for Recursion's REC-994 Phase 2 trial.

To schedule an appointment with the CCM Clinical Center, please call 904-202-2000.

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Events

Strides to Cure CCM

Angioma Alliance turns 20! To note this milestone, join us for our national virtual Strides to Cure CCM 5k on May 15th! Gather your friends and family to walk, run, or roll wherever you are.

Registration is free with a recommended donation of $20 to commemorate 20 years. Raise or donate $20 to receive a limited edition walk t-shirt.

Cavernous malformations can have devastating impacts on those affected, including vision problems, seizures, migraines, and physical disabilities. If the effects of your CCM have left you unable to stride for a cure yourself, we are holding space for you with our honorary runners.

Create a team for your area, join a team, or register as an individual/honorary runner here:

give.classy.org/strides2cureccm

Promise

Each year, Angioma Alliance selects a word of the year that captures a theme and spirit. The 2022 word is PROMISE.

"A declaration or assurance that one will do a particular thing or that a particular thing will happen."

In our case, that thing is better treatments and the cure for CCM. We have moved beyond the HOPE for better treatments, which implies there is doubt, and instead we have moved to the surety of PROMISE. Better treatments and the cure will happen. It is promised.

To purchase this year's team Angioma Alliance t-shirt and join our declaration of PROMISE, visit angioma.singleservemerch.com

Save The Dates!

July 10: PROMISE 2022: Coming Together, Funding the Cure

On Sunday, July 10th, Angioma Alliance will be hosting our annual mega-event featuring live parties around the US and watch parties in our members' homes. With PROMISE 2022: Coming Together, Funding the Cure, we support Angioma Alliance and the research that will fulfill our promise. Please let us know at lindsay@angioma.org if you have auction items to donate or if you'd like to host a party. Stay tuned to Angioma Alliance social media and our email list to learn more.

November 2022 – Scientific Meeting & National Patient Conference

We are gathering in person in November! Happening concurrently with our International CCM Scientific Meeting, our patients will have the opportunity to hear from scientists both in lectures and over meals. We'll also have a chance to meet each other, share stories, and form friendships. This year's meeting will be November with a date/location TBD. Please stay tuned for more info.

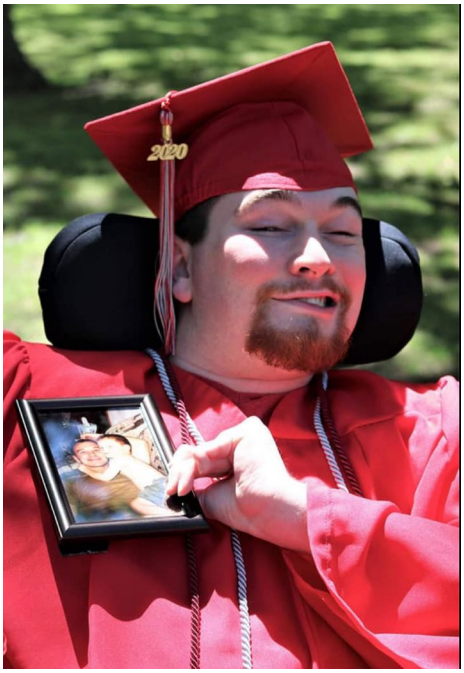
July 7-8, 2023 – Family Conference with Adult & Children's Program

We haven't had a family conference with children's programming since 2015, and we are thrilled to be able to do this again. Please save July 7-8, 2023, for our conference at the Intercontinental Hotel, Miami, Florida. We have reserved a block of rooms with availability starting on July 4th- July 9th. Plan your summer vacation around our meeting. You will be giving your child the gift of a lifetime Kids who attended the 2015 family conference created bonds that continue to this day as they grew up knowing they are not alone.

Joey's Story

The first time Joey's mom Angela heard the term "cavernous malformation" was when he was ten years old. Joey was an energetic, intelligent, and athletic boy of ten. The diagnosis of a CCM in his midbrain turned their lives upside down. On the day of his diagnosis, Joey woke up for school with right-sided numbness and double vision. His symptoms were mild, and his mother believed he was just tired from a busy long weekend and brought him to school. However, after dropping him off, she recalls having a bad feeling "she just couldn't shake" and decided to call the school to check on him. To her dismay, she was told that he was acting strangely and was rubbing his eyes frequently. Angela knew something was wrong and rushed Joey to be evaluated at their local Emergency Room. Joey underwent a CT scan which found a mass in his brainstem. He was sent via helicopter to a larger hospital.

Joey was admitted and given a course of steroids in an attempt to stabilize his lesion. Once he was considered stable, he was sent home with the understanding that the team would work on a safe surgical plan. This surgery to remove Joey's CCM was scheduled for June of that same year. However, pre-op scans showed the lesion had shrunk, and the surgery was not only no longer recommended, but his mom was told that it was no longer safe to operate. Joey and Angela were thrilled. They were sent home to monitor the lesion, which 10-year-old Joey named Bob, with twice-yearly MRIs.



Throughout the years, Joey had several microbleeds. He would exhibit similar symptoms of numbness, weakness, and visual changes and would go to the hospital. Each time, Joey was sent home once he was stable. However, in April of 2016, when he was 18 years old, Joey's CCM started to act up again. He recognized right away that "this one was bad" and went to the ER. The following day his new surgeon told Joey and his mom that it was time for "Bob" to be evicted as he was taking up a large amount of Joey's brainstem. Angela recalls being told that "one more bleed would kill Joey." Joey decided to have surgery to remove the cavernous malformation; his surgery was in May 2016.

After the surgery was completed, his mother was told that his brain scans looked as expected, and it appeared as if Joey would be back on his feet in no time! Unfortunately, this wasn't the case. Joey did not wake up for several days despite multiple attempts. When he finally did wake up, it was clear he was still not fully conscious. Joey was later discharged to a long-term rehabilitation facility, but Joey never fully recovered. It was clear something was seriously wrong following the surgery. His mother sought a second opinion at Mayo Clinic in Jacksonville, Florida, hoping to understand why Joey wasn't recovering. Angela says that her "worst fears were confirmed" during this appointment. The doctor drew a sketch of Joey's brainstem and explained that too much of the tissue surrounding the malformation had been removed. He explained that this was the reason Joey had these devastating deficits.

Currently, at the age of 23, Joey suffers from intense spasticity and neurological storms. He cannot walk, eat or care for any of his needs. He has trouble breathing and requires either a trilogy machine or oxygen at all times. Joey will likely need a tracheostomy in the future as the signal his brain should be sending to remind him to breathe is being blocked. He struggles to move the right side of his body, and due to swallowing issues, he is tube-fed. Joey's feet have turned inward so severely from the spasticity that he cannot stand. Often his pain is unbearable, but Angela shared that medical marijuana has given him some relief. Joey is able to communicate with head movements, and occasionally he's able to speak one word. Angela

explained that despite all he's been through, Joey is still totally aware. She was thrilled to brag about her amazing son graduating from high school when he was 21 with the support of a homebound instructor.

Angela is dedicated to giving Joey as full a life as possible. To give Joey back a little bit of something that brought him joy before his surgery, Angela had a side by side vehicle adapted for Joey! They often go on nature walks, swim with family and friends, and even went on a parasailing adventure!

Angela was frustrated while talking with me about the challenges she and Joey face, particularly regarding the difficulty of finding a medical team to help manage Joey's spasticity and neurological storms. She says the take-home message she wants to send out is that "doctors don't know everything." Get a second opinion, ask all of your questions and if possible, see a doctor who specializes in CCMs.

Darla Clayton

A Trip to Salt Lake City

On Tuesday, March 15, Connie Lee will be in Salt Lake City addressing the staff of Recursion Pharmaceuticals to help them learn about the patient experience, the importance of the CCM Health Index that Recursion is funding for our community, and the promise we hope their drug trial will bring to us. By the time of our next newsletter, the first CCM patient will have received their first dose of REC-994, and there will be Phase 2 enrollment sites open around the country. Please stay tuned to learn more.

While in Salt Lake City, Connie will be visiting with a few people from our community, including Amber Blakesley. If you've ever worn an Angioma Alliance shirt with the iconic bubble logo, you have the indomitable Amber Blakesley to thank. She is the designer of the Angioma Alliance logo, a lifelong creative, and a cavernous malformation survivor.

Amber was a young up-and-coming graphic designer living in New York City and working for Martha Stewart Living Magazine as an Art Director and Designer. She never imagined that a rare disease would upend her life, leading to 3 cerebellar brain surgeries over 4 years and necessitating a move back home to be near family. Amber has additional lesions in other areas of her brain, including a cavernous malformation in her brainstem that has bled several times, further exacerbating her motor challenges.

Despite all that she has been through, Amber hasn't given up. She's been exercising with the guidance of cavernous malformation patient/rehab specialist Steve Cairns and reports that she has made some big improvements. Amber shared that, "He's got me rock climbing, holy cow!" She says rock climbing is so out of character for her, but she really likes it. She continues to fight hard to recover and shared that she feels positive about 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.angioma.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.angioma.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@angioma.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 angioma 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 angioma, 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 Angioma Alliance

Angioma Alliance is a non-profit, international, patient-directe 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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