OAA had a busy summer!

OAA presented Dr. Jerry Vockley with a Continuous Service award during the webinar we hosted in August on New therapies for Combined D/L2HGA & Isovaleric Acidemia. Thanks to IVA parent, Richard Bazzy for designing and arranging for this award. OAA hosted a webinar in September on Understanding the Clinical Trial Process. Dr. Jerry Vockley and Dr. Greg Enns walked us through the clinical trial process and gave us a summary of the recent clinical trials available for MMA and PA. The link to this webinar and others can be found on our OAA website – www.oaanews.org. We are so appreciative to all of medical advisors and researchers who are working everyday with our organic acidemia families. Sadly we lost one of our medical pioneer’s, Dr. Charlie Roe in September. He was instrumental in many advancements for OAA – and for newborn screening.

We are grateful to many OAA donations this year which will continue to use to support all of you. OAA is working on a number of projects – one is going through a ‘revamp’ of the website – so stay tuned for a new look and feel of the site soon! OAA has recently added the following volunteer members to the OAA board – Richard Bazzy, Isovaleric Acidemia parent, Karen Dalton, MMA Cbl C parent, Erin MacLean, MMA Mut o parent, and Allison Wood, Glutaric Acidemia Type 1 parent. On behalf of our current OAA board members, Jana Monaco, Menta Pitre and Cay Welch we welcome these new members to OAA’s board!

In remembrance of Dr. Charlie Roe
August 7, 1937 - September 1, 2021
Thank you Dr. Roe for your life-long dedication to patients with organic acidemias!
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**Richard Bazzy**  
Isovaleric Acidemia Parent

**Karen Dalton**  
MMA Cbl C Parent

**Erin MacLean**  
MMA Mut O Parent

**Allison Wood**  
Glutaric Acidemia Type 1 Parent
OAA Updates

Bette and Tyler - Married September 18, 2021 (Tyler MMA CblA)

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Thanks to Raymonde DeGrace for creating our fabulous 2022 calendar!

Other items are available at our CafePress shop www.cafepress.com/organicacidemiaassociation
Our daughter, Cleo, was diagnosed with Pyridoxine Dependent Epilepsy (PDE-ALDH7A1 / antiquitin deficiency) at a little over a year old. PDE is a rare neurometabolic disorder that has recently been recognized by the OAA as an organic aciduria. Antiquitin deficiency results in an inability to catabolize the amino acid lysine, causing a build-up of neurotoxins (a-AASA, P6C and piperoc acid) in the blood, urine and CSF. While the seizures characteristic of the disorder are normally managed by high dose pyridoxine, the effects of the neurotoxins are more challenging to mitigate. In addition to pyridoxine, a restricted-lysine diet with specialized formula and arginine supplementation comprise “triple therapy”. Even with treatment, however, 80% of individuals suffer developmental delay and intellectual disability.

Perhaps one of the most challenging aspects of this condition is the path to diagnosis. In its classic form, babies are born in a state of epileptic encephalopathy (in some cases the seizures are detected in utero as rhythmic movements felt by the mother or observed via ultrasound). A trial of pyridoxine is typically administered while the infant is in the NICU as part of the neonatal seizure protocol. A third of those affected, however, present with atypical PDE where seizure onset is later. In these cases, it takes a perceptive team to even consider trialing pyridoxine therapy and run the necessary tests to make the correct diagnosis. Unfortunately, at this point in time, the diagnostic biomarker for antiquitin deficiency is too unstable to be obtained from the newborn screen (each time Cleo has her blood tested for her levels, they have to send a frozen sample out of state to a specialized lab and it takes 2-3 weeks to get the results back). Cleo recently participated in a study that looked at the newborn blood spot cards to see whether a novel and more stable biomarker could be used to retrospectively diagnose PDE. The findings are extremely encouraging as all patients with PDE were correctly identified via blood spot card re-analysis. The novel biomarker is therefore viable for the newborn screen and we hope PDE will be added to the list of screened conditions in the not too distant future. It may also mean that her team will soon be able to track her levels more easily and rapidly.

In Cleo’s case, while we enjoyed a smooth, full-term pregnancy and delivery, she was unusually subdued as a newborn. She had an ashen complexion despite repeated normal bilirubin levels, she never cried, and would only feed briefly before falling back asleep. Cleo is my third child. My first two were premature (twins). They were far more alert than Cleo, despite her being almost twice their size at birth. I just sensed something was very wrong. The nurses reassured me that infants are often sluggish at first and to make the most of the peace and quiet as it will be short lived. The lethargy persisted, however, and she never woke up crying for a feed, so I would set an alarm every 3 hours at night to ensure she was fed often enough.

Before we were discharged from the hospital, a pediatrician detected a heart murmur and referred Cleo to a cardiologist. Further testing found an ASD and VSD (a hole between each of the upper and lower chambers of her heart). Initially, everyone naturally blamed Cleo’s reluctance to feed on that. The only person who felt otherwise was Cleo’s cardiologist who was adamant this was not yet cardiac related. In a sense the heart issues served as a red herring. At 2 weeks old, Cleo began to vomit frequently after feeding. She was born at the 75th percentile for weight but by 10 weeks had dropped to 1st percentile. At this point, Cleo was admitted to hospital for failure to thrive and an NG tube was placed. She was also showing some signs of early heart failure so was...
started on a diuretic. While the diuretic seemed to help, the vomiting continued and the various specialists who saw her found no other issues to explain her failure to thrive. After a week in hospital, the team decided to proceed with open heart surgery to patch the holes. We all hoped her feeding would pick up thereafter but at the back of my mind I was skeptical. While her ashen appearance transformed into a pink healthy glow as she recovered in the PICU, her appetite remained poor and the vomiting continued. I was instructed to fortify my breastmilk with formula to boost her caloric intake but that only made matters worse. It was as if she could not tolerate her food but all tests were fruitless. She was perfectly happy until we switched the feeding machine on, to which she’d become visibly uncomfortable. At 5 months old, we reluctantly agreed for the NG to be replaced with a g-tube after she repeatedly regurgitated the tube while vomiting. We accepted that this was just part of her and our lives for the time being. In the meantime, we involved Growing Independent Eaters, a private tube-weaning consultancy, with the hope of weaning her from tube feeding. By 9 months old, her feeding did actually start to improve after we reverted back to expressed milk only and reduced her tube feed volume. I finally felt optimistic; maybe time was all she needed? She also finally started taking some solids. While she was somewhat delayed, she was now able to sit up by herself and was making good progress toward rolling and crawling. Then, at 9.5 months she became ill with a cold. While her cold symptoms abated, during the course of two weeks, she became increasingly fussy and the only thing that comforted her was to be held day and night. This was in contrast to a very happy child who barely ever cried. The fussiness reached what felt like a crescendo when she suddenly fell unresponsive and then started to seize. Altogether the episode lasted about 10 minutes by which point the EMS team was there. Imaging and an initial EEG found nothing amiss. We were told it was just a febrile seizure but, as it so happened, I had recorded a normal temperature just minutes prior. We saw a neurologist and I immediately mentioned her fussiness (which continued post-seizure and was very apparent during the appointment) but she had no explanation. A week later she had her next seizure and was then started on epilepsy medication. An MRI found diffuse cerebral microhemorrhage but why we did not know. The neurologist again wondered if it was a byproduct of her heart surgery and time spent on the heart-lung bypass machine. Each seizure was associated with a temporary loss of skills. She lost the ability to sit up, her hand movements were uncoordinated, she showed no interest in play, and was too fussy to eat so we sadly reverted back to tube feeding. The only thing that brought her comfort was being held for hours on end. After starting her first anti-epileptic medication, her fussiness subsided somewhat but she still wasn’t her old self. She’d make sudden jerking movements or her head would bob up and down while she zoned out. Full blown unresponsive seizures continued and gradually became more frequent, clustered, and prolonged. She went into status 7 times. We were given rescue medication to administer but it was ineffective. Her meds were increased several times and a 2nd medication was added. We became accustomed to dropping everything in order to rush her to hospital. She had a growing collection of cuddly toys from the many ambulance trips and children’s hospital visits. Each time we saw the neurologist, I left feeling like she played down the severity of the situation. I happened across a genetic epilepsy panel that Cleo was eligible for (thanks to a helpful parent in a FB group for parents of children with epilepsy). When I asked about it, however, the
neurologist was dismissive and said “cases like Cleo’s are almost never genetic”. The prolonged nature of the seizures, however, were unusual (most seizures are well under 5 minutes long), her seizures seemed to be mixed in type, which again is less common, and her fussiness and sleeplessness were striking (epilepsy meds usually cause increased sleepiness not the opposite). My thought was, what harm could it do to at least run the panel? After asking several times, begging even, she finally agreed. 3 months of seizures had passed by the time the test was ordered. The results identified 2 variants involving the antiquitin gene, both associated with PDE. I immediately looked it up. “PDE is often characterized by prolonged seizures with associated fussiness”. I knew we very likely had our answer even though it was an atypical presentation. I felt a sense of relief and hope. Diagnostic limbo is a very hard place to be, especially when your gut is telling you that something is very wrong. A urine test was ordered for alpha-AASA (we were not informed how to store the urine, i.e. to freeze it immediately, so it’s a small miracle that the sample even gave a positive result) to confirm the suspected diagnosis. As soon as pyridoxine was started, the seizures thankfully stopped and our beautiful, happy girl re-emerged from the fog. The first 24 hours on pyridoxine, however, were not smooth. Cleo became extremely disoriented as if intoxicated, could barely hold her head up, vomited repeatedly, and then sank into a deep sleep for 15 hours that was difficult to rouse her from (I did not sleep that night). At the time, we assumed it was unrelated as pyridoxine is just a benign vitamin (B6) and she’d recently started another anti-epileptic drug (AED) but I later read that starting this medication can cause transient cerebral suppression in infants with PDE and should be undertaken in an ICU setting. In retrospect, I wish she had been hospitalized and monitored but one of the pitfalls of a rare disorder is that often the medical team knows so little that they are not equipped to give adequate guidance. Fortunately, we’re now with a team that is far more aware of PDE even though Cleo is their first patient; we are part of the international patient registry and they are in close contact with another team in Colorado that has a small number of PDE patients.

We have successfully weaned Cleo off of the AEDs and she is now over 6 months seizure free. Once we were under the care of a metabolic geneticist, Cleo began arginine therapy, a strict low protein diet and medical formula. She was feeding orally by this point but refused the formula despite trying all the tricks so we had to tube feed it. As soon as we did so, however, her appetite dwindled and after 3 weeks she’d lost nearly 10% of her body weight. The levels of neurotoxins in her system normalized but her lysine levels dropped unhealthily low. In Cleo’s case, her off-diet lysine baseline is at the very bottom of the normal range (which is where they want it to be) yet her neurotoxic levels are still high so we are now trying to bring down her lysine a little below normal range so as to reduce the toxins without compromising growth. In short, it’s not easy trying to thread the needle. She’s currently on restricted lysine (16g protein / day) but not on the medical formula and is growing beautifully and taking all solids and liquids by mouth (we use the g-tube for her medications but that’s it). We may have to restart the medical formula in the future if her labs change. Cleo still has some delays but has done a lot of catching up since her diagnosis and starting treatment.

She’s 1.5 now, walks or runs everywhere and oh boy does she climb! Her most recent review found a significant delay in expressive language but otherwise her delays are mild, and she’s making great progress in speech therapy and has started to sign. Her story is yet to be written of course but I think there will always be a question in my mind of “how would things be different had we known about PDE at birth?”. At the very least, I imagine we could have avoided the feeding tube and had a much more normal first year of life. Raising twins was hard but raising a child with a rare, undiagnosed metabolic disorder was a whole new level of hard and quite isolating. Watching her go through open heart surgery was nothing compared to helplessly witnessing her in a state of metabolic encephalopathy. Children with a later onset of seizures tends to fare better than those with classic PDE but the length of diagnostic delay is also a determinant of developmental outcome. There is so much that is still unknown about this condition, such as why some children start to seize earlier than others or why some do better than others (Cleo’s antiquitin enzyme is completely lacking yet she has fortunately had a relatively good outcome so far, developmentally, for example). For that, we are extremely grateful. Her extremely happy and social demeanor despite what she’s been through reminds us daily that we are very fortunate and honored to have Cleo as our daughter. She is such a happy and resilient little girl!

Libby enhopton@gmail.com
Hillsboro, OR
In my fiction fantasy Young Adult novel of 86,480 words, The Element Guardians, a group of individuals have embraced the major constituents that form love, hate, time, space, and matter. The story offers reasons for justifying the great discoveries: utilizing the brain to its maximum by defying the wrongly established measures of thinking and performing. “Element” is also a planet within a cluster of galaxies, protected by five supermen, Guardians representing fire, water, earth, wood, and metal. Each Guardian has a devoted sacred protector animal that talks like humans in the same and only language within the Galaxies.

The reader will thrill to the character of Grossman, an evil woman born in the Planet Element. She assassinated her father and escaped in a tyrannical planet, Dark Sky, where she became a General and eventually a dictator. She swore to obliterate Element with all its inhabitants, including her family. To humans, Grossman represents Satan. Eventually, her army invaded Element, but she did not participate in the aggression. Instead, she tried to escape from Dark Sky into the next Galaxies cluster.

My life has always involved meeting challenges. Throughout my years in school, I was labeled a special-needs student. You see, I was born with a rare metabolic disorder that has left me legally blind and made me slower to learn and pick up on things. As a result, I was told I would probably not be able to go to college, drive a car, or live on my own. I could not join competitive sports, so at the age of 12, I signed up for karate, a sport where I would compete against myself; 13 years later, I am still an active karate student. My Sensei, Darren, has inspired me to never give up in anything I do in life. Martial arts discipline has served me in many areas of life, helping me continue to grow mentally and spiritually.

Furthermore, I went to college for two years and was part of DREAM Program, a curriculum designed by Mercer County Community College for students with learning disabilities. Among my favorite courses was “Anthropology: Myths and Magic”; this instilled in me a love for the story-telling power of mythology.

I hope that you and your team will find the time to read how my story, The Element Guardians was born. My request is from an individual who was frequently told that he was simple-minded—yet not willing to accept that he was so simple.

I would welcome any feedback you have to allow my dream of having this book become a reality. My email is michael.clap@gmail.com. I very much look forward to hearing from you.

Sincerely,
Michael Clapcich
Assalam o aliaakum. With a heavy heart I’m announcing my son is no more in this world. On July 27th before the rising sun. He could not see the day of Tuesday. It was 2.40 minutes when my son heart stop I was with him on his bed his hands are in my hands.

Exactly to understand what’s going on I go back one month before my son was okay and in good health. It was very hot in Oman Muscat and my son start vomiting. As always, in an emergency I gave him Maxijul for 24 hours -- but vomiting didn’t stop so we went to hospital because intake was not very good and he needs more fluids. In the hospital after taking injection and fluids we went back home because he stopped vomiting and ammonia was not very high. Then again after 2 days he was not eating well because his molar teeth were coming in, so I try to give him liquid things and fruits this time again for vomiting. I give him medicine and sodium benzoate syrup as well then still he was not okay. I checked his ketones, which were high and again give 24 hours Maxijul. But again vomiting and went to hospital. Again after taking fluid he was okay and stable. So we went back home after week again same problem so from end of June continuously July 22nd, off and on Shiekh Muhammed was not stable. Otherwise activities normal. So last admission July 22 in emergency again same procedure reports are normal ammonia was 59 so this time I decide to be admitted so that my son problem could be found. Saturday, Sunday was okay but as they try to give oral milk by mouth he did vomit. I told the doctor about amino acid because since last month he is not eating so they decide to give him fats and protein through 1V fluids. Because he stay 2 days and becoming restless he is very sensitive especially when canola blood test taking he was very brave - we are always with him. We are four in family. Me and my husband Muhammad and daughter Laiba and we together but at night husband can’t stay.

So before a day of his death he wanted to go home as my son couldn’t speak only some worlds like baba mama and a sentence go home so he try to go outside canola was swell changing but very tiny veins and with difficulty we can find a vein for putting canola because fluids are necessary for him. Night time he sit and then take his head on my chest then again we try to sleep. Again and again he sat I didn’t know what’s happen to him may be he know that he is going to leave the world.... Ahhhh Monday morning he was not very active. My husband came and he mentioned that what’s happen why he is so lazy I told him at night he couldn’t sleep well irritating due to giving blood test and outside for canola so that’s why he is lazy. So all the day of Monday was okay. At 12 night time he did vomit I told the nurse. Due to ac he has some secretion in throat may be that’s why he vomit and same 40 minutes before he is feeling like vomit. Suddenly at 2.30 am Tuesday and he has severe pain in his abdomen it was pain of separating life from his legs he screams with pain I myself was screaming shouting asking what’s happen to him they gave oxygen he took some fast breathes and his heart stop as I heard doctor said I can’t heard anything they start a procedure like ecg and pump the heart blood came from his mouth and heart. It was the end. It seems everything is ending his struggle -- how strong he was. I can’t explain he was always a smiling child though he had great pain. It was the end of his all pains and his soul rest in peace. He was the flower of Heaven so he went there.
Zachary Jay (Propionic Acidemia)  
June 16, 2000 - September 14, 2021

Zac was, without a doubt, the friendliest child this world could ask for. He was always “waiting or counting Down” the days to see his special people and make-believe places. He was passionate about doing puzzles, especially from pictures he took on his Ipad. He loved all things purple and his shows, especially Barney. He was Barney’s # 1 fan. Zac enjoyed baths in his mommy’s tub, grandma’s house, snow, bubbles, helium balloons, golf cart rides with dad, dancing, Halloween, Christmas, and he couldn’t get enough of his computer. He loved his shows. Zac lived his life with pure joy and happiness, often hugging his caregivers, friends, and family with his famous headlock style hug. He had an extreme love for the people in his life. Zac made a lasting impression on the lives of all who knew him.

Nicholas Joseph (Propionic Acidemia)  
June 16, 2000 - September 12, 2021

Nic was, without a doubt, the sweetest child this world could ever ask for. He was persistent when it came to helping people figure out what he was telling them. He was passionate about expressing his stories through art drawn by those who adored him. Nic had thousands of drawings created and kept some on his wall beside his bed and on his ceiling. He loved his Santa and kisses on the cheek from Mrs. Claus, swimming, shopping, going to stores, the library, grandma’s house, Halloween, Christmas, taking walks to find the ice cream truck, painting and most recently coloring his own pictures. Nic lived life with pure joy and happiness, never letting his disabilities get in the way. He had an extreme love for the people in his life, which includes his family, friends, and caregivers, and was always asking for them to feed his belly and watch his shows with him. He loved watching, Wee Sing, Barney, Sesame Street, Dora and Diego, Blue’s Clues, The Wiggles, Teletubbies, and Team umizoomi. Nic made a lasting impression on the lives of all who knew him.

Kristin (Propionic Acidemia)  
September 28, 1999 - October 5, 2021

Beloved daughter of Russell and Janice, slipped peacefully into the arms of her Heavenly Father after fighting a lifelong battle with propionic acidemia. During her life Kristin overcame many obstacles of physical and mental disability and loved life in her world to the fullest. For Kristin each day was a beautiful day and her smile brought joy to all those around her.

Kristin loved the outdoors, the country, and especially trips to the beach to feel the sea breeze on her face and to listen to the seagulls. Kristin was surrounded by many animals at home which she adored. Her labradors kept an ever watchful eye on her and were rarely out of sight. She was a big fan of Clifford, Elmo, Blues Clues, and swinging a glowing light saber. Being quite musical, Kristin enjoyed the piano, drums, the accordion and humming tunes, but Kristin’s favorite activity was watching and listening to her favorite U2 concert, the louder the better.
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*Feedback card included in each Sample Kit. For every feedback card completed and returned to us, Cambrooke will donate $10 towards the Organic Acidemia Association. Ends Nov 30, 2021.
Red Blood Cell Metabolism in Patients with Propionic Acidemia

Micaela Kalani Roy¹, Francesca Isabelle Cendali¹, Gabrielle Ooyama²,³, Fabia Gamboni¹, Holmes Morton⁴,⁵,⁶ and Angelo D’Alessandro ¹

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Propionic acidemia (PA) is a rare, autosomal recessive disorder engendered by a dysfunctional propionyl-CoA carboxylase (PCC) enzyme [1]. PA has an estimated incidence of 1:100,000 live births in the general population, and a higher prevalence in isolated populations like the Amish Mennonite community [2,3].

PCC is a key enzyme of glycolysis—a cellular process involved in the breakdown of glucose in the body [4]. In patients with PA, PCC function is impaired, and glucose cannot fully be converted into its byproducts. Moreover, the impairment of PCC causes an accumulation of propionyl-CoA and related molecules, which can alter the activity of various metabolic processes and contribute to symptoms of the disease [5,6].

Red blood cells (RBC) are the most abundant cell type in the body and are critical in oxygen exchange and physiological equilibrium [7,8]. Although PA has been correlated with RBC disorders including pancytopenia and anemia, the effects of PA on RBCs have not been fully described [5,9]. In this study, we used metabolomics—a technology that gives a broad window into metabolic processes through quantifying molecules of metabolism—to better understand the effects of PA on RBC metabolism. Because metabolic analysis of blood is a common tool in diagnosing and treating disease, our study aims to expand the current understanding of PA with the goal of informing diagnosis and patient care [10].

RBC are the only cells that perform the essential task of transporting oxygen throughout the body and to the tissues. As a result, they are exposed to greater oxidant challenge than any other cell in the human body. Our results show that this increased oxidant stress results in overactivations of the main antioxidant pathway—the pentose phosphate pathway—in RBCs from patients with PA. Our analyses also identified increases in the levels of markers of mitochondrial metabolism. Since mature RBCs lack organelles, including nuclei and mitochondria, these results may have indicate an increase in the production and circulation of organelle-containing immature RBCs in these patients.

Although this study is limited by its small cohort, it provides foundational information for future studies on the metabolic effects of PA. By describing the dysregulation of metabolic pathways including glycolysis, the PPP, purine, and carboxylate metabolism, we hope to pave the way for continued research on RBC metabolism in PA patients.

Together with EHOD members, I work on an international collaborative research study aiming at identifying:

- Pregnant females affected with Cobalamin Deficiency or Remethylation Disorder
- Pregnant females where the fetus is affected with Cobalamin Deficiency or Remethylation Disorder

Our goals are:

- To document clinical management throughout the pregnancy, with a focus on therapeutic options
- To review the safety data of betaine and hydroxycobalamin as therapies
- To review the acute and long-term clinical maternal and fetal outcomes
- To develop consensus guidelines on their management

If you are interested in participating, please contact Dr. Stepien at the email above.

Research study for patients with PDE or GA I

We are recruiting patients and families for the CHARLIE metabolism Project (CHAnging Rare disorder of LysINe metabolism). This is an international collaboration focused on developing novel therapies for patients with pyridoxine-dependent epilepsy (PDE) and glutaric aciduria type I (GA I). Both substrate reduction therapy (an upstream block of lysine metabolism) and gene replacement therapy will be trialed in model systems such as neuronal stem cells, mouse, and zebrafish models. The CHARLIE project is led by Professor Clara van Karnebeek at the University of Amsterdam UMC in the Netherlands.

Although this is a basic-research focused project, we also want to work closely with patients and families in order to describe the needs and wishes of families and to define goals of care that are essential to improve quality of life. This project (referred to as “patients in the lead”) is led by Hanna Dekker who is the director of the VKS (a Dutch patient support organization). [https://www.stofwisselingsziekten.nl/](https://www.stofwisselingsziekten.nl/)

If you are interested in more information or in participating, please contact Dr. Curtis Coughlin II at the University of Colorado ([Curtis.Coughlin@cuanschutz.edu](mailto:Curtis.Coughlin@cuanschutz.edu), 303.724.3839)
LogicBio Therapeutics Announces Early Clinical Trial Results Demonstrating First-Ever In Vivo Genome Editing in Children

Early data from Phase 1/2 clinical trial in pediatric patients with methylmalonic acidemia showed measurable levels of a biomarker indicating site-specific gene insertion and protein expression

Based on safety data from first two patients, independent Data Safety Monitoring Board recommended continuation of trial, enabling enrollment of children as young as six months and dose escalation

Company remains on track to report additional interim clinical data by end of 2021

LEXINGTON, Mass

LogicBio Therapeutics, Inc. (Nasdaq:LOGC), a clinical-stage genetic medicine company, today announced clinical trial results demonstrating the first-ever in vivo genome editing in children. Early data from the company’s Phase 1/2 SUNRISE clinical trial showed measurable levels of albumin-2A, a technology-related biomarker indicating site-specific gene insertion and protein expression. The SUNRISE trial is evaluating the safety, tolerability and preliminary efficacy of LB-001, the company’s investigational, single-administration genome editing therapy, in pediatric patients with methylmalonic acidemia (MMA).

These results follow a recommendation from the independent Data Safety Monitoring Board (DSMB) overseeing the SUNRISE trial to continue the study without modification. The DSMB’s recommendation was based on an evaluation of the safety data from the first two patients enrolled in the trial. Per the FDA-cleared protocol, albumin-2A detection together with the DSMB continuation recommendation enables LogicBio to begin enrolling two patients in the higher dose (1 x 10^14 vg/kg) cohort (with ages ranging three to twelve years old) and two patients in the lower age (six months to two years old) cohort at the lower dose (5 x 10^13 vg/kg) of LB-001.

“We are very excited to have achieved this significant milestone in the field of genetic medicine,” said Fred Chereau, president and chief executive officer of LogicBio. “These early data indicate that we can precisely edit hepatocytes in vivo to treat a genetic liver disease with a single intravenous infusion using our proprietary GeneRide™ technology. Today’s announcement is a demonstration that homologous recombination genome editing without the use of nucleases is a potential alternative to genome editing technologies in development that use nucleases, such as CRISPR. The ability to insert the correct version of a gene in a cell’s genome without nucleases is an important step to unlocking the potential of GeneRide™ to treat a larger number of genetic diseases.”

SUNRISE is a first-in-human, open-label, multi-center, Phase 1/2 clinical trial designed to assess the safety and tolerability of a single intravenous infusion of LB-001 in pediatric patients with MMA. LB-001 is designed to non-disruptively insert a corrective copy of the MMUT gene into the albumin locus to drive lifelong therapeutic levels of MMUT expression in the liver. LB-001 is based on the company’s proprietary GeneRide technology, which uses homologous recombination, a natural DNA repair process, to enable precise editing of the genome without the need for exogenous nucleases and promoters that have been associated with an increased risk of immune response and cancer.

“MMA is a rare, life-threatening genetic disorder for which there are no treatments addressing the underlying cause of the disease. By demonstrating for the first time ever that in vivo, nuclease-free genome editing in pediatric patients is achievable, we are one step closer to bringing a safe and effective genetic medicine to children suffering from MMA and, potentially, other early onset genetic diseases where early intervention is critical to achieve optimal health outcomes,” said Daniel Gruskin, MD, chief medical officer of LogicBio. “I would like to thank the patients, their families and the investigators who are participating in this landmark trial. We look forward to continuing to progress the clinical study to better understand the biochemical and clinical effect of this genome editing therapy.”
The Company remains on track to present additional interim data by the end of 2021.

**About the SUNRISE Trial**

The SUNRISE trial is an open-label, multi-center, Phase 1/2 clinical trial designed to assess the safety and tolerability of a single intravenous infusion of LB-001 in pediatric patients with methylmalonic acidemia (MMA) characterized by methylmalonyl-CoA mutase gene (MMUT) mutations. Seven leading centers in the United States and one in Saudi Arabia are expected to participate in the trial. With the aim of evaluating LB-001 at an early age, the SUNRISE trial initially enrolled 3-12 year old patients and, following a recommendation from the trial’s independent Data Safety Monitoring Board and detection of a biomarker indicating site-specific gene insertion, is permitted to enroll infants as young as 6 months old. The SUNRISE trial is designed to enroll up to 8 patients and evaluate a single administration of LB-001 at two dose levels.

**About LB-001**

LB-001 is an investigational, first-in-class, single-administration, genome editing therapy for early intervention in methylmalonic acidemia (MMA) using LogicBio’s proprietary GeneRide™ drug development platform. GeneRide technology utilizes a natural DNA repair process called homologous recombination that enables precise editing of the genome without the need for exogenous nucleases and promoters that have been associated with an increased risk of immune response and cancer. LB-001 is designed to non-disruptively insert a corrective copy of the methylmalonyl-CoA mutase (MMUT) gene into the albumin locus to drive lifelong therapeutic levels of MMUT expression in the liver, the main site of MMUT expression and activity. LB-001 is delivered to hepatocytes intravenously via liver-targeted, engineered recombinant adeno-associated virus vector (rAAV-LK03).

Preclinical studies found that LB-001 was safe and demonstrated transduction of hepatocytes, site-specific genomic integration, and transgene expression. LB-001–corrected hepatocytes in a mouse model of MMA demonstrated preferential survival and expansion (selective advantage), thus contributing to a progressive increase in hepatic MMUT expression over time. LB-001 resulted in improved growth, metabolic stability, and survival in MMA mice. The U.S. Food and Drug Administration (FDA) granted fast track designation, rare pediatric disease designation and orphan drug designation for LB-001 for the treatment of MMA. In addition, the European Medicines Agency (EMA) granted orphan drug designation for LB-001 for the treatment of MMA.

**About Methylmalonic Acidemia (MMA)**

Methylmalonic acidemia (MMA) is a rare and life-threatening genetic disorder affecting approximately 1 in 50,000 newborns in the United States. In the most common form of MMA, a mutation in a gene called methylmalonyl-CoA mutase (MMUT) prevents the body from properly processing certain fats and proteins. As a result, toxic metabolites accumulate in the liver, in muscle tissue and in the brain. Symptoms include vomiting, lethargy, seizures, developmental delays and organ damage. There is no approved medical therapy addressing the underlying cause of the disease. To manage the symptoms, patients go on a severely restrictive, low-protein, high-calorie diet, often through a feeding tube. Even with aggressive management, these patients often experience life-threatening metabolic crises that can require recurrent hospitalizations and cause permanent neurocognitive damage.

Because of this risk for irreversible damage, early intervention is critical and newborns are screened for MMA in every state in the United States.

**About LogicBio Therapeutics**

LogicBio Therapeutics is a clinical-stage genetic medicine company pioneering genome editing and gene delivery platforms to address rare and serious diseases from infancy through adulthood. The Company’s genome editing platform, GeneRide™, is a new approach to precise gene insertion harnessing a cell’s natural DNA repair process potentially leading to durable therapeutic protein expression levels. The Company’s gene delivery platform, sAAV™, is an adeno-associated virus (AAV) capsid engineering platform designed to optimize gene delivery for treatments in a broad range of indications and tissues. The Company is based in Lexington, MA. For more information, visit www.logicbio.com, which does not form a part of this release.
On behalf of the team at LogicBio we hope that your families are keeping well. As LogicBio continues to work on its investigational gene therapy candidate for methylmalonic acidemia (MMA), we wanted to remind you that to stay current on the status of this, and our other programs, you are welcome to sign up for updates at www.logicbio.com.

**Where can we go to learn more about LogicBio’s technology?**

LogicBio has several genetic medicine educational resources, including videos, available at our company website [www.logicbio.com/patientsandfamilies](http://www.logicbio.com/patientsandfamilies) and also on our dedicated informational clinical trial website [www.sunrisemma.com](http://www.sunrisemma.com). The OAA also has webinars and information available on their website.

We always encourage families to speak with their physician to learn more about gene therapy, gene editing, and other advances in research. In addition, several rare disease advocacy groups have developed comprehensive genetic medicine resources for the rare disease community. Two of these are:

- [https://patienteducation.asgct.org/](https://patienteducation.asgct.org/)
- [https://rarediseases.org/tag/gene-therapy/](https://rarediseases.org/tag/gene-therapy/)

**Are there ways to get involved in LogicBio’s work?**

The answer is YES! As part of our mission to help improve the lives of families living with rare genetic diseases, we are always looking to partner with families on disease awareness initiatives. This may be in the form of caregiver advisory boards where we seek input from family members of children affected with MMA. We are also constantly expanding our communication efforts to help increase awareness about living with MMA via family profiles. If you may be interested in sharing your story with us, please get in touch at patients@logicbio.com.

As this is the last OAA newsletter in 2021, we wish you all a happy holiday season and best wishes for 2022!
Gene therapy is making a difference in the lives of patients with previously untreatable genetic diseases. Most of these rare diseases result from a defect in a single gene. Gene therapy aims to deliver working copies of the gene into affected organs and tissues to correct the underlying genetic defect. The potential tools for such targeted gene delivery have been studied for many years in animal models, but now are finally coming to clinical fruition. This includes the possibility of treating inborn errors of metabolism, especially those involving the liver, such as methylmalonic acidemia (MMA). The majority of individuals with MMA have a deficiency in a gene called methylmalonic CoA mutase, or MMUT for short, which results in the body’s inability to process certain fragments of proteins and fats. This metabolic defect can lead to a build-up of toxic substances causing bouts of serious illness called metabolic crises. The liver is a key organ involved in this processing of proteins and fats and therefore delivery of a fully functional MMUT gene into the liver has the potential to greatly reduce the severity of disease and improve quality of life. This line of thinking is further supported by the clinical benefit that many MMA patients exhibit after successful liver transplantation. The advantage of gene therapy is that it does not require the availability of a suitable organ to transplant or complex surgery, nor does it require lifelong immune suppression.

The use of adeno-associated virus (AAV) vectors is one of the most advanced and extensively studied approaches to deliver working copies of genes. It has been studied in animal models of MMA and used extensively in human gene therapy clinical trials for other genetic diseases. AAV itself is a harmless virus. The modified AAV used for gene therapy cannot make copies of itself because the genes of the virus have been removed and replaced with a therapeutic gene, such as MMUT. Notably, the outer structure of the virus particle, called the capsid, allows the therapeutic AAV vector to enter the target cell and to unload its genetic cargo (i.e. the correct version of the MMUT gene). Some types of AAV selectively target liver cells, which enables targeted delivery of the MMUT gene to the liver cells. After unloading of the MMUT gene, the AAV capsid is degraded but the MMUT gene stays within the target cell. The new MMUT gene uses the liver cell’s machinery to produce the correct version of the MMUT enzyme, which restores the ability of the cell to break-down protein and fats and reduce the buildup of methylmalonic acid and other toxic metabolites. This strategy has been demonstrated in mouse models of MMA in the laboratory headed by Dr. Charles Venditti at the National Human Genome Research Institute (NHGRI).

Metabolic disorders, such as MMA, can affect a child from birth. Most cases of severe MMA require immediate management and early intervention to prevent metabolic crisis and minimize tissue and organ damage. Despite best efforts, patient management is very challenging due to the variety of stressors (e.g. diet, infection) that can trigger metabolic crisis. Thus, gene therapy is likely to provide the most benefit when applied at an early age.

One challenge with treating young children is that the AAV vector is non-replicating, and gene therapy delivers only a limited number of MMUT gene copies into the body. Over time, as the child grows, their liver cells will continue to multiply, but the number of transferred MMUT gene copies will not. Therefore, the therapeutic benefit may decrease over time if the remaining MMUT gene copies cannot keep up with the metabolic demands of a growing child. Thus, it is possible that an MMA patient treated with AAV-MMUT as a child will require additional therapeutic treatment during their lifetime. The ability to re-dose AAV could provide significant benefits to patients, including re-dosing to help more patients to achieve therapeutic benefit and redosing to restore activity in patients that have lost therapeutic benefit (Figure 1).

Figure 1. Re-dosing has the potential to provide therapeutic benefit to those successful gene therapy treatment and redosing in an animal model of methylmalonic acidemia.
patients that fail to achieve therapeutic activity after the first dose (Top). Re-dosing could also help to restore therapeutic activity to those patients that have lost therapeutic benefit (Bottom).

However, there are significant biological barriers to re-treatment with AAV gene therapy vectors due to the patient’s immune response to the AAV capsid. Although the AAV vector is no longer a virus, it is dressed in the coat of a virus (the capsid), and thus treated by the immune system as a potential threat. The immune system produces antibodies against the AAV capsid, much like it would produce antibodies to an actual virus or to a vaccine. These antibodies circulate in the blood and stand ready to block the AAV vector by binding to the capsid surface and tagging it for elimination by the immune system. These circulating antibodies will form after the first treatment with AAV and effectively prevent the ability to re-administer AAV gene therapy.

Selecta Biosciences has developed a technology called ImmTOR that is designed to selectively prevent unwanted immune responses to AAV vectors and other biologic drugs. ImmTOR consists of nanoparticles containing a drug called rapamycin (a well-known and FDA approved drug used to prevent organ rejection in patients receiving kidney transplants). In contrast to rapamycin, which requires life-long daily administration to prevent organ rejection, ImmTOR is designed to be dosed around the time of AAV administration to inhibit the immune response to the AAV capsid by selectively inducing immune tolerance. Immune tolerance is the process by which the immune system regulates itself to prevent unwanted immune responses to the body’s own proteins. The immune system can ‘learn’ to become tolerant of other harmless proteins, such as dietary proteins or proteins from bacteria that normally colonize the gut. ImmTOR facilitates specific immune tolerance induction when co-administered with biologic drugs, such as AAV vectors. Animal studies have shown that ImmTOR inhibits immune responses to AAV vectors enabling successful re-administration of gene therapy. ImmTOR has also been studied in humans in combination with an enzyme therapy called pegadricase to treat severe gout, a non-genetic disease. Like AAV, pegadricase is a highly immunogenic drug. When used alone, pegadricase induces strong antibody response and cannot be re-dosed, but when combined with ImmTOR it has been successfully administered up to 6 times in humans. Over 250 patients have been treated with ImmTOR, which is currently in Phase 3 clinical trials, the last phase of clinical testing prior to marketing.

Based on this knowledge, scientists from Selecta Biosciences and NHGRI decided to test if treatment with AAV-MMUT, an AAV vector designed to treat MMA, combined with ImmTOR would suppress the development of antibodies against AAV and thus allow for vector re-dosing. Separately, Selecta scientists have recently shown that co-administration of liver-targeting AAV vectors and ImmTOR also led to an increase in the expression of the AAV-delivered gene after just a single treatment. However, this was not done using a therapeutic gene such as MMUT. Thus, there were two separate questions that scientists were trying to answer in the new study: 1) Would there be a beneficial effect of ImmTOR on initial AAV administration in a mouse model of human MMA disease? 2) Would co-administration of AAV-MMUT and ImmTOR decrease immune responses to AAV and, consequently, enable therapeutic redosing? It is important to mention that re-dosing of AAV gene therapy and ImmTOR in an animal model of human disease had never been tested before.
therapies in juvenile mice, as a model for gene therapy in young children. Mice were treated at approximately 4 weeks of age (roughly correlating to a child 3-8 years of age) and then again 8 weeks later (when the mouse becomes a young adult) with AAV-MMUT alone or combined with ImmTOR. These mice were then followed for a year after treatment initiation (a middle-aged mouse). As seen before, administration of AAV-MMUT was beneficial and resulted in a dramatic improvement in metabolic status, weight gain and survival. A further decrease of plasma levels of the key toxic metabolite, plasma methylmalonic acid (pMMA), was observed after treatment with the AAV-MMUT was administered in combination with ImmTOR. This difference was even more profound after a second treatment, as the mice treated twice with AAV-MMUT + ImmTOR showed further reduction in pMMA while the mice treated twice with AAV-MMUT alone showed no further benefit. The mice treated with AAV-MMUT by itself developed high levels of antibodies against the AAV capsid after the first dose, which would be expected to inhibit the ability of AAV-MMUT to reach the liver during the second dose. In contrast, there were no anti-AAV antibodies detected after the initial treatment when AAV-MMUT was co-administered with ImmTOR. As a consequence, re-dosing of AAV-MMUT and ImmTOR provided additional benefit with further decrease in pMMA levels and increases in body weight. A similar trend was observed for a biochemical disease biomarker, fibroblast growth factor 21 (FGF21), which was earlier shown by Venditti’s lab to be an MMA factor 21 (FGF21), which was earlier shown by Venditti’s lab to be an MMA factor. In other words, this meant that more therapeutic AAV had entered liver cells and more MMUT enzyme was made, resulting in lower toxic metabolites and disease markers when AAV-MMUT was administered in combination with ImmTOR, especially after re-dosing. This was further confirmed at the end of the study when mouse tissues were analyzed. Although livers from all AAV-MMUT-treated mice showed a dramatic improvement compared to untreated MMA mice, this benefit was even more pronounced when AAV-MMUT was administered in combination with ImmTOR. Importantly, co-administration of AAV and ImmTOR was well tolerated by MMA mice with no adverse effects seen throughout the study. Collectively, it appears that combining of ImmTOR and AAV not only inhibits the antibody response against AAV capsid, but may also improve vector entry into target cells and enhance the expression of therapeutic MMUT gene in the mouse model of MMA.

These observations suggest that the combination of ImmTOR and hepatotropic AAV-MMUT gene therapy has the potential to provide therapeutic benefit to MMA patients and be superior to a conventional single-dose of AAV gene therapy thanks to two contributing factors. First, ImmTOR can limit the detrimental impact of anti-AAV antibodies on gene therapy with the goal of enabling re-dosing of AAV vector and second, it may increase vector entry into liver cells and elevate therapeutic gene production upon initial dosing. ImmTOR also has the potential to modify the inflammatory response in the liver to avoid long term daily immunosuppressive medications such as steroids that are commonly used in gene therapy trials. The safety and efficacy of the AAV vector combined with ImmTOR must be demonstrated in clinical trials, which we anticipate starting in early 2022.

This multi-pronged mechanism of ImmTOR action makes it an attractive candidate to enhance systemic gene therapeutic applications, particularly in those clinical indications where repeat vector dosing may be necessary. Liver-directed gene therapy for metabolic diseases such as MMA presents a strong case for ImmTOR co-administration. Early intervention (in children and even infants) is highly desirable to prevent disease progression, and the target organ is destined to grow substantially over time, resulting in vector dilution. The rapid and enhanced expression of the AAV delivered gene may enable therapeutic benefit at lower doses of AAV and faster onset of the therapeutic effects. Furthermore, mitigating the formation of anti-AAV antibodies by ImmTOR provides an ability to re-dose vector over time, maintaining or restoring the therapeutic benefit of the gene therapy.

New data published by our scientific collaborators at St. Jude Children’s Research Hospital in Science Translational Medicine describe the effect of PZ-3022 in a mouse model of propionic acidemia (PA).

Individuals with PA cannot break down parts of protein and some types of fat due to either a missing or a non-functioning enzyme called propionyl-CoA carboxylase (PCC). When this enzyme is not working properly, there is thought to be a shortage of coenzyme A (CoA), resulting in cells in the body being starved for energy.

**PA mouse model**

In this paper, the scientists used a mouse model of PA that have a PCC enzyme which is mostly non-functional. This mouse model was originally developed by Dr. Michael Barry’s laboratory at the Mayo Clinic in 2016. In prior studies it has been established that, these mice have changes in biomarkers including high levels of C3-carnitine and an elevated C3:C2 carnitine ratio in blood samples and in the liver, similar to PA patients. Furthermore, the PA mice experience heart complications, similar to some PA patients, including increased heart weight compared to healthy animals.

**Treatment of a PA Mouse Model with PZ-3022**

For the first time, the authors of this paper characterized CoA in these PA mice. They observed a shortage of free CoA (CoASH) and C2-CoA in the liver, supporting the idea that CoA depletion occurs in this disease. PZ-3022 increased free CoA (CoASH) and C2-CoA in the liver of PA mice compared to untreated mice. Treatment of PA mice with PZ-3022 also reduced C3-carnitine and the C3:C2 carnitine ratio in the liver and reduced the C3:C2 ratio in plasma. Overall, these data suggest that PZ-3022 treatment improved the metabolic state of the PA mice.

Previous work by other scientists suggests that mitochondria, the “powerhouse” of the cell, do not function properly in PA. The Tricarboxylic acid cycle, (TCA cycle; also sometimes called the Krebs cycle or citric acid cycle) is a series of chemical reactions in mitochondria that cells use to break down organic fuel (sugars, fatty acids, and some amino acids) to harvest energy for cells. In this paper, our collaborators at St. Jude show that TCA cycle intermediates (chemicals in these reactions) are elevated in the blood and urine of PA mice compared to healthy mice, suggesting the mitochondria are not working properly. PZ-3022 reduced the high levels of TCA cycle intermediates observed in the plasma and urine of PA mice, suggesting that PZ-3022 treatment improves mitochondrial function in PA mice.

CoA Therapeutics is developing a similar compound, BBB-671, an oral therapy currently under investigation in a Phase 1 study (NCT04836494) in healthy volunteers and patients to assess safety and determine an appropriate dose.
The HERO (Help Reduce Organic Acids) Study is evaluating an experimental drug for methylmalonic acidemia (MMA) and propionic acidemia (PA). The study drug, called HST5040, is an oral therapy designed to correct metabolic abnormalities associated with MMA and PA. HST5040 may distribute to multiple affected tissues and have the potential to be active throughout the body, including the kidney, liver, brain, heart and muscles.

The HERO Study is recruiting participants age 2 and older with MMA or PA. The study is not enrolling patients who have had transplants at this time.

All drugs, study visits and assessments will be provided at no cost. Participants may receive stipends to cover meals and travel related to study visits.

To find out if there is a study site near you visit: MMA-PAHero.com

The safety and effectiveness of HST5040 for the treatment of MMA or PA have not been established.
Advancing mRNA Medicines in PA and MMA

For the past 10 years, Moderna has been working to advance mRNA as a potential therapeutic option for rare genetic diseases that are caused by defects or deficits in proteins expressed by liver cells.

Moderna is taking a different approach to address the underlying cause of these diseases including Propionic Acidemia (PA) and Methylmalonic Acidemia (MMA) by delivering mRNA therapeutics intravenously (IV) to potentially stimulate production of therapeutic proteins in the liver in ways that cannot be achieved with other technologies. Our approach aims to help the body make its own missing or defective protein (in this case, PCC or MUT).

- mRNA technology does not change the genetic information of the cell, and it is short-acting.
- It acts like traditional drugs that can be adjusted over time based on the dose and frequency needed.
- In simple terms, we are working to provide physicians and patients with a “controllable” way to start and manage their therapy over time.

Clinical Trial Updates

As a company deeply committed to developing vaccines and potentially life-saving medicines for patients around the world, we are pleased to provide an update to the Organic Acidemia Association on our Propionic Acidemia (PA) and Methylmalonic Acidemia (MMA) activities over the past several months. We also welcome you to learn more about our ongoing clinical trials including full inclusion and exclusion criteria by visiting https://trials.modernatx.com or https://clinicaltrials.gov

Phase 1/2 Paramount Study for Propionic Acidemia Successfully Completes Enrollment of First Cohort

We are proud to share that Moderna has completed enrollment of Cohort 1 of the Paramount Study and is now enrolling participants in Cohort 2 at research sites located in the United States, Canada, and the United Kingdom. The Phase 1/2 Paramount Study is designed to evaluate if an investigational treatment called mRNA-3927 is safe in individuals one year of age and older with PA. mRNA-3927 is an investigational intravenous (IV) infusion treatment that instructs a persons’ body to make a PCC enzyme that works.

First Patient Dosed in Phase 1/2 Landmark Study of mRNA-3705 for Methylmalonic Acidemia

We are also excited to announce that Moderna has dosed our first MMA patient in our Phase 1/2 Landmark Study. The Landmark Study is open to enrollment in the United Kingdom and Canada; and is designed to evaluate if an investigational treatment called mRNA-3705 is safe in individuals one year of age and older with MMA. mRNA-3705 is an investigational intravenous (IV) infusion treatment that instructs a persons’ body to make a MUT enzyme that works.

We are especially energized by the possibility of delivering on the promise of mRNA for patients in need. The efforts happening at Moderna and beyond our walls are exciting because they signify the potential of what we can achieve together in support of rare disease patients worldwide.”

RUCHIRA GLASER, MD, MS, FACC
Senior Vice President, Head of Rare Disease, Moderna
Thank you for the opportunity to share our story which I know many of you will identify in some way with your own experiences.

If I am completely honest the years have been nothing short of an emotional rollercoaster. Turmoil, constant worry and fear of the unknown mixed with the joy of reaching a milestone, gratitude for each day, each birthday, never taking life for granted.

Lachlan was born 2 November 2002 and diagnosed with MMA Mut-o by the newborn screening test at 12 days old. He was admitted into the RCH, ICU in metabolic crisis. Like many of our warriors, Lachlan’s start in life was rough. Although his birth went well, initially he had slight jaundice and wasn’t feeding properly but nothing to worry about (or so we thought). We were excited to be given the green light to go home and start our new life as a family. Over the next couple of days things didn’t feel quite right. We arranged a lactation nurse to visit to help with the feeding issues and mentioned the groaning noises he was making during his night feed while he was sleeping. I questioned my gut feeling was growing concern there whether this was normal and although noisy babies could be. But the following day night time, we would be surprised at how we weren’t experiencing anything different from any new parents settling in and if we walked through the hospital nursery at night time, we would be surprised at how noisy babies could be. But the following day I noticed Lachlan had vomited some of his feed while he was sleeping. I questioned whether this was normal and although my gut feeling was growing concern there were no other obvious signs. Our saving grace call came that afternoon when a doctor from the Royal Children’s Hospital rang to say Lachlan’s newborn screening test had shown a high level of chemical in his blood and to bring him into hospital immediately. Little did we know at the time “the doctor” was Head of the Metabolic Team. From the moment we arrived at the hospital, while the medical team appeared calm things moved fast. Lachlan was admitted and as the hours passed Lachlan’s condition deteriorated. “Dr. B” took my husband and me into a little room nearby to tell us they had established our son had a rare metabolic condition called MMA, possibly Mut-o, as he was non b12 responsive. He was in metabolic crisis and they were transferring him to ICU. While they were doing everything possible, the reality was he may not survive and suggested that if we wanted to call in family then not to delay. We were in our worst nightmare. I remember sitting in that little room in ICU with my beautiful (now late) husband, both of us in complete shock praying to God to just let him survive and we would take him any way he came and do everything to make his life as best we could. As immediate family arrived “Dr B” came in again and somehow very calmly explained the process of treatment and said the next 24 – 48 hours were critical. Although the chain of events of those next 48 hours were somewhat of a blur, some of those images and feelings are still so clear to this day. Miraculously, thanks to the incredible work by “Dr B” and the metabolic team and the person in newborn screening who picked up the discrepancy in the first instance, our little fighter survived. After a number of weeks in the neo natal ward, our little “chipmunk” was coming home. I called him this with love as when we were finally able to leave the ward for a walk within the hospital there was this tiny little baby in a big hospital pram with his great big beautiful brown eyes peering over the blanket. Taking Lachlan home was both incredibly joyous and daunting as we had so much to learn. Our heads were in a whirl calculating daily intake of protein, calories and medications not to mention being first time parents, but we didn’t care as we felt so incredibly lucky. For years, each time we visited the hospital for Lachlan’s clinic appointments, the amazing “Dr B” (who was Head of his metabolic team for next 16 years) would always say to Lachlan “here is the young man who caused me some sleepless nights”.

Fast forward almost 19 years, with countless hospital stays to keep him stable due to gastro or other childhood illnesses, doctors and therapists appointments, blood tests, nasal gastric tubes and at the age of 4, the devastating loss of his father under his belt, we have the most remarkable young man in our lives. Yes, he has his health challenges, his weekly medication box is pretty full and he is closely monitored by both the renal and metabolic teams but Lachlan’s positive outlook on life, his tenacity and his resolve, his strong will not to let MMA define him gives me the strength I need. To anyone who ever says you can’t - he says I CAN. Despite all the bumps along the way, Lachlan successfully completed Year 12 VCAL and is currently doing a furniture and cabinet making course which he loves. He works part time, is learning to drive and can’t wait to buy his first car. Whilst we always tread with an element of sensible caution, we have also done our best to ensure Lachlan participated in activities others wouldn’t think twice about. Like the time in secondary school when he was desperate to attend a four-day camp
to a remote part of bushland in Victoria (Australia) with no mobile reception. Both sides of my brain started their usual battle as they had done so many times before like when he was 3 years old trying to decide if I should send him to day care “with all the germs” until his metabolic doctor suggested quite matter of factly “the sooner he goes the better, as you can’t wrap him up in cotton wool.” Here we go again - how could I entrust someone else with his care in this environment? How would we get him out of there quickly if he became unwell? But we went to work. His wonderful outdoor education teacher was so happy and went to great lengths placing extra vehicles along the way (although he did say he would carry him out of there if need be), accommodating his food requirements and medical management plan with the promise he had the satellite phone and yes he assured me the battery was charged. To ease my mind, I also contacted Air Ambulance Victoria to ask about their process and length of time it could take to get someone out of the remote bush in the case of an emergency. They were incredible and offered to work with the teacher to map out exactly where they were situated and entered all of Lachlan’s medical emergency plan into their system so that in the event, they received a call they were ready to go. Lachlan had an amazing four days and arrived home unscathed, tired but elated to have had this experience with his school mates. We all slept well that night. Obviously the MMA journey affects everyone in the family and I am not going to lie it has been a tough gig at times particularly as a sole parent juggling full time work and the mental load of the constant underlying worry but we have muddled our way through with the help of supportive employers & work colleagues, family and close friends who I have been able to reach out to when three wheels have fallen off the bus and the fourth is about to go, who drop everything to help in an instant without question or judgement. Although it’s hard to ask sometimes, I have learned people want to help. These people I cherish and am indebted to. Lachlan also has a wonderful 15-year-old brother Christian (unaffected) and the bond between them is very strong. Over the years, Christian has been ferried off to family or friends during hospital stays, sometimes in the middle of the night, last minute cancellation of parties, weddings and holidays when things took a turn, accepting that’s just the way it is without complaint. I am so extremely proud of Christian being so caring and supportive of his brother and I know it is not easy on him as he worries about his brother too. They are both incredibly resilient young men and that is I guess what adversity creates. This journey has given us the awareness to cherish our children and embrace life in a way that perhaps we may not have otherwise. Although it’s hard to stay in the present and not think too far ahead given the progressive nature of MMA, I try to reflect on my late husband Victor’s words to me, “don’t worry about what tomorrow will bring, just do today”. We have so much gratitude for the incredible Metabolic Team at The Royal Children’s Hospital and now The Royal Melbourne Hospital where Lachlan has transitioned as an adult. We are now riding on the wings of hope that one of these new treatments will come sooner rather than later, work and work well as without hope we have nothing. Blessings to you all – I feel we are an extended family, understanding each other’s journeys, in ways others cannot, differ as they may, and I am thankful. And to Lachlan and Christian if you read this, you are my superhero warriors.

Daphne
MMA – Mut o Parent,
Melbourne Australia
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I would also like to take this opportunity to talk a little about the MDDA (Metabolic Dietary Disorders Association) a wonderful Association supporting and advocating with Government for families predominantly PKU and with PA, MMA IVA and other rare protein IEMS under their umbrella in Australia.

We are very fortunate to have the support of the MDDA and also appreciate the amazing work of Kathy Stagni and the OAA which is invaluable to the families in Australia. My role with the MDDA is the MMA Link representative, in the coming months we hope to work with families with other organic acidemias to leverage common issues, especially with some emerging clinical trials targeting more than one of the OA conditions. Our mission is to continue working towards raising awareness and a key advocacy priority to work with companies who have clinical trials to establish Australia as a trial site. A high priority for the MDDA is to establish a contact registry including capturing all rare inborn errors of protein metabolism. The purpose of this registry is to provide data to organizations considering research and or clinical trials in Australia and position Australia to take advantage of emerging therapies, like gene and cell therapies that offer hope to families for potential treatments. Australia is fortunate to have very experienced and dedicated clinicians who have expressed interest and are very supportive of our efforts for this to happen. We hope some of the gene therapies that are emerging will ultimately be of benefit to many of the rare protein IEMS. I can be contacted at daphne.doukas@mdda.org.au

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Organic Acidemia Association (OAA) provides information and support to parents and professionals dealing with a set of inborn errors of metabolism collectively called organic acidemias. The OAA is a volunteer organization registered with the IRS as a 501(c)(3) non-profit corporation. Donations to the OAA are tax deductible. OAA publishes a newsletter three times a year, hosts a Google Group for information exchange and maintains a website and Facebook page. Services are funded by corporate and individual donations. Annual membership donation of $25 (US) and $35 (international) plus $5 for the family roster is requested, but not required. Our 501(c)(3) non-profit status qualifies OAA for United Way donations through their write-in option. If there is a write-in option, just write “Organic Acidemia Association” in the blank line on your pledge card.

Donations can also be made at OAA’s website through the “PayPal” and the “Network for Good” option.

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- This newsletter does not provide medical advice. You should notify your health care provider before making treatment changes.

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