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Organic Acidemia Association



OAA Newsletter • Family Stories • Family Matching • Family Conferences • Research Funds Awarded • National Advocate for Newborn Screening

Parent Support, Education & Awareness www.oaanews.org

A support group for families living with methylmalonic, propionic, isovaleric, and other organic acidemias

Happy Fall! It's been a busy summer! We held a successful FOD/OAA Family Forum in Pittsburgh, PA in June. Thanks to all the volunteers that helped to make it happen! We were happy to host again with our longtime friends Deb Lee Gould and the FOD Family Support Group. Our conference coordinator, Erin MacLean did an outstanding job organizing registrations and coordinating with the hotel. Thank you, Erin! We hope to plan another family forum sometime in the Summer of 2026. We have not decided where or when – but if you are interested in helping to plan and organization, please let me know.

2024 OAA Family Forum

OAA is also in the process of transitioning our OAA Patient Registry with NORD to a new platform. We hope to have this complete sometime in the first quarter of 2025. More information will be communicated as we move closer to this date.

This issue includes our 2023 financial summary. We thank you for your continued support in supporting all we do to support families and research for those living with organic acidemias. Also included in this issue are stories from those living with organic acidemias as well as their caregivers. Research and surveys are also summarized in this issue. I'm excited to share that OAA will host Beth Beyer, our previous OAA Executive Director in a Zoom webinar on "The Afterlife: A Hypnotherapist's View". Read page 5 that outlines what to expect from this webinar.

As always, I appreciate your support and it's my pleasure to represent our community.

Kathy

Around Our Community

Dr. Mary Ampola, metabolic clinician from the Boston area:

As you may know, our mother Mary Ampola passed away on June 8th. She was an amazing physician, friend, mother, & grandmother. We invite friends & family to gather in Atlanta or Boston to celebrate her life & accomplishments.

- The ATLANTA Celebration of Life will be Saturday, October 26th from 4-6pm.
- The BOSTON Celebration of Life will be Saturday, November 2nd from 4-6pm (this would have been her 90th birthday).

Locations will be determined. Refreshments will be served. Attendees will have an opportunity to share memories of Mary if they choose. Further details will be shared closer to the event.

We plan to make picture montages, so we invite you to share pictures of Mary. You can send them to Dave at dampola@gmail.com.

This post is public. Please share with anyone who may be interested and ask them to email leeampola@gmail.com to get on our list for updates.

Thank you, Leanna and David Ampola.

In this issue

Organic Acidemia Association

9040 Duluth Street
Golden Valley, MN 55427

Phone: 763.559.1797
Fax 866.539.4060
www.oaanews.org

Kathy Stagni
Executive Director
Propionic Acidemia Parent
9040 Duluth Street
Golden Valley, MN 55427
Phone: 763.559.1797
mkstagni@gmail.com

Menta Pitre
Legacy Director
MMA Cbl C Parent
menta@oaanews.org

Cay Welch
Legacy Director
Glutaric Acidemia,
Type 1 Parent
cswelch1@verizon.net

Jana Monaco
Advocacy Liaison
Isovaleric Acidemia Parent
jana.monaco@verizon.net

Richard Bazzy
Director
Isovaleric Acidemia Parent
johnnyb1979@yahoo.com

Karen Dalton
Director
MMA Cbl C Parent
JKdalt@comcast.net

Allison Wood
Director
Glutaric Acidemia Type 1 Parent
alnm1613@gmail.com

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Thank you to all of our volunteers and sponsors.
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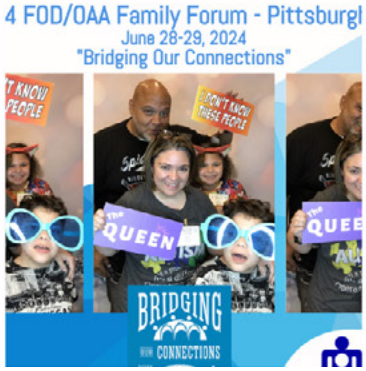
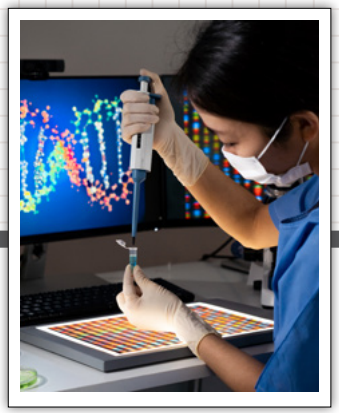


Genespire Presents Positive Preclinical Proof of Concept Data

at the ASGCT Annual Meeting



Data provides preclinical validation for Genespire's liver-directed lentiviral gene therapy in a mouse model of methylmalonic acidemia

Abstract received the ASGCT Excellence In Research Award

Milan, Italy, 9 May 2024 – Genespire, a biotechnology company developing off-the-shelf gene therapies for pediatric patients affected by genetic diseases, today presented positive preclinical data at the 27th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) currently taking place in Baltimore, MD, USA. These data demonstrated long-term preclinical efficacy of the Company's liver-directed integrative immune shielded lentiviral vector (ISLV) based gene therapy in a mouse model of methylmalonic acidemia (MMA).

MMA is a rare, genetic metabolic disorder most frequently caused by a faulty gene coding for the mitochondrial enzyme methylmalonyl-coA mutase (MUT). People with this condition are unable to break down and use certain proteins and fats found in food and, as a result, circulating methylmalonic acid accumulates in the body, causing damage to the brain, liver, kidneys, and other organs. At present there are no disease-targeted drugs approved for MMA, and affected patients suffer high levels of morbidity and have a heavily reduced life expectancy.

In the study presented at ASGCT, intravenous administration of an ISLV encoding a human MUT transgene was evaluated in a mouse model of MMA. Treated mice showed a rapid, substantial, and long-lasting (>1 year) reduction in circulating methylmalonic acid, normalization of weight and complete survival. Additionally, ISLV administration led to a systemic effect, resulting in a significant reduction of methylmalonic acid levels not only in the liver but also in the brain and kidney, suggesting an extrahepatic benefit achieved through liver-mediated detoxification.

This work was performed by Dr. Elena Barbon, post-doctoral fellow, and Dr. Alessio Cantore, Group Leader, at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), in collaboration with Genespire. Dr. Elena Barbon received the ASGCT Excellence In Research Award for this abstract. This award is granted by the ASGCT to the top 15 abstracts received from ASGCT members or associate members.

Alessio Cantore, Group Leader at SR-TIGET and co-founder of Genespire added: "These compelling data provide evidence for the efficacy, safety, and extrahepatic benefit of our integrative immune shielded lentiviral vector (LV)-based gene therapy and important preclinical validation."

Julia Berretta, CEO at Genespire, commented: "Receiving the ASGCT Excellence In Research Award provides further external validation on the quality of our research and promise of our technology". She added, "We believe that our unique ISLV gene therapy approach, allowing for stable gene transfer and long-lasting expression of the therapeutic gene, may be optimally positioned to treat MMA patients."

For further information, please reach out to the Company.

Is It Possible to Journey to the Spirit World?

Greetings OAA Family,

If you have been part of OAA for 25 years or less, you may not know me, nor recognize my name. So let me tell you a little bit about myself. After Laurie Asten had created the OAA, she passed it along to me around 1990. In those days, there wasn't really a good way for parents to connect with each other, except by telephone. We sent out a newsletter created from articles by medical professionals and families, including pictures of our children. We received some assistance from donations, including from Sigma-Tau Pharmaceuticals.

We were so happy to be able to connect with everyone – to seek information and provide it to those who needed to know. We wanted to know to try to find the best treatment for our son who was diagnosed at 4 months of age with PA, especially since some conventional treatments didn't work. Seth had an amazing life, albeit in a wheelchair and attending school with an aide. He had a great sense of humor and touched so many people. He passed away when he was almost 15 years old. Eventually, Kathy Stagni agreed to be OAA's Executive Director and continue the important mission of empowering families – and she's done stellar work!

So, it has been 20 years since our son died. Wow. Some things haven't changed. My husband and I have been married for 42 years, and we live in the same house in Reno, Nevada. Instead of dealing with wheelchairs, IV's, PICC lines, g-tubes, IEP's and a specialized diet...a picture of Seth is now located on the OAA Memorial webpage.

G-d forbid that any of us should have to walk this path of having our children die before us. After all, that's not how it's supposed to work, right? For those who walk this path, how do you cope? How do you manage your day? Everyone has their own method. For me, it was to study more - - a whole lot more. So now, my work includes being a spiritual hypnotherapist to connect people to the Spirit World. It is not based on any particular religion. It's based upon the work of what is now hundreds of thousands of cases done by practitioners. My studies included Quantum Healing Hypnosis Technique (QHHT – by Dolores Cannon), Between Lives Soul Regression (BLSR – by Dr. Linda Backman), and Life Between Lives (LBL – by Dr. Michael Newton). My role in getting clients to so they can interact on their own with the Spirit Realm has been my passion – and Seth was certainly my inspiration. Sessions are often done by Zoom.

To have people take a journey to their "higher self" (also called subconscious or soul), a good hypnotherapist doesn't give suggestions. A hypnotherapist is not a psychic, a medium or even a channel. My role is to facilitate clients in relaxing and ask open-ended questions, asking what the client notices and what comes into their awareness. The client is the one who responds to the questions while they journey.

If you told me this was possible 20 years ago, my reaction would have been complete disbelief. Now, it's a different story because of so many clients and especially having the experience myself. It has been my honor and privilege to assist parents to connect with the Spirit Realm where we can find answers beyond our earthly existence as souls.

My practice is completely sliding scale based upon whatever the client can afford – and with this group, my request would be

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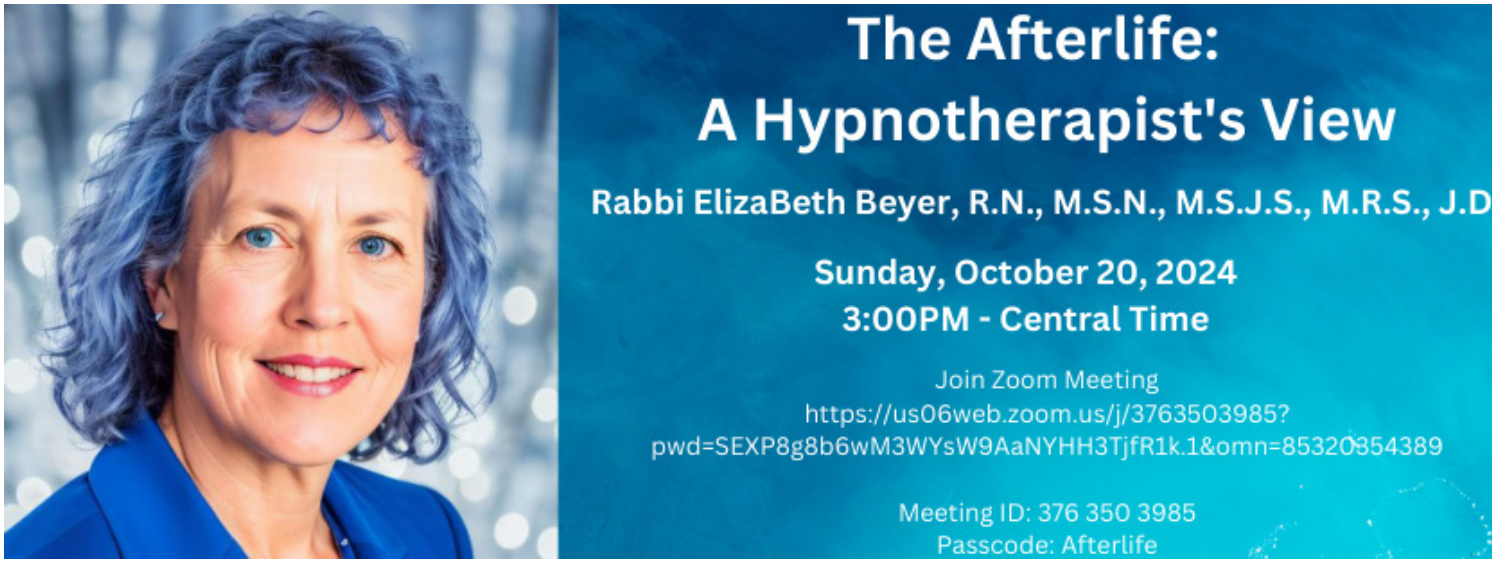

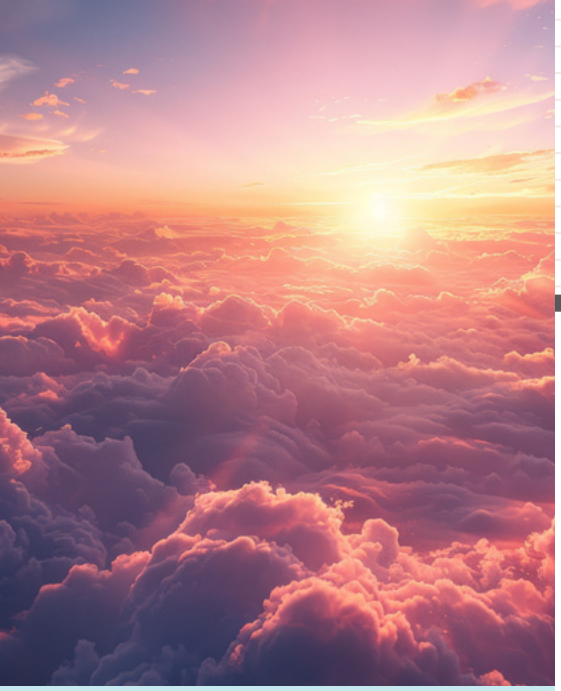

[Spirit World **continued**]

to request a donation to OAA. Sessions are 3-4 hours and often require two sessions, according to the Life Between Lives protocol. There are also wonderful places online for healing information and community sharing, such as Helping Parents Heal Group (for those whose child has passed on) on Facebook or local Compassionate Friends for parents/siblings.

Kathy has kindly offered to have OAA host a Zoom meeting for those who are interested in the journey of the soul – for any reason. If you'd like more information, consider watching Dolores Cannon or Dr. Michael Newton on YouTube or reading Newton's, "Journey of Souls" or Cannon's, "Between Death and Life." Also, please attend the Zoom meeting. Feel free to send in your questions in advance, if you wish. www.RenoLifeBetweenLives.com or BethBeyerQHHT@gmail.com Looking forward to meeting you and sharing my passion for this amazing, transformative and life-changing work!

Beth Beyer, RN, MSN
www.RenoLifeBetweenLives.com

In Memory of Seth Beyer, PA
10-20-89 to 8-13-04

Eli

Glutaric Acidemia, Type 1
Age 3

Eli's condition was diagnosed with the newborn screenings. Grandpa Mike, (me), was there at his birth and I even created a storybook in real time of the event. Eli seemed to be a perfectly normal baby until he had a crisis at 5 months old, on New Years Eve! His mom, my daughter, was a single parent and they lived with Grandma. Caring for Eli became too overwhelming for them as I believe they did not understand the severity of GA1. Eli was diagnosed as 'failure to thrive" and eventually went into Foster Care at two years old. I had not been able to see Eli for several months because the relationship between my daughter and I had been strained. In July of 2023, I decided to go over without invitation to their home to see Eli. When I arrived, they were just leaving for a doctor's appointment. Having been to almost all of Eli's other doctor visits, I decided to go to that one too. The doctor said they wanted to see Eli back in one week. So, knowing that, I showed up for that appointment also. However, Eli was not there. The receptionist checked the computer to see if something had changed and said that Eli had been admitted to the hospital. I went to the hospital wing of the medical complex to see if I could get in to see Eli. The nurses would not let me in but did call the social worker in charge of Eli's case. I spoke to her and found out that Eli had been removed from his home, admitted to the hospital for nutritional needs, and was going to be placed in foster care! At this point, Eli was just a few days over 2 years old and only weighed 22lbs. His weight had plateaued for many months and needed immediate intervention to prevent further potential complications. In talking with the social worker, she asked me if I could get to the courthouse in an hour because the first hearing regarding the placing of Eli in state custody was to begin. And of course I would be there! God works in mysterious ways. I firmly believe God directed me and all the circumstances that happened that day. I established with the courts that I was next of kin, grandpa, and that I would do everything possible to adopt and take care of my grandson. And that day, Aug 01, started out me just going to my grandson's doctor appointment. Well, a new journey in my life was about to begin that I am forever grateful for in allowing him to live his life and realize potentials he may never had had before. This little guy is worth it all!

Eli came to live with us on September 15, 2023. He spent just over a month in foster care, but I was there several times a week learning how to care for him. When Eli finally did get here, Sandra and I were familiar with the GTube and feeding pump because of those visits.

It was a Friday when Eli arrived, and by Monday he was back in the hospital due to a virus. He was a sick little boy. We spent a week with him in the hospital. The nurses were great, they showed us more about caring for him. We had official GTube training! We learned to be his advocates during his hospital stay. Since then, he has been on track and gaining weight; growing fast! In no time at all it seemed, Eli shot up to 36 lbs. We started out with weekly appointments at the genetics clinic and are now down to every 4 or 5 months. Eli has been learning so much in the past year. Within the last two weeks, he received an I pad like assistive speech device and is working hard to learn that. He is so smart and outwits us a lot! He is all boy! He

received a wheelchair in March and had it mastered in about a week. He likes to show off his antics like spinning in circles and trying to pop wheelies! He has a newfound freedom! And he loves it.

When Eli was 5 months old, he suffered a metabolic crisis. The MRI showed the basal ganglia was affected. Altogether he has had seven hospital stays. His speech is impaired, and he is diagnosed as developmentally delayed. He has good use of his arms and hands. His legs and feet are his big challenge. He is so strong and has a will that does not stop. He will work and work to accomplish any task. He is very strong willed and usually always wants to wheel himself. When he tries to say something, and we don't understand, he patiently repeats it numerous times. We eventually understand and are getting better at communicating all the time. About one month ago, he said a complete sentence. While changing his diaper at 3am, he said "I want to turn the light off!" It was so very exciting. Eli knows several things in sign language. Sandra was in the kitchen with him one day with her back to him. He coughed and Sandra said, "Eli you sound like you need a drink." She handed him his cup and he took a drink. After that, he fakes a cough any time he wants a drink of water. When asking for a car or truck he sticks his tongue out. In the Disney movie Cars, Lighting McQueen sticks his tongue out to tie in the big race. Thus, Eli associates cars with sticking his tongue out! There are other little communications he has developed over time that will not be found in the ASL handbook, but it works for him. Eli understands everything we say so we can only imagine how frustrating it must be for him to know what he wants to say but not be able to express it. We do have to watch what we say in front of him, especially if we know it is not something he is going to want to do. He will react immediately according to his desire to either do it or not.

Eli just turned 3 years old this summer and now is attending preschool. He struggled at first since it was his first experience being away from home. The first week was rough but now he waves and tells us "Bye" when we drop him off. He rides the big yellow bus home and is just so very happy to see Sandra and I when he gets home. On day three he brought home an accident report. He had been on the playground that has a bit of a slope, a thing he loves, and he puts his hands in the air, and lets the wheelchair go! He hit the fence and cut his lip. As we said before, he is all boy! He loves going fast. He is making friends at school and learning so many new things. He waves to everyone smiling and leads his 5 or 6 classmates in line back to their homeroom. He seems to excel at the tasks they give him. We do worry about the exposure to colds and the flu. The staff is aware of his fragile health and keeps us posted on even the slightest sniffle going around. Preschool will be very good for Eli.

It has been one year since Eli came to live with us. Caring for him is hard work but seeing how much he has grown is very rewarding. Our most recent doctor's visit had them comparing where he was a year ago and where he is now. We are with him every day and you lose track of where he was when he amazes you every day. When we first got him, he was barely rolling over or sitting up on his own. Now he will take off in an army low crawl on the floor. And he will roll and roll away really fast when we play with him. When he is in his wheelchair, look out! He will ram you! We call him the bulldozer. He has such a contagious laugh and loves to play "sneaky sneak" with us and say "boo"! We wouldn't want to ever be without him! Eli is just so much fun. And it doesn't stop there. Eli brightens up a room. His smile is contagious, and his laugh brings others to laughing. People tell us what a wonderful thing we have done, but the truth is that Eli gives happiness to everyone he meets and helps in his own way in making this a better world for all!

This past summer has been very exciting for our family. Eli has been learning and experiencing new things like swimming and visiting exciting places like Mt Rushmore, but the highlight of the year was going to Pittsburgh for Family Forum's conference with Organic Acidemia Association / Fatty Oxidation Disorders Family Support Group this past June. We met families from all over the USA whose little kiddos are living with all sorts of metabolic disorders. We exchanged names and ideas and things we do to help our little warriors. We also got to speak personally with the doctors and researchers who work tirelessly to bring hope to all of us. It was all very reassuring and quelled our concerns and fears that our Eli was out here fighting this with not a lot of support. Yes, it's good that we get great support from our own doctors and metabolic staff, however, it's also nice knowing we can reach out to others who are "living" the same struggles. We stepped into this fight for Eli about a year ago. Discovering this conference was one more thing we can do to better understand our child's struggles and better prepare ourselves for the future. The information received and the contacts we made at this conference were invaluable in our journey with Eli.

Mike and Sandy
wagner1559@pm.me
Oskaloosa, KS

A better understanding of disease mechanisms opens new treatment avenues

Research into the organic acidemias is gaining momentum. In the niche of propionic acidemia (PA), a type of organic acidemia we study at Oxford, there are now ~900 scientific publications on record in the National Library of Medicine. Half of these articles were published in the last decade, reflecting the exponential growth of research activity. This scientific literature is a mix of clinical observations, basic research studies using lab animals or cells, and reports of trials from across the globe. If we can maintain this balanced progress, I am convinced the collective effort will translate to benefit patients and their careers.

Autumn marks the start of a new academic year, which is also a good time to reflect on progress made over the past 12 months by our research community. A widely discussed milestone was the interim report of the first-in-human trial of mRNA therapy for PA, published in Nature by Koeberl et al. The preliminary findings report that a life-threatening metabolic episode is less likely in those patients who received the therapy. This news is encouraging, and we look forward to subsequent reports. It is reassuring that the mRNA particles did not trigger an adverse immune reaction, one of the fears associated with gene therapy. During the past year, the PA mouse model (developed by Dr Barry and colleagues in the early 2010s) has proven to be a very useful asset for research. The mouse allows a larger scale of testing that can narrow-down drug candidates to a shortlist that are most likely to benefit human patients. In that area, we closely follow the milestones of Dr Venditti who reported promising results with gene therapy in mice using adeno-associated virus particles for delivering the healthy PCC genes. Aside from advances in gene therapy, last year has provided more compelling evidence that diet is important. A study by Wang et al showed that a major source of propionate in the hearts of PA mice is sourced from the gut, where bacteria ferment foods into short molecules, including propionate. This study highlights the importance of looking at the disease from a systemic viewpoint, that is, considering the intact system which has all relevant systems of the body. Their study opens new avenues for testing in humans. A study by He et al reported that fasting alleviated the metabolic alterations in PA mice, pointing – again – to the importance of diet. These findings make a compelling case to consider diet alongside gene therapy for patients affected by PA and other organic acidemias.

Our research group in Oxford has been busy testing diets supplemented with beta-alanine, a substance we normally source from a healthy diet. We confirmed that this is well tolerated by mice and can be taken in substantial quantities either as a free molecule or a derivative called carnosine. We believe that beta-alanine will be well tolerated in PA patients because already it is consumed as a supplement by athletes and body-builders. Beta-alanine is distinct from another amino acid, alanine, in terms of structure. Whereas alanine is a building block for proteins, its 'beta' relative is used to synthesize histidyl-dipeptides that provide essential protection from oxidative stress, particularly in the heart. Conveniently, the body normally sequesters beta-alanine to the heart, offering a way to piggyback useful therapeutic cargo to where it is needed most. We reason that more antioxidant protection can alleviate some of the effects of propionate by helping the heart clear this substance more efficiently. The idea came from our study using the PA mouse that showed more protection in male PA mice which, incidentally, have more beta-alanine in their hearts. We published tthose charitiescle in Nature Cardiovascular Research, that you can access freely at: https://www.nature.com/articles/s44161-023-00365-0 and we are delighted that charities, including the OAA, could help us with grants. We think this can be an important dietary supplement, but more work is needed to build a convincing case. We hope to start a larger scale study soon. I am pleased to report that KC Park, who worked on PA in our lab, was awarded a prize at a major cardiac research conference in August for the work leading up to these new studies!

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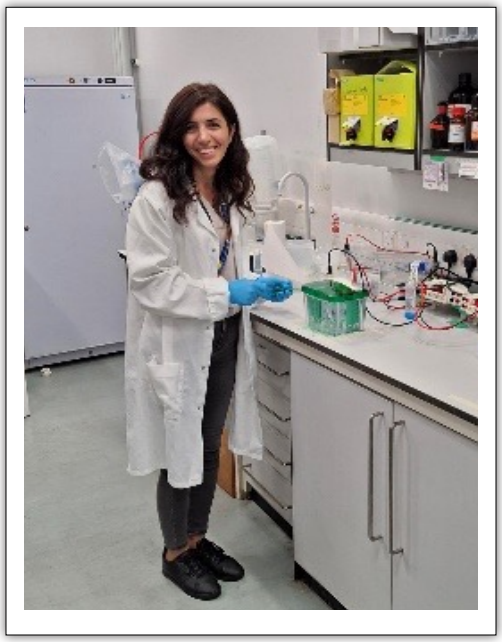


Dr Gul Simsek is performing a western blot analysis of histones extracted from cardiac cells that had been treated with propionate, to see how this substance affects the structure of genes and their activity.

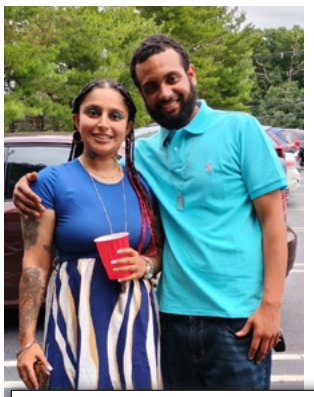
Over the past year, we have also investigated how the build-up of substances in the blood of PA patients might affect the structure of genes. DNA is wrapped around proteins called histones that act as scaffolds. Those scaffolds that are "open" can produce a message that results in the production of specific proteins coded by the gene. This mechanism is one way in which cells control gene expression. The process is affected in PA patients, so it is important to understand how the histones are modified. Our team is looking into specific histone modifications that are different in the PA mice, and we might reverse these. By acting early, such an intervention could delay or even stop some of the deleterious effects on the heart and brain.

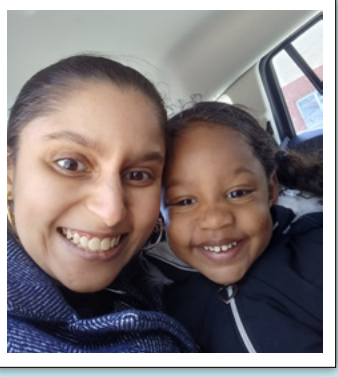
Progress, whether in Oxford or in other labs, cannot happen without the help from our funders. The OAA has been tremendously helpful in enabling our research. As an academic partner, we understand that delivering value for money is critical, especially for areas that do not normally attract larger grants because of the perceived 'niche area'. We hope that by sharing these results, you are assured that your efforts are put to a good use.

Pawel Swietach
Professor of Physiology
Department of Physiology,
Anatomy & Genetics
University of Oxford

Charisma

MMA, Mut 0
Age 30





Hello everyone, so a lot has happened over the last few years, but I wanted to share an update with you all.

Today is September 8, 2024, I am turning 30 years old. As we all know, living with MMA is difficult, changes to our bodies and organs overtime. I have this eye condition called isolated uveitis, it makes it difficult to see sometimes, I follow up with an eye specialist. So currently, I wear glasses and can't drive at night, because my vision is worse at night. Back in July 2022, I got diagnosed with (CKD) Chronic Kidney disease, Stage 3; I manage it by decreasing my salt intake and drinking plenty of water, staying hydrated daily. Some days are rough, but as MMA progresses it turns to renal failure eventually. I had 2 ectopic pregnancies, sadly: in 12.30.22 and 02.01.24. Back in 2020 I got divorced, but I'm getting married again finally 06.03.25. My kids are 9 and 5 years old.

Even though life has been throwing curveballs my way, I'm still alive and striving to be well. Also, me and my fiancé are in the process of IVF hoping to be blessed with one last bundle of joy.

Please feel free to contact me by email, do not hesitate to email me charismatic0994@gmail.com any questions or just feel like talking email is the best way to reach me.

Charisma
New Jersey

2024 FOD/OAA Family Forum Memorial Poster

Jonathan

MMA Mut o

Age 14

Jonathan was diagnosed with methylmalonic acidemia (MMA) at age 2 following a traumatic brain injury that led to the discovery of his condition. As a result of his diagnosis, he lost his gross motor skills and became confined to a wheelchair. After spending 55 days at Levine Children's Hospital, Jonathan was able to come home.

Living with his mother, Loree, and two sisters, Cayla and Carli, the family adapted to a new lifestyle, learning to navigate their challenges together. Jonathan has since made remarkable progress through intense speech, physical, and occupational therapy, demonstrating dedication and determination to regain his physical abilities.

He has participated in various activities, including the OAA metabolic conference, metabolic studies at the NIH, Camp CLT, University of North Carolina Charlotte Dance Marathon and the Brownies and Burpees charity event for children with disabilities for the past seven years. A highlight of his journey was a Dream on 3 wish trips, where he met Steph Curry and attended a Warriors game. He also shared a memorable moment with Cam Newton during a Carolina Panthers game.

Jonathan's passion for basketball led him to join the Charlotte Rollin Hornets wheelchair basketball team in January 2017, where he continues to learn new skills and thrive off of his development. As an 8th grader, he works hard in class by asking and answering questions with enthusiasm, actively engages with peers and staff.

In addition to his academic pursuits, Jonathan is involved in church activities at Sanctuary Charlotte, participating in Generation Joshua and Teen Church. His vibrant personality and resilience inspire those around him.

Jonathan loves to travel to different places and document his experiences. He is a new fan to WWE and attended Friday Night Smackdown and Saturday Wrestle Mania. He is also modeling with Dillard's department store.

Our motto is Jonathan has MMA however MMA does not have Jonathan. We will continue to explore and experience life as we see it.

Loree
Charlotte, NC
Loreecoliver@gmail.com

Facebook Page: https://www.facebook.com/profile.php?id=100077687953253

Around the Community: Dylan at Culver's

It was a dream of Dylan's to work at Culver's and some very special people made this happen! Thanks to the Culver's in Woodbury, Minnesota on Tuesday, June 18th this dream came true! This is a fundraiser for the Organic Acidemia Association and a portion of the proceeds from that night will go to them! This organization is near and dear to our hearts as Dylan's disease, Propionic Acidemia, is one of the diseases under the umbrella of Organic Acid disorders. They currently provide support to families who get these devastating diagnoses as well as fund different studies and trials all over the world who are trying to find treatments and even a cure for Dylan's disease. With these diseases being so very rare the funding for these studies is close to nonexistent, so anything we can do to help them, help Dylan, we fight every day to do. Dylan was over the moon for this opportunity – and thanks to Culver's this location also hosted another fundraiser in July! OAA received a total of $1220 from Culver's and other supporters of this fundraiser! We are so very grateful! #DylansDreamTeam #propionicacidemia

moderna

landmark study

Moderna is pleased to share that the Phase 1/2 mRNA-3705-P101 study is currently enrolling.

The Landmark Study is evaluating an investigational treatment called mRNA-3705. mRNA-3705 has the potential to instruct the body to produce the methylmalonyl-CoA mutase (MUT) enzyme, which breaks down certain proteins and fats and metabolizes methylmalonyl-CoA. The investigational treatment is administered as an intravenous (IV) infusion.

For more information about Moderna's rare disease studies, please visit **PAMMARareDisease.com** or scan the QR code.

Key Eligibility Criteria

- ≥1 year of age
- Diagnosis of MMA due to MUT deficiency confirmed by molecular genetic testing
- Cannot have had organ transplant

Countries

- United States, Australia, Canada, France, Netherlands, Spain, United Kingdom

Number of Participants

- up to 63

This progress is only possible because of the commitment of the study participants, their families, the investigators, and the study teams. Moderna is grateful, and we thank everyone for their efforts as this program progresses.

https://clinicaltrials.gov/study/NCT0489931(

Summer 2024 Ask the OAA Dietitians

Hot Topic:

OAA Diet/Formula: To Blend or Not To Blend

Summarized/Prepared by OAA Medical Advisors: Elaina Jurecki and Keiko Ueda

A survey was conducted to gather OAA community opinions about offering homemade blended food or commercially available blended formulas for nutrition support of individuals living with an organic acidemia (OAA). All responses were collected anonymously and those completing the survey were informed that responses would be summarized and published in an OAA community newsletter. We greatly appreciate all the survey responders who volunteered their time and shared their comments.

Who responded to this survey?

- 56 individuals responded to 15 survey questions between July 9, 2024 thru Aug 7, 2024.
- 93% identified as caregivers for an individual living with an OAA.
- 75% live in the USA or Canada, while 25% live in Europe, South Africa, or Australia.
- OAA disorders represented by survey responders included:
  - Methylmalonic acidemia (37%)
  - Methylmalonic acidemia+Homocystinuria (15%)
  - Cobalamin cofactor disorders (2%)
  - Propionic acidemia (28%)
  - Glutaric acidemia (11%)
  - Isovaleric acidemia (4%)
  - Others: 3MCC, HMG-CoA lyase deficiency and Combined Malonic and Methylmalonic acidemia disorder.
- 77% have health insurance coverage assistance for their OAA diet, formula refills, metabolic clinic appointments and OAA monitoring lab costs.
- 23% do not have health insurance coverage assistance; 3 responders had partial coverage, 2 responders did not have an OAA specific diet nor OAA formula.

What type of OAA protein restricted diet were followed?

- 84% followed a doctor supervised OAA specific diet restriction in foods; while 16% do not follow an OAA specific diet restriction in foods.
- A wide variety of dietary protein restrictions were reported ranging from: 1g/d, 8g/d, 10g/d, 12g/d, 17g/d, 18g/d, 20g/d, 21g/d, 24g/d, 25-30g/d, 28 g/d, 30g/d, 35g/d, and 114 grams per day. 4 responders shared that they were not on a protein restricted diet. This response is to be expected given the OAA conditions represented by responders to this survey.
- 2 responders had protein goals based on weight 0.875g/kg or 0.8g/kg
- 1 responder limited diet to: 60mg lysine/kg/d
- 24% followed safe feeding recommendations by their speech language pathologist (SLP) or occupational therapist (OT) due to feeding difficulties or dysphagia to reduce risk of aspiration and other feeding complications.
- 41% drank an OAA formula by mouth 59% did not drink any OAA formula by mouth.
- 39% were tube fed an OAA specific formula. and commented their formula included multiple ingredient formula recipes; one responder blended foods with some breastmilk, and another shared that formula was only available for an emergency.
- 80% did not include a formula company blended formula (made from whole foods), and 20% did include a formula company blended formula (made from whole foods) Responders commented; tube fed, fed by mouth, and too high in protein requiring additional non-protein calories.
- 85% had no concerns about including home-made blended foods or a formula companies blended formula (made from whole foods) in their OAA diet given by mouth or tube fed,
- 15% shared their concerns. including:
  - protein precision/calorie concerns,
  - getting clogged/not counting protein correctly,
  - interested but not knowing enough about this option/not sure what to give
  - concern of over restricted diets possibly causing harm/long term issues
- 80% stated they were satisfied with their current doctor supervised OAA diet, but 20% stated they were not satisfied, and comments included:
  - no OAA specialized doctors in their country,
  - interest in blending foods/ incorporating real/more natural foods but lack of knowledge how to do it
  - interest in more dietitian involvement with food help
  - wanted to know specifically how much protein to eat or not eat
  - shared that their medical team didn't want to consider change from status quo for their adult living with an OAA
  - wanted to know why their adult was taking GA specific formula when younger individuals were not
- 68% stated they were comfortable asking their doctor and dietitian about including blended whole foods/formula in their OAA diet plan, and 11% stated they were not.

The Pros and Cons

This survey showed that 85% of responders stated interest in including blended whole foods in their OAA formula/tube feedings, some responders commented on their lack of guidance or knowledge on how to do so. Tube fed blenderized formulas made from blended whole foods may provide an intact protein source and nutrients similar to meals eaten by mouth. Home-made blenderized whole food-based formula may be measured and mixed with commercially available OAA disorder specific formulas to help meet an individuals' daily nutrition goals. Resources are available with detailed information on how to safely prepare foods and store home-made blended formulas and purees made from whole foods.

- Motivating factors for using whole food blended formulas include:
- personal preference to feed whole foods and add variety to diet intake
- sharing and enjoying the same foods and variety as the rest of the family
- addressing feeding intolerance problems including gagging, vomiting and constipation that may be related to medical concerns common in OAAs e.g. dysphagia, reflux, delayed gastric mobility, or constipation
- individualizing food choices and calculating protein or OAA specific amino acid content to meet daily OAA diet goals when medically indicated
- stimulating intake by mouth with whole foods for those that receive most of their nutrients from tube feedings as medically indicated and safely tolerated

There are risks to consider with feeding whole food blended formulas to individuals living with OAAs that may contribute to metabolic instability including:

- too much variation of nutrients resulting in inadequate and unbalanced diet intake not meeting an individuals' daily OAA nutrition goals
- excessive protein or OAA specific amino acid content above an individuals' daily OAA diet goals and metabolic tolerance
- inadequate or excessive calories, vitamins and/or minerals in whole food blended formulas
- potential risk of food born illnesses due to unsafe home blending methods, preparation, and storage, which may pose health risks particularly for immunocompromised individuals
- increased cost and time required to plan and prepare home blended formula
- increased risk of clogging the feeding tube requiring medical interventions
- age and developmentally unsafe diet advancements and introduction to foods, particularly for infants and children <3 years of age
- increased aspiration risk of feeding foods or liquids that may contribute to respiratory illness in individuals with feeding difficulties or dysphagia

OAA Metabolic Diets → Making it just right!

It is important to discuss with your metabolic clinic team if using a commercial or home-made blended formula is safe for you or your individual living with an OAA. Always follow food safety guidelines in the preparation and storage of home blended whole food formula ingredients. If dysphagia or aspiration are concerns, consult Speech or Occupational therapists for individualized safe feeding recommendations. If you include a homemade whole foods blended formula, always check your formula recipes with your metabolic team to ensure that it meets and does not exceed OAA metabolic nutrition goals and most of all does not risk compromising OAA metabolic control.

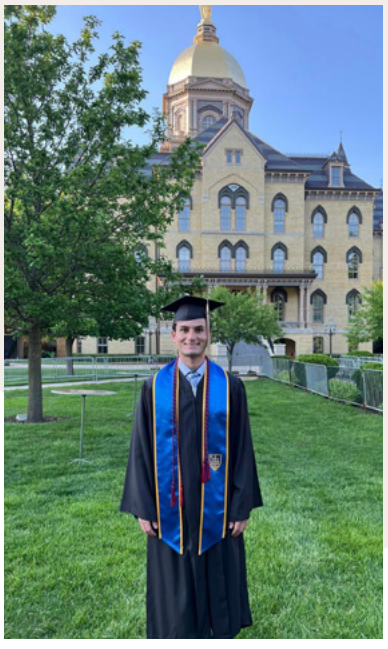
This survey and summary is not intended to provide medical advice or direction; continue to discuss individualized OAA diet and feeding plans with your medical team.

Resources and References:

- Tube Feeding Tips: Blenderized Diet Pros and Cons - Oley Foundation
- ANHI blenderized feeding patient infographics
- Nutricia Learning Center Blenderized Diets, April, 2023 Webinar Slides BTF for IEM
- Testing Methods IDDSI Framework

Around the Community:

Connor, MMA, CblA, graduated this spring from the University of Notre Dame with a degree in Finance, pictured below.



Moderate Fasting: Friend or foe for patients with propionic acidemia?

Guo-Fang Zhang,
Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition,
Duke University Medical Center, Duke Molecular Physiology Institute, Durham, NC 27701, USA

Patients with propionic acidemia (PA) suffer from a deficiency in propionyl-CoA carboxylase (PCC) due to mutations in the PCCA or PCCB genes. This malfunctioning enzyme results in an inability to metabolize propionyl-CoA, a metabolite derived from propionate, certain amino acids, odd-chain fatty acids, and cholesterol side chains. Propionate, propiogenic amino acids, and odd-chain fatty acids are primary contributors to propionyl-CoA production. To prevent the accumulation of this toxic metabolite, current therapeutic strategies include low/special protein diets, antibiotics, and carnitine supplementation.

Fasting and prolonged exercise are typically discouraged for patients with PA because they increase amino acid catabolism and the oxidation of odd-chain fatty acids, leading to higher levels of propionyl-CoA. However, no basic research has been done to thoroughly investigate these conditions. In our recent study, we explored the metabolic changes in Pcca-/-(A138T) mice after a 23-hour fast, and the results were surprising, contradicting conventional expectations 1.

To provide context, the Pcca-/-(A138T) mouse model used in this study was developed by Dr. Michael Barry's group. Mice completely lacking the PCCA gene die within 36 hours of birth, limiting research opportunities. To overcome this, Dr. Barry's team created an adult hypomorphic PA model using a transgene bearing the human PCCA protein with the A138T mutation 2. These mice exhibit typical PA metabolic symptoms but otherwise show no severe phenotype, aside from lower growth rates and body weights. Our metabolic flux data, derived from stable isotope-based tracing, indicated reduced PCC activity in most organs except the skeletal muscles, heart, and pancreas 3. Thus, Pcca-/-(A138T) mice represent a model of mild PA.

Overall metabolic improvements in Pcca-/-(A138T) Mice by a 23-hour fast

After fasting for 23 hours, plasma levels of propionylcarnitine (C3), acetylcarnitine (C2), methylcitrate, and citrate were measured and compared to non-fasted Pcca-/-(A138T) mice. Surprisingly, C3 was significantly reduced, and the C3/C2 ratio dropped to one-third of the levels observed in fed mice. Methylcitrate was also reduced by half, and the methylcitrate/citrate ratio significantly decreased. These unexpected findings suggest that fasting may improve metabolic alterations in Pcca-/-(A138T) mice. This raised the question: Why do the metabolic changes in PA improve after fasting instead of worsening? We further investigated the sources of propionyl-CoA production and its disposal mechanisms to understand the underlying mechanisms.

23-Hour fast reduces microbiome-derived propionate production

Propionate, a short-chain fatty acid, is primarily synthesized by the gut microbiome 4. It is activated to propionyl-CoA by acetyl-CoA synthetase short-chain family member 3 (ACSS3). Microbiome-derived propionate is a significant contributor to propionyl-CoA production, though its exact contribution is difficult to quantify. A striking finding was that microbiome-derived propionate production decreased by 75% after 23 hours of fasting. This reduction in propionate production may lead to less propionyl-CoA synthesis, thereby improving the metabolic status of the mice. How fasting alters the microbiome's food availability and composition requires further investigation.

Fasting enhances carbon flux from propionyl-CoA to gluconeogenesis

Propionyl-CoA serves as an anaplerotic substrate, replenishing the tricarboxylic acid

(TCA) cycle when intermediates are depleted by cataplerosis including gluconeogenesis. Using 13C-labeled propionate, we examined how fasting influences gluconeogenesis and anaplerosis. Our results showed that carbon flux from propionyl-CoA to glucose synthesis in the liver, kidney, and intestine increased significantly after 23 hours of fasting. This enhanced flux may help reduce propionyl-CoA accumulation and improve overall metabolic alterations in Pcca-/-(A138T) mice.

Propiogenic amino acid catabolism increases modestly during fasting

To evaluate the contribution of propiogenic amino acids to propionyl-CoA during fasting, we administered 13C-labeled valine (a branched-chain amino acid) and threonine (a precursor of 2-ketobutyrate) to both fasted and fed Pcca-/-(A138T) mice. Valine-derived propionylcarnitine labeling remained unchanged during fasting, with only a slight increase in BCAT activity and 3-hydroxyisobutyrate labeling. However, threonine metabolism significantly increased after 23 hours of fasting, although this did not result in an increased propionyl-CoA pool. These findings suggest a moderate increase in amino acid catabolism after 23 hours of fasting, but without a net rise in propionyl-CoA levels.

Odd-chain fatty acid oxidation and propionyl-CoA production during fasting

Fasting typically promotes fatty acid oxidation, and patients with PA are advised to avoid fasting and prolonged exercise due to concerns that odd-chain fatty acid oxidation could exacerbate propionyl-CoA accumulation. Our metabolic profiling of Pcca-/-(A138T) mice after a 23-hour fast confirmed a significant increase in fatty acid oxidation, with elevated levels of ketone bodies and acylcarnitines. Importantly, even-

chain fatty acid oxidation was predominant, with C2 levels rising significantly more than C3 levels, reducing the C3/C2 ratio. This aligns with theoretical models, as the complete oxidation of a C17 fatty acid produces 7 acetyl-CoA molecules and only 1 propionyl-CoA molecule. Consequently, the increase in fatty acid oxidation during fasting does not appear to pose a significant risk for increasing C3/C2 ratio.

Study limitations

These findings challenge our prior understanding of PA, but we acknowledge the limitations of this study: (1) this research was conducted in mice, and its relevance to humans remains uncertain and (2) the Pcca-/-(A138T) model represents a mild form of PA, so the effects of fasting on patients with severe PA may differ.

Conclusion

Lifestyle, diet, and daily activities impact the progression of PA, and fasting is generally discouraged. However, this recommendation lacks substantial scientific evidence. In this study, we used Pcca-/-(A138T) mice to investigate the impact of a 23-hour fast, finding that fasting improved metabolic alterations by reducing microbiome-derived propionate production, increasing propionyl-CoA anaplerosis for gluconeogenesis, and boosting C2 production from fatty acid oxidation. These results warrant further investigation in human studies, particularly in PA patients with varying severities.

References

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3. He, W., Wang, Y., Xie, E.J., Barry, M.A., and Zhang, G.F. (2021). Metabolic perturbations mediated by propionyl-CoA accumulation in organs of mouse model of propionic acidemia. Mol Genet Metab 134, 257-266. 10.1016/j.ymgme.2021.09.009.
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OAA Financial Summary 2023

Each year we report the financial status of the OAA, highlighting our accomplishments and the source/use of funds received.

In 2023, we received nearly $97,000 in grants, donations and investment income. We sincerely thank the following donors who contributed over $10,000 to the OAA: Moderna, Selecta Biosciences, Hemoshear Therapeutics, CoA Therapeutics, Donovan Controls and The Gary S. Stevens Donor Advised Fund.

We awarded financial grants to the National Institute of Health (NIH – Dr. Chuck Venditti's team) and Oxford University in the UK in the name of the OAA.

Our outreach included the OAA Newsletter, Facebook and other social media presence.

The following are events that OAA participated in 2023.

- »Speaker on Rare Disease Day at CoA Therapeutics in San Francisco, CA February 2023
- »OAA participated in Rare Disease Day at the University of Minnesota – March 2, 2023
- »OAA hosted a Zoom Webinar on ABLE Accounts – March 2023
- »OAA exhibited at SIMD Conference in Salt Lake City – March 2023
- »OAA hosted Zoom Webinar - OAA Family Chat - Donate Life Month - April 2023
- »OAA exhibited at Abbott Conference in San Antonio, TX – May 2023
- »OAA hosted Zoom Webinar - OAA Dietitian Chat - June 2023
- »Social media campaigns created by University of Minnesota students in collaboration with OAA – Fall 2023

As you can see, it was another successful year of delivering visibility for our OAA families and contributing to the long-term prospect of realizing cures for our OA disorders.

Thanks to everyone who contributed and/or participated in organized fundraisers for OAA in 2023 – below are a few of the fundraisers – please let me know if you are interested in creating a fundraiser for OAA.

- »Rare Disease Day Tshirt fundraiser: raised $1341.52
- »Jaehnke Family Tshirt Fundraiser: raised $212.62
- »Facebook Fundraisers: raised $1305.56
- »OAA Calendar fundraiser: raised $547.59
- »Amazon Smiles program (now discontinued) $784.31
- »Norwex Fundraiser raised $40.00
- »Medtronic Foundation Donation: $900.00

Financial Summary

Revenue	**FY2023**
Contributions & Grants	$90,784
Interest Income	$6,512
Total Revenue	**$96,803**
Expenses	
Grants	$75,600
Staff Expenses	$49,900
Accounting/Office	$16,547
Printing/Publications	$14,396
Conferences/Travel	$7,854
Total Expenses	**$164,297**
Cash Assets (12/31/22)	**$689,296**
Cash Assets (12/31/23)	**$620,936**

Organic Acidemia Association
9040 Duluth Street
Golden Valley, MN 55427

oaanews.org

ANNUAL DONATION / CHANGE OF ADDRESS

Please accept $_____ as our annual tax deductible donation to the Organic Acidemia Association.

Suggested membership donation is $25 (US) and $35 (international). Extra funds are welcome and can be designated for research, OAA operating expenses, or to help others attend conferences.

Remember the newsletter does not get forwarded when you move!

Name: _____

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City State Zip:_____

Email: _____

Mail to: OAA
9040 Duluth Street
Golden Valley MN 55427

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 an 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.

- The information contained herein does not necessarily represent the opinions of our Board of Medical Advisors or Board of Directors
- Letters and photographs sent to OAA become the property of OAA and may be used or edited at the discretion of the OAA staff.
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