It's been a snowy, long winter here in Minnesota — but I promise it will be beautiful come July! Our next family conference is planned in Minnesota on July 6-7, 2018. OAA and our long-time partner, FOD Family Support Group will again host the conference in Bloomington, MN (near the Mall of America). We are grateful to our host sponsor, Mayo Medical Laboratories as well as our many other sponsors/supporters. We have included our preliminary agenda in this newsletter – but most do register online via Eventbrite: www.eventbrite.com/e/2018-fodoaa-international-metabolic-conference-registration-37104930153

Check out OAA's website for the most up-to-date information on the conference and a link to reserve your hotel room - oaanews.org/2018-fodoaa-national-metabolic-conference.html.

This is a conference you won’t want to miss!

February 28th was the 10th Annual Rare Disease Day – a day to share awareness for our rare disorders. Stephanie Carleton and myself represented OAA at Rare Disease Event at the University of Minnesota. OAA also hosted an exhibit table at the SIMD (Society for Inherited Metabolic Disorders) conference last month in San Diego, California. This is an exciting opportunity for OAA as we share awareness of our rare disease community and our Natural History Registry with the many researchers/physicians in attendance. Much of the conference was meant for professionals, but I had the opportunity to attend some of the sessions and review the over 11 posters what were presented on our disorders. Next to our exhibit table was a new non-profit organization that OAA is collaborating with – the HCU Network America. Many of the HCU disorders overlap with OAA – those that relate with homocytinuria. Be sure to check them out at: hcunetworkamerica.org. Our rare disorders have the attention of several companies who are moving new treatments through the pre-clinical process and hopefully clinical trials will be started soon. Two of these companies have shared articles in this issue.

This is exciting times for our rare disorders!
# Medical Advisors

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**MARGIE MCGLYNN AND DANAE BARTKE AT SIMD**
**REPRESENTING HCU NETWORK AMERICA**

**KATHY STAGNI REPRESENTS OAA AT SIMD**
Epimutations and cblC

Patients and their families are critical allies in the search for the mechanisms underlying disease. Our laboratory at McGill University in Montreal has been studying inherited diseases involving the vitamins folate and vitamin B12 for more than forty years. Many of the known patients in North America have had their diagnosis made or confirmed in our laboratory. The basic approach is to use cultured cells from skin to classify patients into distinct groups. The OAA community will recognize these groups as resulting in elevated levels of either homocysteine, methylmalonic acid (MMA) or both in blood or urine. These diseases are associated with important clinical manifestations, including anemia, developmental delay and neurological disease. Many individual patients and their journeys have been described in the pages of the OAA newsletter. Over the years hundreds of patients with an inborn error of metabolism have been given a diagnosis through cellular studies in our laboratory. We have also been able to discover most of the genes responsible for these diseases.

The cblC disorder is the most common cause of methylmalonic aciduria combined with homocystinuria. This disease is most often diagnosed in the newborn period because of newborn screening for elevated MMA. Other patients are diagnosed because of the onset of symptoms in the first year of life, with still others diagnosed in childhood, adolescence or even adult life. In addition to the elevated MMA, patients also have elevated homocysteine levels. The disorder is autosomal recessive, meaning that affected individuals have two mutant copies of the causal gene, one inherited from their mother and the second from their father. Since identification of the causal gene for the cblC disorder, called MMACHC, mutations have been identified in over 600 patients. In nearly all cases, two causal mutations have been identified as is predicted for an autosomal recessive disorder. However, in a small number of patients only a single MMACHC mutation, or no mutation, has been identified.

We and our collaborators in France, Switzerland and the United States have identified an unexpected cause for the cblC disorder in several of these patients. This work was recently published in the journal Nature Communications. The MMACHC gene is on the short arm of chromosome 1, and is overlapped by a second gene, PRDX1, that is read in the opposite direction. In a small number of cblC patients, there are mutations in the PRDX1 gene that remove the polyadenylation signal; this signal under normal conditions terminates messenger RNA synthesis. In the presence of these mutations, the PRDX1 message continues across the MMACHC gene and into the MMACHC promoter region. There, it causes methylation, a chemical change in the promoter that turns the gene off: the MMACHC gene is no longer transcribed and no MMACHC protein is produced. This means that although there is no mutation in the MMACHC gene itself, its function is lost.

Changes in methylation patterns that result in altered gene expression have been called “epimutations” and are not usually inherited from one generation to another. However, in this case the PRDX1 gene is expressed in all cells of the body, and its expression turns off MMACHC expression. This means that the MMACHC promoter methylation is inherited as if it were a typical sequence variation mutation: the methylation change was identified in skin cells of fathers and a grandfather who had passed the PDX1 mutation to affected patients. The change was also seen in the sperm of the fathers.

This work, done in co-operation with families demonstrates a new mechanism for gene inactivation in inherited metabolic disease. We plan to look for a similar mechanism in many other such diseases. For the families, we have provided an explanation for why a second mutation was not found in the patients. It also provides them with the ability to perform accurate carrier detection and molecular diagnosis.

We are continuing our studies on patients with presumed inherited diseases of vitamin B12 metabolism in whom causal mutations have not been found.
My husband and I welcomed Molly Addison at 3:11 am on Mother’s Day 2015. She weighed 6 pounds and 14 ounces. Molly did so well after delivery that we were on our way home two days later.

At Molly’s 5 day old check up with her pediatrician, we were told she was absolutely perfect! Later that afternoon, the pediatrician personally called and asked for us to come back in because Molly’s newborn screening results had come back abnormal for 3-MCC. I immediately asked, “What?! Is it something serious?” All she could say was she would have to research it more and hopefully have answers for us by tomorrow.

We rushed to the doctor’s office and they attempted to take blood and urine samples from both me and Molly. After 3 hours of trying unsuccessfully to draw Molly’s blood from multiple locations, we were sent home with directions to go to the local children’s hospital in the morning. I will never forget looking into Dr. Ford’s eyes and hysterically crying. She immediately responded with a hug and told me she was going to take excellent care of Molly and that we had no reason to worry yet because Molly was doing absolutely amazing and thriving so well. She did not want to tell me anything about 3-MCC until she knew exactly what to expect and what to tell us.

I can’t say this enough, but Dr. Ford and her nurse, Ashley, are two of the greatest people in this world that I have the privilege of knowing.

After we returned home from Molly’s blood draw, Dr. Ford called and said, “When we hang up the phone, I want you to go to this website and read the very first line.” I went to the website and the very first line read, “Children diagnosed with 3-MCC at birth never need any special treatment and can live healthy lives with typical growth and development.” I knew at that moment Molly was going to be okay and that we had chosen the best pediatrician for Molly.

Two weeks later, we received a call from the Emory University Genetics Department. They confirmed Molly has 3-MCC. Three days later, my husband and I drove to Atlanta to meet with Dr. Gambello at Emory Genetics. Dr. Gambello said “Yes, Molly has 3-MCC and I do not think she will ever have problems with it, but we like to keep an eye on kids with 3-MCC so you will come in for checkups with me every 6 months, then once a year, then once every 2 years, and so on. She needs no special diet, she has no special needs, just keep an eye out for anything abnormal.” I remember looking at my husband and we both had tears in our eyes while smiling. Our baby girl was going to be okay.

Molly continued to thrive and was a happy, bubbly baby. We followed up with Emory Genetics at 6 months and again at 12 months. At each appointment we were told Molly was doing amazing. She was hitting all her milestones and eating like a champ. A year flew by and before we knew it Molly was eighteen months old!

On December 12, 2016, I woke Molly up as usual and gave her whole milk in her cup. I sat with her on the couch while she was fully waking up. I went into the kitchen to start her breakfast and Molly came into the kitchen not long after. When I turned around to look at her, she vomited all over the kitchen. I remember thinking, “oh goodness, our first stomach bug!” Less than 5 minutes later Molly became OVERLY silly. It almost reminded me of a drunk person who can’t stop laughing and being goofy. Molly was 19 months at this point, and all of a sudden, she had trouble walking. After she would stumble, she would become very irritated and cry non-stop. It was a cycle that kept repeating. I didn’t initially think it was her 3-MCC. I immediately called Molly’s pediatrician and she wanted to see Molly. While I waited for Molly’s appointment, something told me to look at the paperwork we received on 3-MCC.

As I read the symptoms, tears filled my eyes because she was exhibiting every symptom. I got her to Dr. Ford and she checked Molly out and I showed her the paper I read. She told us to get to the ER and take Molly’s emergency protocol letter with us. She told us she would call her fellows and give them a heads up since most ERs are not familiar with metabolic disorders.

When we got to the ER Molly’s blood sugar was 54. They started her protocol immediately and she was on D10 before I could blink. Within hours, Molly started to perk up. The ER doctor came into the room and told us Molly had metabolic acidosis and that she would be admitted. They
Children diagnosed with 3-MCC at birth never need any special treatment and can live healthy lives with typical growth and development.

A few weeks later, on April 9th, I documented that Molly had a high fever. No other symptoms, just a high fever.

The next month at Molly’s 2 year well check, I brought up to Molly’s pediatrician the possibility of Molly having periodic fever syndrome. These fevers were happening every 4-6 weeks. Dr. Ford never questioned my thoughts, and we both agreed that we would start treating her with a steroid at the first sign of fevers. Periodic fever syndrome has absolutely nothing to do with her 3-MCC, I think it just complicated the 3-MCC part because it brought on the high fever and appetite decrease.

By late May, Molly was in the hospital with vomiting and a high fever. We took her as soon as she woke up and started vomiting in hopes of getting the D10 going and getting a late-night discharge. She was not acidotic and we all felt she would eat better at home. We were discharged around 10pm that day. Three days later, Molly was admitted again for acidosis. We stayed a couple of days, and we all agreed, we should have never gone home on the first day. We started realizing at this point that Molly becomes acidotic quickly after she begins vomiting and her blood sugar has trouble stabilizing while sick without the help of D10. The geneticist explained to us that this is a typical and expected part of 3-MCC.

Molly continued to be admitted to the hospital about every 6 weeks until November 2017. Each time was either from an ear infection or her periodic fever syndrome. She stopped eating and we could not get her to eat or drink any carbs. Each admittance she had metabolic acidosis and our geneticist told us each of her hospital stays were related to her 3-MCC.
Molly’s biggest complication is she isn’t a fan of food. She will eat some sweets, but she only likes them in small amounts. I truly feel that if Molly had not been such a picky eater, we could have avoided a lot of her hospital visits.

Molly got tubes her ears in November 2017, and as I write this, we are officially 4 months hospital free. This is the longest we have stayed out of the hospital since she was 19 months old. 2017 was a long, hard year for my girl. I want every parent to know that even though 3-MCC is a mild disorder in comparison to other metabolic disorders, it still is very serious and it’s so important to be the advocate for your child. We had a long road with Molly, but I feel so much better as she gets older because she’s close to understanding how important her eating and drinking are and how important it is to stay well.

Find a pediatrician who truly advocates for your child. You need someone who takes you seriously, even if your child just has a common cold. Dr. Ford, Molly’s pediatrician has always taken me seriously, especially after Molly’s first metabolic crisis. She didn’t look at me like I was crazy when I brought up periodic fever syndrome. I remember her taking an hour with me one time after Molly’s 4th or 5th admittance where we tried to come up with every plan possible to keep Molly out of the hospital. I know I say it a lot, but there will never be enough good things to say about Molly’s pediatrician. She has truly blessed our lives with her care for Molly. I also credit Dr. Pavaluri, Molly’s hospitalist, for her amazing efforts to learning about 3-MCC and how it directly effects Molly. She read up on 3-MCC from asymptomatic kids to kids who had experiences like Molly. She also was the one who noticed Molly’s CRP levels and high liver enzymes. Because of her hard work and dedication to Molly, we were able to take a lot of information and questions to Molly’s geneticist and dietitian to get answers. We now have a new emergency protocol that was made specifically for Molly since we know how her body works when she doesn’t eat and is fighting an illness. Molly’s care team is just as important to us as Molly is to them, and our family is so appreciative of Molly’s medical care team.

Molly is completely on track development wise. She walks, talks, and plays just like a little girl her age should. We’re so relieved all of Molly’s hospitalizations have not had an impact on her development. I truly believe it is because of the quick and swift action of both her pediatrician getting us admitted and her hospitalist wasting no time getting Molly started on her D10.

I hope our story, while intimidating and a little scary, gives any other 3-MCC parent a sense of relief and a sense of what to expect and when to know to get immediate care for your child.

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GA1 Research Fund Started at NORD

Good news GA1 families - OAA set up a GA1 Research Fund with NORD! NORD’s Research Grant Program provides seed grants to academic scientists for translational or clinical studies related to development of potential new diagnostics or treatments for rare disease. In at least two cases, NORD grants have resulted ultimately in FDA-approved treatments for patients.

Visit [https://salsa3.salsalabs.com/o/51076/donate_page/research-program](https://salsa3.salsalabs.com/o/51076/donate_page/research-program). There is a drop down with several other research funds - just look for Glutaric Acidemia, Type 1. If you prefer to send a check - please add “D12080” in the check summary.
Annabelle Grace was born September 20, 2016 and like many children with Propionic Acidemia (PA) she went into metabolic crisis a couple of days after birth. After talking to our genetics team in December 2016 we started pursuing the option of a liver transplant for Annabelle. Even though we managed Annabelle’s care so meticulously she would still end up in the hospital every couple of months for high ammonia levels above 100 (often for no reason and with no detected illness). Annabelle had a g-tube placed when she was two weeks old, but even with pushing fluids and using sick day formulas we found it difficult to keep her metabolically stable (we checked her ketones EVERYDAY). We tried Carbaglu (which is supposed to help lower ammonia) along with high doses of Carnitine and Bicitra (Sodium Citrate), and those medications didn’t even seem to help control her metabolic instability. Her ammonia on a “good day” seemed to hover in the 60’s or 70’s, and even the night before her transplant her ammonia was 71. We realized early on that Annabelle had a very severe mutation, and we were told by many medical professionals that she was one bad illness away from another metabolic crisis that could cause serious brain damage.

After talking with other families, we were told that the Children’s Hospital of Pittsburgh was the place to go for transplant. The only liver transplant option in our state (North Carolina) was Duke University, but they had never performed a liver transplant on a child with PA. In April 2017 we ventured up to Pittsburgh, PA for Annabelle’s liver transplant evaluation and immediately fell in love with everything this hospital had to offer. Annabelle was officially listed for transplant on May 2, 2017. We immediately started fundraising and used the assistance of COTA (Children’s Organ Transplant Association) which we cannot recommend enough. Within three months our team of volunteers raised over $50,000 for COTA in Honor of Annabelle to help with any transplant-related expenses.

On August 9, 2017 we got “the call” that would forever change our lives, and we quickly rushed to Pittsburgh. We were very fortunate that our first call was “the call” that gave Annabelle her new liver. She went back for surgery around 10:30pm that night and they finished her surgery around 9am that next morning. After surgery Annabelle spent about one week in the PICU. After that week the transplant team moved her to the transplant recovery unit where she stayed until she was discharged. Around two weeks post-transplant Annabelle did encounter a small episode of rejection. Even though “rejection” sounds scary it is very common early on in transplant, and mild cases like Annabelle’s are generally treated with some high-powered IV steroids for a few days. Annabelle was discharged on August 30th and only spent a total of 21 days in the hospital. The transplant/genetics teams in Pittsburgh told us to prepare for complications (as is common with Organic Acidemia patients), but overall Annabelle had very few complications from her transplant surgery for which we are thankful.

After getting discharged we were required to stay in the Pittsburgh area until the transplant team decided she was stable enough to return home to North Carolina. Luckily, the Ronald McDonald House there is amazing, and instead of hotel rooms they have small one-bedroom apartments making it possible to live there for an extended period. Plus, it is one of the few Ronald McDonald Houses where it is connected to the hospital, so even when Annabelle was inpatient we were able to easily access their services (homemade meals, laundry, therapy pets, etc.). We stayed in Pittsburgh until late November mainly going to the hospital for weekly labs, therapies, and clinic visits. The team had to keep changing her medications weekly so that her liver numbers and her EBV levels (Epstein-Barr Virus that she acquired from her donor) maintained a healthy balance. Our total stay in Pittsburgh was a little over three months, which we were prepared for since the transplant team told us prior to surgery to expect to stay there anywhere from three to six months depending on the amount of complications.

Since we’ve been home it has been a bumpy road. The transplant team told us that the first winter post-transplant is always very difficult, and they were right! Annabelle has been living in a bubble all winter, but she has still been in and out of the hospital the past few months due to illnesses from her immunosuppression. When we do have to go to the hospital its more for treating the illness caused from her immunosuppression rather than treating her underlying metabolic disorder.
When you get a liver transplant it really is just trading out one disease (PA) for the other (transplant) in hopes that treating the transplant gets easier in time.

Even though the liver transplant brings a whole new set of issues (more frequent bloodwork, more meds, lifelong immunosuppression), we know that Annabelle is more metabolically stable on a day-to-day basis. Even when she does get sick we don’t worry as much about the significant possibility of brain damage because her ammonia levels stay within the normal range or are only slightly elevated. The highest her ammonia has gotten post-transplant has been 98 (from frequent vomiting), and her new normal on a “good day” now averages in the 30’s. It’s also been amazing to see the developmental progress she’s been making post-transplant. She’s so much more alert, and her overall energy level and muscle tone have increased greatly.

Since Annabelle’s transplant we have been able to come off of Carbaglu and Bicitra, but she is still receiving Carnitine (which we were told she’ll be on for the rest of her life). Her feeding skills are still lacking and getting her to eat by mouth is still a struggle. However, she’s getting feeding therapy and making progress, so we are hopeful that she’ll eventually eat enough food by mouth to come off of her formula. Her protein intake can be less restricted now, but since she’s primarily tube fed her metabolic dietitian has been conservative (1.3g/kg) and hasn’t tried to push her protein as long as her amino acids stay within the normal range. The main food advantage post-transplant is that we don’t have to weigh her solid foods now and we just go by the nutrition label. Also, if she throws up we don’t have to immediately pump more formula back in her; now we just let it go unless the vomiting becomes excessive. There’s a lot more wiggle room in her overall stability, and we aren’t “living on the edge” every single day like we were pre-transplant.

We know the decision to transplant your child is a difficult one, and we’re very open to discussing our journey with any families that would like to speak with us. Please feel free to see more about our journey at www.CotaforAnnabelleGM.com where you’ll be able to find our blog posts, as well as, a link to Annabelle’s Facebook Page where you can see photos and videos from our transplant journey.

MIKE, CHARITY, AND ANNABELLE
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We just take one day at a time and enjoy the present because that is just what it is, a present!

as peer mentors, Mike was able to attend academic classes such as college reading, pre-algebra, Myths and Magic, anthropology and history just to name a few, participate in recreational activities, participate in career exploration and was able to acquire skills necessary to enter the world of work. We won’t even mention the emotional and social boost this had on his psyche or the group of friends he made and still talks to.

Was it all “peaches and cream”? Of course not. We had our share of rotten apples to deal with but we, and more importantly Mike, kept at it. He was so determined to make it work. After two years of driving one hour each way, twice a week while working full time and trying not to ignore my husband and other son, we took a look at our long-term goal. Mike had certainly met many short-term goals and now it was time to revise or update our plan. Although we were very proud of Mike for all that he was accomplishing, we had to come up with a more definitive plan. We started looking at the Continuing Education certificate programs offered at Mercer and came upon this popular program designed for the student interested in pursuing a career as a veterinary assistant. Mike was able to successfully complete all modules of the certificate program which included: Introduction to the Veterinary Profession, Nursing Skills-Part I, Nursing Skills-Part II, Laboratory Skills and an 85-hour Clinical Externship.

Was it all “peaches and cream”? Of course not. It was an entire family effort that helped Mike with studying, reading, making enlarged index cards, doing homework, emailing instructors, so on and so forth. His 85-year old nonno (grandfather) played a big role in acting as a tutor/mentor. One year later and 5 attempts at the 100 questions, timed, national certification exam (not to mention tears and sweat), Mike did it, he passed with flying colors. I will never forget the sight of him running out of the exam room, jumping and smiling and crying out “whooo hooo, I did it!” Priceless and worth every mile we drove back and forth, all the crying and all the times it became frustrating.

We are grateful for all the resources, supports and good-hearted people out there who are part of Mike’s life. He has received services from the Commission of the Blind and Visually Impaired since birth. He receives assistance from Division of Developmental Disabilities. He has Medicaid. He receives services from Advancing Opportunities, an agency that provides job coaches/development. Currently Mike is working two days a week for a logistics family owned company and the other two days a week he is doing an internship at a local animal hospital. He attends karate a few times a week and the local YMCA. He enjoys music, going to the movies with his brother, getting together will some friends that he met while in the Vet Program, going on walks and his two dogs. He is enjoying life!

We visit Dr. Charles Venditti and his genetic team once a year. He has recently started seeing new genetic MD in New Jersey that is following some teens with CblC. We still try to organize events to raise monies for Dr. Venditti’s research.

Just last week Mike was invited back to Mercer to present a keynote speech. Every year the New Jersey Department of Education’s Office of Special Education Professional Development sponsor’s this conference featuring accomplished students and young adults with disabilities who have demonstrated exemplary self advocacy and leadership skills. What an honor!

Is it all “peaches and cream”? Of course not. Mike goes on many interviews that are a dead end. Mike social circle is not as large as other young adults his age. Mike is aware that his eyesight cannot be corrected to a normal level. He knows he will never drive and that he takes longer to read something. He is very well aware that he is not being called back from these interviews because of his vision and other challenges. But Mike also knows that he is not giving up. He has come so far and will wait for however long it takes to find the person who will give him a chance. He has the support of family, friends and agencies. He has learned independence, determination and self advocacy. This is a direct quote from Mike: “No matter who tells you different, if you put your mind to something and work hard, you will achieve what you set out to do!” Thanks for letting us update you on Mike’s life.

JOSEPHINE AND ROBERT
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Elaina Rose was born April 23rd, 2017 weighing 6lbs 12oz and had a head full of beautiful brown hair and she was absolutely perfect. Everything was going great; we got discharged to go home on Day 2. Once we were home, and we weren’t even home a full hour, Elaina had a blue spell and we had to quickly call 911 and rush her by ambulance to our local children’s hospital. We were told, at this time, that Elaina had left over amniotic fluid and more than likely this episode would not happen again and a little over 24 hours we were discharged to go home. For the next 4 months, Elaina was not thriving. We had a list of problems: failure to thrive, delays, vomiting, in and out of the hospital, severe GERD/reflux, constipation issues, vocal cord paralysis, hypotonia, and the list goes on and on. I was sick of being told that no one knew why my daughter was so sick, so fragile, so weak and I wanted answers for my sweet girl. I would not settle for that answer!

I pushed and pushed to get answers and finally one specialist finally did a more detailed test, an Organic Acid Screen, and we discovered Elaina had a very high amount of Methylmalonic Acid in her urine and from there the testing took off and we found out our sweet little, Elaina Rose had Methylmalonic Acidemia. My husband and I were freaked out by such a big and complex word and we felt so alone at the time and we felt clueless. At 4 months old, my daughter was so sick, and I was so worried because for 4 months doctors had let this go on in her little body. For the next 7 months, Elaina consulted and currently follows with an awesome geneticist and metabolic nutritionist and since getting the proper medicines, diet, and medical care she needs; she’s a complete different kid; she’s thriving, she’s full of life, she’s full of attitude, and she’s full of sass. Elaina receives: Hydroxocobalamin injections, Levocarnitine, and other medications for her other medical issues. Elaina is also on a dairy and soy free diet. We have undergone numerous genetic tests, but have yet to determine type, they believe she has a very very rare form of MMA. During these past 11 months, Elaina has undergone MRI’s with anesthesia, a g-tube placement, and will eventually need a port. We have more worries ahead such as an upcoming MRI of her brain to look at the grey matter and a follow-up with cardiology because Elaina now has a heart murmur after going into acidosis/crisis so many times. Elaina has also dealt with many admissions/episodes of metabolic acidosis/crisis and with each episode she goes through, I learn about resilience, strength, and hope a little more each time. Watching my sweet, sweet girl being poked and prodded, restrained, waking up from anesthesia, fighting for her life: is an absolute heartache and I wish I could take this disorder from her. But at the same time, I’ve learned how resilient my sweet, Elaina Rose is, and she is a true warrior and I know she will conquer BIG things in her lifetime. I have hope for my daughter and I believe in my daughter! She has more strength than my husband and I combined. She’s my little lioness! We have also adopted a quote as we travel among this unknown journey, “One Day at a Time, One Moment at a Time.” If I can give parents one piece of advice, it’s to say this to yourself numerous times a day! Don’t dwell on the past, don’t think about the what-if’s of the future, live and enjoy the today; today is always a gift. Rare warriors are the absolute strongest!
We all greatly desire new treatments to improve the quality of life for people with organic acidemias. In order for progress to be made, scientists need to better understand how these rare diseases work and identify ways to reduce the build-up of toxic acids that cause so much damage. HemoShear Therapeutics is a biotechnology company that is generating important insights that may lead to new therapies for propionic acidemia (PA), methylmalonic acidemia (MMA) and maple syrup urine disease (MSUD).

**Modeling Human Disease to Discover Therapies:** HemoShear, in collaboration with the Children’s National Rare Disease Institute (CN-RDI), has recreated models of organic acidemias in the laboratory by using tissue from patients who have donated their livers after transplant. The company’s unique technology is able to mimic human diseases to enable their scientists to study errors in the metabolic process and gain deep understanding of the course of diseases.

“To successfully meet the challenge of developing treatments for complex diseases like PA and MMA, we are advancing beyond animal research and static cells in a petri dish,” said Brian Wamhoff, PhD, Head of Innovation at HemoShear. “Our innovative platform combines the power of dynamic human biology and computational science to generate insights that may lead to new therapies to improve the lives of these children.”

Through these insights, HemoShear is now in the early stages of drug discovery – designing and assessing drugs to bypass errors in metabolism and lower the levels of toxic substances that build up throughout the body. They began their drug discovery program in 2016 and are progressing rapidly to identify compounds that may be effective at reducing the symptoms associated with PA, MMA and related diseases.

“HemoShear has already advanced our understanding and treatment of PA, MMA and MSUD,” said Marshall Summar, MD, director of the CN-RDI. “These diseases strike right at basic human metabolic function, leading to a cascade of complications from birth through the entire lifespan. If HemoShear can uncover the fundamental functioning of metabolism that is so important in these diseases, then we will be far down the path toward developing targeted treatments.”

**Steps to the Clinic:** Once HemoShear has identified a promising drug candidate through rigorous assessment with their disease model in the laboratory, followed by additional nonclinical testing, then they may apply for permission to test this compound in clinical trials. Clinical trials assess the safety and effectiveness of drugs in patients who volunteer to be participants at medical research institutions. This process can take a few years as clinical trials with experimental drugs must demonstrate substantial evidence of safety and efficacy before being considered for approval by the FDA for treating patients.

**Meet the Company:** Members of the HemoShear research team will attend our July meeting, where they will lead a workshop on the drug discovery and clinical trial process. This will give our families the opportunity to learn more from them directly and ask questions about their progress.

You can learn more by visiting the company’s website at [www.hemoshear.com](http://www.hemoshear.com).
Contribute to the Future of Metabolic Disease Research

You can play an important role in advancing research to cure metabolic disorders. The Coriell Institute for Medical Research is currently looking for new samples from affected individuals with inherited metabolic disease to add to the NIGMS Human Genetic Cell Repository. Those samples will be available to researchers around the world who are working to advance the diagnosis, treatment and prevention of these disorders. There are two ways to donate – give blood onsite at the 2018 FOD/OAA National Metabolic Conference or have a collection kit sent directly to your doorstep.

If interested, please contact the NIGMS Repository (Julia Keklak at jkeklak@coriell.org / 856-536-3170).

Contact us today to contribute to the medical advancements of tomorrow.
A Novel Message
RNA Therapeutic Approach
for the treatment of methylmalonic and propionic acidemias

MODERNA THERAPEUTICS, CAMBRIDGE, MA

Moderna Therapeutics is a seven-year old company focused exclusively on developing medicines and vaccines using messenger RNA (mRNA). mRNA plays a critical role in human biology, carrying the “blueprint” of proteins from the genetic code contained in DNA. When a person has a genetic condition, the person’s DNA makes certain mRNA with some mistakes in it, and the resulting protein does not work correctly or at all. Moderna is making mRNA to make normal functioning protein as a potential therapy for certain diseases. Unlike gene therapy, mRNA does not insert DNA into the nucleus nor does it make a permanent change to DNA, and mRNA therapy can be dosed in a drug-like way so that individual response may be managed over time. Moderna currently has several ongoing clinical trials to evaluate the safety and efficacy of mRNA as a vaccine and as cancer treatment in people.

Recently, Moderna announced that the company is developing two potential mRNA therapies for MMA and PA: (1) mRNA-3704 is an mRNA therapy to make MUT enzyme in liver as a potential treatment for MMA due to MUT deficiency, and (2) mRNA-3927 is an mRNA therapy to make PCCA and PCCB proteins, which together form the PCC enzyme, in liver as a potential treatment for PA. The evidence that helped advance mRNA-3704 (MUT) was published in the scientific journal Cell Reports, which reported the preclinical efficacy and safety of MUT mRNA therapy in MMA mice. The MMA research was conducted in collaboration with Dr. Charles P. Venditti and his colleagues at the National Human Genome Research Institute, National Institutes of Health (Bethesda, MD) under a Cooperative Research and Development Agreement (CRADA). The company also just announced in March that mRNA-3704 (MUT) has been granted Orphan Drug Designation by the FDA. Moderna is currently working to move both mRNA therapies for MMA and PA into clinical studies as soon as possible, to see if the therapeutic effects observed in mice will be seen in people with MMA or PA.

To support the advancement of these mRNA approaches, Moderna will conduct a global, observational clinical study of MMA mut and PA (MaP study) to better understand these diseases and to help identify what are the most relevant problems (clinical endpoints) that people with MMA mut and PA have to face. Information learned from the MaP study may be used in future treatment trials to see if there is an improvement due to therapy. Additionally, the data from people who participate in MaP may be used as a comparison to data from people who participate in clinical studies that are conducted to evaluate the safety and effectiveness of mRNA medicines.

In the MaP study, your doctor will work with you to collect information at 6-month intervals for up to 3 years, concomitant with your routine check-ups, so that no additional doctor visits or tests outside of routine check-ups are required. Your doctor and his/her staff will enter information into the study so that there is no additional work for participants aside from completing short quality of life questionnaires and providing a small sample of blood at each visit. The blood will be analyzed at a central laboratory to help us better understand disease biomarkers that could be used in future treatment trials. The study will additionally collect information such as frequency of metabolic decompensations and hospitalizations. Moderna is working with multiple sites throughout the US, UK, France, Germany, Italy, Spain and other countries to participate in MaP. If you are interested in participating in the MaP study, please contact Kathy Stagni or ask your doctor. In addition, OAA has recently started an online natural history study which is patient-driven and includes people with all organic acidemias, including MMA and PA. We encourage your participation in their important study as well. The goal of these studies and the NIH studies is to move the field forward in gaining greater understanding of the challenges that people with organic acidemias experience and the impacts on health and quality of life. If you have MMA mut or PA, you can participate in all studies at the same time, if you choose to, in order to maximize your contribution to furthering the understanding of the course of these diseases and their impacts on people.

As a company, we are committed to leverage our unique platform to the benefit of patients with rare genetic diseases, and are inspired by the opportunity to help people with MMA and PA. We recognize and are driven by the urgent need for an effective treatment. We look forward to working with OAA as we move to quickly advance these potential medicines and to engage with and learn from the community in the months and years ahead.
Agenda: **Friday JULY 7**

**FOD OXIDATION DISORDERS GROUP**

7:00 - 8:00 am Hot Breakfast for Conference Registrants – Atrium

8:00- 9:00 am Introductions by Deb & Kathy – Tamarack Ballroom (and then OAA moves to Cedar Ballroom)

**Keynote Speaker** – Piero Rinaldo, MD, Ph.D. [Kids room open – Nokomis Room]

<table>
<thead>
<tr>
<th>Tamarack Room</th>
<th>Cedar Room</th>
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| 9:00 - 9:45 am | D. Holmes Morton, MD  
Central Pennsylvania Clinic, Belleville, PA  
**TOPIC:** TBD |
| 9.45 - 10:30 am | Oleg Shchelochkow, MD: NHGRI/NIH  
Chuck Venditti, MD, PhD: NHGRI/NIH  
**TOPIC:** TBD |
| 10:30 - 10:45 am Break | 10:45 – 11:00 am Break |
| 10:45 - 11:30 am | Susan Berry, MD  
University of Minnesota  
**TOPIC:** TBD |
| 11:00 - 12:00 pm | Kim Chapman, MD, PhD, FACMG  
Children’s National Medical Center  
**TOPIC:** TBD |
| 12:00 - 1:00 pm LUNCH BUFFET for Conference Registrants - Atrium | **Presentation/Award**  
Richard Bazzy, parent  
Parent Introductions |
| 1:30-3:00 – Sibshop – Open to siblings ages 5-18 Room | Jerry Vockley, MD, PhD  
Children’s Hospital of Pittsburg  
**TOPIC:** New therapies for OAs |
| 3:30 - 4:15 pm | Dr. Irini Manoli, NHGRI/NIH  
**TOPIC:** TBD |
| 3:15 - 4:15 pm | Dr. Mark Korson  
**TOPIC:** Mitochondrial Dysfunction in OAs |
| 4:15 - 5:00 pm | Summary and THANK YOU’s |
| 5:00 pm | 6 - 9 pm **RECEPTION** and Cash Bar for Conference Registrants/Speakers/Sponsors– TAMARACK BALLROOM |

**ORGANIC ACIDEMIA ASSOCIATION GROUP**

**Network with specific FODs in groups**

Jerry Vockley, MD, PhD  
Children’s Hospital of Pittsburgh  
**TOPIC:** New Therapies for FAODs

**10:30 - 10:45 am Break**

Susan Berry, MD  
University of Minnesota  
**TOPIC:** TBD

Melanie Gillingham, PhD  
Oregon Health Science University  
**TOPIC:** FOD Nutrition Guidelines

**12:00 - 1:00 pm LUNCH BUFFET for Conference Registrants - Atrium**

**1:30-2:30 pm**

D. Holmes Morton, MD  
Central Pennsylvania Clinic, Belleville, PA  
**TOPIC:** Emergency Protocols/Q&A

**1:30 - 2:30 pm**

Stephen Kahler, MD  
Arkansas Children’s Hospital  
**TOPIC:** TBD

**1:15 – 2:15 pm**

**Presentation/Award**  
Richard Bazzy, parent  
Parent Introductions

Jerry Vockley, MD, PhD  
Children’s Hospital of Pittsburg  
**TOPIC:** New therapies for OAs

Dr. Irini Manoli, NHGRI/NIH  
**TOPIC:** TBD

Dr. Mark Korson  
**TOPIC:** Mitochondrial Dysfunction in OAs

**5:00 pm Summary and THANK YOU’s**

**6 - 9 pm **RECEPTION** and Cash Bar for Conference Registrants/Speakers/Sponsors– TAMARACK BALLROOM**
# Agenda: Saturday JULY 7

## FATTY OXIDATION DISORDERS GROUP

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 - 8:00 am</td>
<td>Hot Breakfast for Conference Registrants – ATRIUM</td>
</tr>
<tr>
<td>8:00 - 8:15 am</td>
<td>Intros by Kathy &amp; Deb in each room - Remember PICS at 9:15am! Kid’s Activity Room - NOKOMIS ROOM</td>
</tr>
</tbody>
</table>
| 8:15 – 9:15 am | Separate Networking for FOD and OAA – each Group meet in your own room.  
FOD—Teen/Adult pane  
OAA – Young Adult Panel  
OAA – “The drug development process for a rare disease.” |
| 9:15 am – 9:30 am | Break & PICTURE OF EACH Individual GROUP WITH YOUR T-SHIRTS!  
Meet by the FOD and OAA wall Banners |
| 9:30 – 10:15 am | Joint Presentation – Susan Berry, MD MHealth/University of Minnesota |
| 10:15 – 11:00 am | Joint Presentation – Dr Christopher Boys. Pediatric Neuropsychologist, University of Minnesota |

## ORGANIC ACIDEDEMIA ASSOCIATION GROUP

<table>
<thead>
<tr>
<th>Time</th>
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<tr>
<td>11:00 – 12 noon</td>
<td>BOX Lunch in Atrium</td>
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<tr>
<td>12:15-1pm</td>
<td>JOINT Presentation – Dr. Mark Korson</td>
</tr>
<tr>
<td>1:00 – 1:45</td>
<td>Joint Presentation – Professional Panel (most of our Speakers)</td>
</tr>
<tr>
<td>1:45-2pm</td>
<td>Ending ceremony and slideshow</td>
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See You in 2020!
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 & 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.
- Names or information will be kept confidential only if specifically requested in writing
- This newsletter does not provide medical advice. You should notify your health care provider before making treatment changes.

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: _______________________________
Address: ______________________________
City State Zip: _________________________
Email: _______________________________

Please make the following changes to my address, phone number, or email address.

OAA Google Group
OAA's main mission is to empower families with knowledge about organic acidemias. If you would like to connect with other families who share the same or similar diagnoses, please join our private OAA Group. Visit the OAAnews.org web site to sign up.

OAA IS ON FACEBOOK - donations can be sent through our “Cause” Page, connection with other parents can be found through our private “OAA Group” and private “Fan” Page.