



# 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](http://www.oaanews.org)**

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

## Organic Acidemia Association

9040 Duluth Street  
Golden Valley, MN 55427

Phone: 763.559.1797

Fax 866.539.4060

[www.oaanews.org](http://www.oaanews.org)

### Kathy Stagni, Executive Director

Propionic Acidemia Parent

9040 Duluth Street  
Golden Valley, MN 55427

Phone: 763.559.1797

[mkstagni@gmail.com](mailto:mkstagni@gmail.com)

### Menta Pitre, Director

MMA Cbl C Parent

207 E. 14th PL

Larose LA 70373

Phone: 985.856.5631

[menta@oaanews.org](mailto:menta@oaanews.org)

### Cay Welch, Director

Glutaric Acidemia, Type 1 Parent

P.O. Box 427

Ridgway, CO 81432

Phone: 970.316.1780

[cswelch1@verizon.net](mailto:cswelch1@verizon.net)

### Jana Monaco, Advocacy Liaison

Isovaleric Acidemia Parent

3175 Ironhorse Dr.

Woodbridge, VA, 22192

Phone: 703.497.1216

[jana.monaco@verizon.net](mailto:jana.monaco@verizon.net)

Stephanie Carleton and Josh McMahon

OAA Natural History Registry

Coordinators



## Our Organic Acidemia Disorders got great visibility on Rare Disease Day!

Josh McMahon, (dad to Leo, MMA Cbl A) and I had the pleasure of taking part in a Rare Disease Program held at the University of Minnesota. We were able to share information about the OAA and our patient advocacy with the local community. I was also honored to represent the OAA in a video testimonial produced by Moderna Therapeutics to raise awareness about their research into improved treatments for MMA and PA disorders. You can find a link to the video on the oaa website at [www.oaanews.org](http://www.oaanews.org).

Another pharmaceutical partner, LogicBio, asked another OAA parent to speak at an event in

Massachusetts. Here's an update from Erin and Charlie MacLean on the LogicBio program.

On February 28, 2019, we celebrated Rare Disease Day at LogicBio in Cambridge, MA. The Logic Bio team is working on gene therapy for MMA. Logic Bio asked OAA if a new England MMA mut0 family would speak too their staff on Rare Disease Day. The goal of the event was to have their entire team have a one on one interaction with an MMA family. We were able to tour their labs and observe how they perform cellular experiments. Prior to our arrival they

**CONTINUED ON PAGE 5**

# In this issue

A new hepatic biomarker in MMA	3	Nikki Elizabeth - Glutaric Acidemia, type 1	12
Memorial: Lara, MMA Mut 0	5	Moriarty - Isovaleric Acidemia	14
LogicBio	6	Metabolic Balancer App	15
Mia & Cadi - Isovaleric Acidemia	7	Research Corner	16
Mason - Methylmalonic Acidemia, Mut 0	8	Ammonia Monitoring	18
Medical Food Coverage Insurance Tips	9	Help Us Teach Physicians about OA's	19

# Medical Advisors

<p>Dr. Olaf Bodamer FACMG Boston Children's Hospital Hunnewell 539, 300 Longwood Ave. Boston, MA 02215</p>	<p>Elaina Jurecki, MS, RD BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949</p>	<p>Mendel Tuchman, MD Professor of Pediatrics, Biochemistry &amp; Molecular Biology Children's National Medical Center 111 Michigan Avenue, NW Washington, DC 20010-2970</p>
<p>Stephen Cederbaum, MD Mental Retardation Research Ctr./NPI 635 Charles E. Young Dr. South Room 347 Los Angeles, CA 90095-7332</p>	<p>Stephen G. Kahler, MD Univ. of Arkansas for Medical Sciences Clinical Genetics Division Slot 512-22 Arkansas Children's Hospital 800 Marshall St. Little Rock, AR 72202-3591</p>	<p>Keiko Ueda, MPH, RD, LDN Clinical Dietitian Specialist Biochemical Diseases (Metabolism) Program British Columbia Children's Hospital 4480 Oak Street, K3-211 Vancouver, BC V6H 3V4 Canada</p>
<p>Kimberly A. Chapman, MD, PhD, FACMG Assistant Professor of Pediatrics Section of Genetics and Metabolism Children's National Medical Center 111 Michigan Avenue, N.W. Washington, D.C. 20010</p>	<p>Mark Korson, MD VMP Genetics, LLC Director of Physician Support Director of Education 5579 Chamblee Dunwoody Road Suite 110 Atlanta, GA 30338</p>	<p>Charles P. Venditti MD, PhD Genetic Disease Research Branch National Human Genome Research Institute National Institutes of Health Bldg 49, Room 4A56A Bethesda, MD 20892-4472</p>
<p>Carla Cuthbert, PhD, FACMG, FCCMG Chief, Newborn Screening and Molecular Biology Branch And the Newborn Screening Quality Assurance Program, Division of Laboratory Sciences, NCEH, Centers for Disease Control and Prevention 4770 Buford Highway, MS-F43 Atlanta, GA 30341</p>	<p>Piero Rinaldo, MD, PhD Biochemical Genetics Laboratory Department of Laboratory Medicine Mayo Clinic 200 First Street SW Rochester, MN 55905</p>	<p>Jerry Vockley, MD, PhD Professor of Human Genetics &amp; Pediatrics Chief of Medical Genetics Children's Hospital of Pittsburgh 3705 Fifth Avenue Pittsburgh, PA 15213</p>



**GET PAID for your opinion & benefit OAA at the same time.**

Patients (14 and older) and Caregivers (family, friends) of any disability, disorder, syndrome, disease or condition are provided an opportunity to voice their opinions through surveys and interviews to improve medical products and services.

Join the community on-line and **earn a Dunkin' Donuts, Starbucks or CVS gift card.** We receive \$5 for each qualified sign up. Refer others and we will benefit each time. Your information is confidential, and your email/name is never shared. You may be invited to participate in surveys from time to time, where you will earn cash.

**Use this link and join today!**

<https://www.goneplatform.com/newdesign/site/rarepatientvoice/panelchoosecountry.php?panelID=a612d4jbc&s1=organicaacidemiaassociation>

# A new hepatic biomarker in MMA: Mice Help Patients

Irini Manoli MD, PhD and Charles P. Venditti MD, PhD

Organic Acid Research Section, National Human Genome Research Institute

National Institutes of Health – Bethesda, MD 20892

[manolii@mail.nih.gov](mailto:manolii@mail.nih.gov) | [venditti@mail.nih.gov](mailto:venditti@mail.nih.gov)

This article provides a basic summary of a paper we recently published entitled “FGF21 underlies a hormetic response to metabolic stress in methylmalonic acidemia.” Our manuscript describes the construction of a new mouse model of MUT MMA, and its use, in combination with patient samples, to identify a previously unrecognized hormonal axis that is massively dysregulated in both the patients and mice. Of special importance, we further describe the use of this hormone, called Fibroblast Growth Factor 21 (FGF21), as a biomarker to measure the efficacy of liver-directed gene therapy in MMA.

Before we discuss the details of our scientific discovery, we would like to express our deepest appreciation and gratitude to all the patients and families who participated in our research at NIH. In our paper, we report the results of FGF21 levels in the blood and studies using liver and kidney samples that were donated by patients at the time of surgery. All these samples were of critical importance to prove that our observations in the mice were occurring in patients with MMA. We have published the information and our paper, including all the graphs, figures, tables, gene expression data, etc are **freely available** to anyone with an internet connection; the citation and links are at the end of this article.

Why do we need more mouse models and what can we learn from them? By the end of this article, we will hope to help you understand the importance of animal models, how they can be used to provide insight into disease processes, and what the ramifications can be for patients. With so many different mouse models of MMA, why do we need another? The first MMA mice we made, so called knock-out mice, were very sick animals, and usually die within the first few days of life. Having such severe and affected mice was indeed useful, and we published a number of very important papers testing gene therapy in these mice. In fact, they remain as the “gold standard” to test the efficacy of new treatments for MMA because the experimental read-out can be answered simply, and usually within a week, by answering the question: do the MMA mice survive after they receive the therapy? Using this approach, we have developed and tested both adenoviral and adeno-associated viral gene therapies for MMA with great success, and have used the neonatal lethal MMA knock out mice to find the lowest dose needed for treatment. Only the most potent treatments can rescue the full knock out mouse. However, the main limitation of the full knock out MMA (and PA) mice is the severity, and need to treat so early in life, which makes extension of the research observations more difficult. As examples, consider that a newborn mouse has the equivalent gestational age of a very premature human baby, perhaps in the 20-25 week of age range, and 9 mouse days = 1 human year.

Our first studies used these very sick MMA mice to answer the question: how effective is correction of the liver to the phenotype (appearance and behavior) seen in MMA mice? To do this, we used transgenesis to create mice that expressed the missing enzyme (MUT) only in the liver. These mice, called ALB MMA, are a rough equivalent of what it might be like if a baby with MMA was born with a liver transplant. As predicted, the ALB MMA mice were very healthy and active, and rescued from the lethal effects of mouse MMA. In parallel, we performed liver directed gene therapy experiments in the MMA knock out mice, and also could show that when a virus brought the MUT gene into the liver immediately after birth, the mice benefited like they did with a liver transgene, and were rescued from death.

We were next faced with a theoretical question: what would be the effect of restoring the missing enzyme in a given cell type, or tissue?

Using an approach akin to what we did to probe liver effects, we made mice that expressed the MUT enzyme in the muscle (skeletal and cardiac) of the MMA knock out mice and explored the effects. We call these mice MCK MMA mice after the promoter used to drive the expression of MUT (MCK).

The first important observation made with these mice relates to survival: the expression of the MUT enzyme in the skeletal muscle rescued the MMA mice from lethality. This was very exciting because it further supported a previous observation that the MUT enzyme was expressed in all cells, and suggests that any cell that is missing the enzyme might be helped if it could make MUT. The other basic and critical observation was that the MCK MMA mice, while they survived, were fragile, growth retarded and had very high levels of methylmalonic acid in the blood. If the mice were stressed, for example, by getting wet in their cages from the water bottles, they died.

And despite being fed a mixture of high fat mouse food, a maple syrup like jelly that mice LOVE, and fruit, the MCK MMA mice do not grow like normal mice, in fact are severely growth retarded and typically only achieve about 50% the weight of the littermates that do not have MMA.

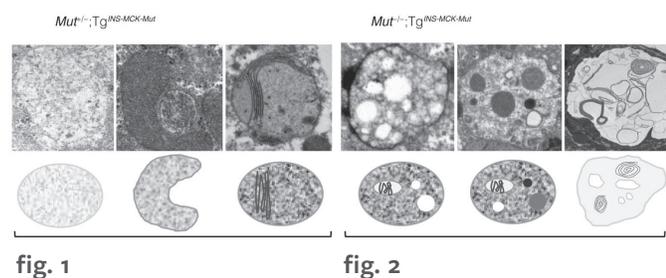
To understand why this was happening, we conducted a number of studies that are described in great detail in the manuscript. In brief, we suspected, and proved, that the MCK MMA mice had a severe mitochondrial dysfunction syndrome of the hepatocyte, the main cell of the liver, and the proximal tubule, similarly, an important cell in the kidney. We were able to characterize the cellular changes in the



CONTINUED ON PAGE 4

liver using electron microscopy, which enables the visualization of mitochondria (normally too small to see with a regular microscope), and make a comparison to the pattern seen in liver samples that were donated from patients. The combination of mouse and human studies enabled us to visually reconstruct the pathway that shows how mitochondria “self-destruct” due to MMA. This is depicted below in the patient samples where the progression begins with an enlarged and pale mitochondrial (fig.1), that then folds in upon itself, and we believe, eventually gets engulfed into a cellular structure called an autophagolysosome (fig.2).

Hepatic ultrastructural changes in  $Mut^{-/-};Tg^{INS-MCK-Mut}$  animals replicate the pathology seen in MMA patients.



Because the MCK MMA mice replicated the classic clinical findings seen in MMA patients, such as severe growth failure, liver mitochondrial dysfunction, chronic renal disease and a very low tolerance to different stressors (fasting, cold, high protein), we used the mice to model a metabolic crisis by exposing them to a fasting challenge. A major source of morbidity, hospital admissions and, in the most severe cases, mortality, are the episodes of metabolic instability and rapid deterioration when patients are stressed and have an accompanying reduced food intake. Control and mutant MCK MMA mice were therefore fasted and then sacrificed, and their livers removed. The livers were then used to profile the expression of all the genes in the genome (~ 20,000 genes) to identify markers that would be candidates to measure in MMA patients to assess the severity of the dysfunction in their hepatic mitochondria. We found many new candidate biomarkers with this genomic approach, and by analyzing the pattern of changes in the genes with our bioinformatics colleagues, discovered that MMA, whether in a mouse or person, causes stress pathways to be chronically activated to adapt (ei hormesis) to the metabolic injury that accompanies the enzyme deficiency.

One hormone, Fgf21 (fibroblast growth factor 21), was extremely elevated in the MCK MMA mice and further studied in patients. FGF21 is an important but only recently recognized hormone that is made by the liver. In patients with MMA, we found that

the levels were highest in the sicker and more severely affected children, but normalize after liver transplant, with changes that were greater than conventional metabolites, such as serum methylmalonic acid levels. It should be noted that serum [MMA] does NOT normalize after liver, kidney or combined liver-kidney transplantation in patients with MMA. To directly test this prediction, we treated the MMA MCK mice with a liver-directed gene therapy vector. This virus, an adeno-associated virus (AAV), was designed to only express the MUT gene in the liver, nowhere else, and was given to the MCK MMA mice at a dose that has been given to other patients (not with MMA) in different studies. We found that after treatment with a single and relatively low dose of our new liver directed AAV gene therapy vector, the MMA MCK mice had marked metabolic improvement, increased weight gain and activity, and showed a drastic reduction in the levels of FGF21 in the blood. Thus, FGF21 represents an ideal biomarker to not only help predict which patient might have more severe liver mitochondrial involvement, but also to monitor the efficacy of new hepatic treatments, such as gene and mRNA therapy, for MMA and related disorders.

Hopefully, we have described how this new mouse model offers a unique platform to study disease mechanisms and test advanced therapies for MMA. As organ transplantation for methylmalonic acidemia becomes more available, and promising genomic therapies move closer to clinical trials, selecting patients who may derive the most benefit from available treatments will become challenging. Additional clinical and laboratory parameters that can indicate the severity of specific organ involvement can help families and their physicians decide between an isolated kidney or liver, as opposed to combined liver-kidney transplant, and perhaps between new experimental treatments. Moreover, monitoring each organ’s positive or adverse reaction to the different therapies will be critical for the success of any new treatment for MMA.

This massive study was conducted over many years at NIH, had over 30 co-authors with aggregate expertise in biochemical genetics, laboratory methods, bioinformatics, gene therapy, statistics and mouse genetics, and is the culmination of our deep collaboration with the patient community, who, with the NIH, has offered continued encouragement of our research efforts. Many of our students who helped with these mice were supported, in part, by the Angels for Alyssa (MMA Research Fund), Cure for Clark, and the Organic Acidemia Association. We would again like to express our appreciation for the amazing dedication of the patients and their families for participation in our clinical research protocol and invite comments and questions by email.

## CITATIONS

Manoli I, Sysol JR, Epping MW, Li L, Wang C, Sloan JL, Pass A, Gagné J, Ktena YP, Li L, Trivedi NS, Ouattara B, Zervas PM, Hoffmann V, Abu-Asab M, Tsokos MG, Kleiner DE, Garone C, Cusmano-Ozog K, Enns GM, Vernon HJ, Andersson HC, Grunewald S, Elkahlon AG, Girard CL, Schnermann J, DiMauro S, Andres-Mateos E, Vandenbergh LH, Chandler RJ, Venditti CP. FGF21 underlies a hormetic response to metabolic stress in methylmalonic acidemia. *JCI Insight*. 2018 3(23). PubMed PMID: 30518688; PubMed Central PMCID: PMC6328030.

<https://insight.jci.org/articles/view/124351>



requested questions from their team. The main questions they had were regarding early diagnosis, treatments (medical formulas), daily living, family struggles, determining when child is becoming ill due to MMA and relationships with physicians/support organizations. We shared the story of our son, Andrew, age 17, MMA mut0 who passed away December 2018. After our presentation we did a question and answer session. We were impressed with the team at LogicBio. They were eager to listen, truly empathetic and very supportive of MMA gene therapy and the OAA organization. Thank you to LogicBio for the wonderful visit and all the hard work to advance gene therapy for MMA.

**Visibility.** It's the key ingredient to get rare diseases such as organic acidemias onto the radar of lawmakers and bio-tech companies, our two greatest allies in managing the lives of our children and moving ever forward toward a cure!

If there is an event in your local area and you would like to help give OAA visibility, let me know. I can send you everything you need to help educate attendees about our disorders and inform them about the parent advocacy and support available from the OAA.

*—Happy Spring, Kathy Stagni*



# Lara

**METHYLMALONIC ACIDEMIA, MUT 0  
NOVEMBER 7, 2000 – APRIL 24, 2018**

Dearest Lara,

We will ever be thankful...

For the love that you conveyed.

For the joy that you portrayed.

And for never being afraid.

For being entertaining.

For enduring without complaining.

For your "in the moment" training.

For shaking burdens from your shoulder.

For never getting older.

For having the courage of a soldier.

For singing out of tune.

For acting like a loon.

For discovering another moon.

For putting up a fight.

For dancing with delight.

For the shining of your light.

For inhabiting your space

And joining the human race

With that smile upon your face.

For overcoming lack.

For always bouncing back

When life would go off track

For closing all the rifts.

For getting lost in lifts.

For being Gods greatest gift.

For the strength that you displayed.

For the beauty you never betrayed.

For calling a spade a spade.

These words try to convey,

In your unique and loving way

You showed us how to seize the day.

For walking the path of the few

And just for being you

Thank you, thank you, thank you!

# Tell us about **LogicBio**



Fred Chereau is the president and CEO of LogicBio Therapeutics, a biotechnology company in Cambridge, Mass., that is advancing an investigational therapy for methylmalonic acidemia (MMA). We sat down with him to talk about his work.

What kind of treatments are you pursuing?

We're developing a new form of genome editing based on a technology called GeneRide <https://www.logicbio.com/generide>. It uses a viral vector to carry into the patient's cells a corrective transgene that's capable of taking over the duties of the mutated gene causing the patient's disease. That part is nothing new - it's a common and well-validated technique used in many gene therapies. What comes next is what makes GeneRide different.

Unlike other gene editing approaches, we don't bring "molecular scissors" into the cell's nucleus to cut the patient's DNA. Nor do we bring in an external promoter to "turn on" the new gene we've just delivered. Those techniques have demonstrated risks, so we avoid them. Instead, we harness the cell's natural repair mechanism, known as homologous recombination. That allows us to insert our transgene in precisely the right spot - next to a powerful promoter that can activate the new gene even as it continues to perform its normal functions.

When the new gene turns on, it begins expressing the proteins that the patient has been lacking. What's more, the new transgene remains integrated in the patient's genome even as his or her cells divide, so the therapy should be durable. That's very important, especially in treating children as you want the therapy to continue to work as they grow.

Our goal with these therapies is to reduce symptoms and forestall progression of the disease. We hope to make a significant difference in patients' lives by treating them early before their disease advances.

## **Have you tested this yet in patients?**

We're moving very methodically through the R&D process. We have demonstrated proof of concept that GeneRide works in multiple animal models. We are now conducting additional studies in preparation for submitting a request to the U.S. Food and Drug Administration to launch clinical trials in patients.

## **Why are you focusing on MMA?**

As readers of this newsletter know all too well, there's a huge unmet need for therapies to help individuals with MMA and other organic acidemias. We have spent time with these families

and have been truly moved by their strength in the face of a disease that has few treatments. (Here, we share <https://www.logicbio.com/patient-focus> the story of one remarkable family living with MMA on our website.)

We also firmly believe that MMA is a disorder that is well-suited to be treated by our GeneRide approach. Early intervention is critical to combat the devastating effects of the disease. Our preclinical research demonstrates that we can safely and precisely deliver corrective transgenes to the liver of newborn mice. By editing the patients' genomes so they begin producing the key enzymes they lack, we hope to be able to prevent or minimize the devastating damage caused during the metabolic crises that are characteristic of MMA.

## **Will all patients with MMA be eligible for your clinical trial, or only certain mutations?**

Each of our therapies will deliver a different corrective transgene. Our first program will target *MUT* MMA and will insert a functional copy of the *MUT* gene into the patient's genome. Therefore, we will only be able to enroll patients with *MUT* mutations in our first trial. If successful, we will be looking at other mutations in future programs.

## **What ages will be eligible for the clinical trial?**

We are still working with the FDA on the specifics of our first trial. In general, our approach is aimed at pediatric patients.

## **What other diseases do you hope to treat?**

We are working now on other diseases that target the liver, including Crigler-Najjar syndrome, alpha-1 antitrypsin deficiency, and hemophilia B. Down the road, we hope to expand into rare genetic diseases that target muscles and the central nervous system.

## **What's your message for patients with organic acidemias?**

We have enormous admiration for the strength and determination of individuals living with organic acidemias and their families - and we have enormous admiration, too, for all the work that OAA does to educate the public and advocate for the community.

We want everyone to know that this is an exciting time in the biotech field, with great strides being made in addressing rare genetic diseases. We believe the new therapeutic approaches being explored by LogicBio and other companies hold real promise. We all feel a great urgency to bring novel treatments to patients, and we're working hard to do just that.



Mia and her sister Cadi celebrating St. David's Day 2019.

# Mia & Cadi

## ISOVALERIC ACIDEMIA

### AGES 7 AND 5

As I sit here writing this article, a wave of emotions overcome me. It is only natural as I look through photos of troubled times when my children suffered a metabolic crisis or were admitted to hospital.

I have two children with Isovaleric Acidemia (IVA). I am eternally grateful to medicine and am lucky to have the close monitoring and care of consultants, doctors and nurses thanks to the National Health Service here in Wales. My story chiefly focuses on my eldest daughter who had a challenging start to life. She is a true hero.

On April 29th, 2011, Prince William married Kate Middleton however, she was not the only Princess to be born on that day! My first daughter, named Mia Gwennlian was born on April 29th, 2011 @8:23am weighing 4lb 51/2 oz. She was premature at 34+3 weeks. All went well with the birth and Mia appeared to be in good health. She

was monitored well in SCBU and was feeding via NG tube on expressed milk. The nurses noticed Mia's complexion change as the days went by, and by day 7, there were concerns of lethargy, a possible urea cycle disorder (which I had never heard of) and consequently, Mia stopped having milk immediately. Then things took a dramatic turn for the worst. Mia suffered seizures and was put in Intensive Care. On the 8th of May 2011, I had an early morning phone call... Mia had deteriorated overnight and I was to come immediately with my family as things were not looking good. Looking back, I don't think I realized the seriousness of the call... too numb to think the absolute worst, I rang my family and we drove straight to Glangwili hospital in Carmarthen, a 30-minute drive from home. Visibly emotional, I just prayed Mia would somehow overcome whatever this urea cycle disorder the Doctor talked about as I just stared at my limp, beautiful baby girl, lying there in the incubator with lines coming out from many places. (As I look through photographs of Mia's first week, only now do I notice her complexion change and she looks unwell).

True to my optimistic nature, I had faith that medicine would help Mia get better and she was taken in ambulance to The University Hospital of Wales, Cardiff, which is just over an hour's drive away. I will always remember the driver and Doctor warning me not to follow the ambulance as in case of emergency, they would have to stop and treat Mia. It was horrifying. But I knew somehow Mia would be fine.

As a healthy 30 year old and first-time mother, I just could not comprehend how this could be happening to my baby girl and to my family! Mia was diagnosed and treated for IVA. Thankfully, each day was an improvement on the last. Mia was reacting well to treatment. Following a total of six weeks in hospital, Mia was discharged and I was finally able to take my baby home. The consultant was unsure of what damage the ammonia (around 800 mark) had caused and to just take each day at a time. Mia suffered developmental delays and did not meet any of her milestones with the Health Visitor as a baby/toddler but she has certainly caught up by now!

Mia had many hospital admissions from birth til 5 years. Now, fingers crossed things are more settled. Any viral infection with vomiting or diarrhoea would impact on her health and we would be back in our second home. The emergency regime really helped and our stay at hospital would be around 48 hours. We all know how emotionally draining and stressful it can be. We were happy when in January, 2015 Wales included Isovaleric Acidemia to the newborn screening panel.



Fast track to 2019... Mia is now approaching her 8th birthday. Where on earth did time go?! She is a happy, sociable young lady who is thriving at her own pace. She enjoys school and is making average progress in National Tests (pffft who cares about them!) In her spare time, Mia attends a performing arts class which she really enjoys. She is the bravest girl I know. The greatest role

“

*It is nice they have one another for support...*

model to her sister, Cadi, who also has IVA (although did not suffer the complications like her sister). It is nice they have one another for support as they grow up and face further challenges with their health.

I do not really know what the future holds. I know my children will give 100% in all aspects of life and I will always protect them from harm. If I am honest, it scares me to the core when I read about the sufferings of children

with organic academia. I am hopeful both girls grow up and lead as much a normal life as they can. I will try to keep them as healthy as possible and carefully keep counting those proteins!



Lastly, as I sit here writing this article, it is a reminder of how brave I am too. I am lucky enough to have a loving and supportive family and friends who are always there for me. With life being so busy, it is hard to find moments to reflect... a big tap on the back to us as parents for all we do in raising our beautiful rare disorder children.



ANGHARAD  
CARMARTHENSHIRE, WALES  
[angharad81@msn.com](mailto:angharad81@msn.com)

# Mason

MMA, MUT 0  
AGE 22



**M**y son Mason has MMA mut 0. He is now 22 years old and is doing so well that I wanted to write another little story for this fantastic newsletter. He did appear some years ago. Just a brief history. Like everyone else's story he was very sick when he was born and had trouble being diagnosed. This common thread is well written about and I try not to remember much of it, but I know that many people are still there. There were not many happy stories 22 years ago. I want to focus on the present as I never thought it would be possible. Mason had a liver transplant at 18 months. His kidneys failed at 7. He had a kidney transplant at 8. His kidney again failed at 18 and he received another transplant at 20. He has had extended periods of great health as he is having now. He is a very happy active outgoing young man who gets the very best out of life. He may also read this so I will remain positive. He has a car, a job and savings that he wants to put towards an investment property. We have been blessed with a health system that does the hard things well and the simple things (talking) terribly. The result is a well boy and a cranky Dad. I have been on many committees to discuss departments sharing information etc. I won't get started. (Positive.) Of course, Mason still has many medications and relatively few doctor's appointments. We are both enjoying his good fortune.

BEST WISHES TO YOU AND YOUR FAMILIES – DAVE, NSW AUSTRALIA  
[davidgordon97@gmail.com](mailto:davidgordon97@gmail.com)

# Medical Food Insurance Coverage Tips

for all types of inherited metabolic diseases and rare genetic disorders in the USA

Raenette Franco

Compassion Works Medical

[raenettef@compassionworksmrs.com](mailto:raenettef@compassionworksmrs.com)

The complexity of the health care system can overwhelm even the savviest patient and/or clinical professional. That is why Compassion Works Medical was created to hold hands with patients and alleviate the clinics time through the difficult process of medical food insurance coverage.

Compassion Works Medical is founded by Raenette Franco, CEO and Certified Billing and Insurance Specialist. Raenette has been inspired to share her hands-on experience with medical foods insurance coverage specialized in all types of inherited metabolic diseases and rare genetic disorders. Compassion Works Medical works with you and for you, providing guidance and supporting you with compassion and integrity. Ms. Franco specializes only in medical food coverage and has been battling insurance coverage for medical foods for over a few years in addition to fighting for the Medical Nutrition Equity Act on Washington's DC Capitol Hill. Compassion Works Medical collaborates with patients' current insurance policies, and fights for state mandated coverage.

Every case is unique and different. Understanding your options and insurance terminology is essential to obtaining the coverage that you deserve!

## LET'S START WITH THE BASICS:

*What is a Medical Food?* You may hear these words often and could be confusing to the words "formula" or "dietary supplements".

■ **MEDICAL FOODS** are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who requires use of the product as a major component of a disease or condition's specific dietary management (i.e. designed for a certain disease) and intended to be used under medical supervision.

■ **FORMULA** is basically the same thing as a medical food as they are made from the building blocks of foods.

■ **DIETARY SUPPLEMENTS** are not generally designed for a certain disease, but are used in contribution to maintain a disease such as added vitamins. Dietary supplements are sometimes added to patient's dietary management.

*What is Enteral?* Enteral is a medical term used for a feeding method either oral or tube feeding; Hence Enteral formula.

## Overall Medical foods, dietary supplements and enteral formula are common words uses for insurance coverage.

**Coverage for medical foods and dietary supplements** are generally covered under medical benefits and supplied by a durable medical equipment (DME) distributor by using the description of coverage. However, medical foods are also covered under pharmacy benefits by product only, just a little tougher to maneuver insurance coverage.

**Coverage for special injectable vitamins:** Are you or your family member on injection vitamins such as cyanocobalamin/hydroxocobalamin ML (B-12)? If yes, coverage for this special vitamin could be challenging. This special injectable vitamin may or may not be covered under pharmacy benefits. Some pharmacy benefits does not cover these products and considered over the counter. To obtain coverage, it requires jumping through loop holes. However, the health insurance benefits for cyanocobalamin/hydroxocobalamin ML could be covered under your medical benefits. Since the skin is pinched or broken such as with an injection and the place of service is at your clinic. If your clinic could administer the vitamin and bill your insurance company, it would be the best affordable route.

The insurance language under medical benefits for Hydroxocobalamin ML use HCPCS code J3420 and for Pharmacy benefits it is under an NDC number (i.e. 00591-2888-30). The place of service is at the office – Usually injected at the physician's office under medical benefits.

CONTINUED TO PAGE 10

# Insurance coverage tips

To start investigating coverage for your dietary management, it is recommended to start with your medical benefits first. Sometimes when we get a prescription we automatically think it's a pharmacy benefit and that's natural, however, if you have a prescription for medical foods or dietary supplements it's best to check with your medical benefits first.

Below are eight tips below to better understand your medical food and dietary supplement insurance coverage:

## **RULE NO. 1: NEVER TAKE NO FOR AN ANSWER!**

- 1. Insurance Terminology**
- 2. Difference between Medical and Pharmacy coverage**
- 3. Reimbursement issues between insurance company and supplier**
- 4. Verifying Insurance Benefits before placing an order**
- 5. Medical Food Exclusion Removal**
- 6. Gap Exceptions for policies with no out-of-network benefits**
- 7. Be prepared for a prior authorization before covered services**
- 8. Got Medicare or Medicaid? Best Avenue for medical food coverage.**

It's important to understand your health plan's guidelines for medical food coverage by thoroughly reading through your health plans summary of benefits to find out if your medical foods and dietary supplements are covered. Start by looking under durable medical equipment benefits (DME) and non-covered services including exclusions. Key words: ENTERAL, MEDICAL FOODS, NUTRITION, FORMULA, SUPPLEMENTS.

### **1. Insurance Terminology:**

Medical food and dietary supplements coverage is a complete foreign language to the health insurance industry. There are certain terminologies used to help obtain the most accurate coverage details with your health plan's benefit specialist such as:

- Service codes (also known as HCPCS codes) used to describe the medical foods, enteral formula, dietary supplements and vitamins (i.e. B4155, B4157, B4162, B9998, S9435, S9435, J3420). These codes could be administered orally, tube feeding or vitamin injection. Injections are usually done at the clinic and not at home for proper coverage.
- In-network and out-of-network to help determine the most affordable way to obtain your dietary needs. Also known as participating or non-participating.
- Know the difference between prior authorization and predetermination. Prior authorization is required before coverage and predetermination is not required before coverage, but helps avoid any future denials.
- Diagnosis driven plan: This is a plan that will only cover if the diagnosis code such as your medical condition(s) matches the description of service. Your diagnosis codes starts with a letter (i.e. ICD-10: E71.121). If it matches then you are covered. Diagnosis driven plans are easily mistaken as not covered, so if your benefit specialist mentions that it's not covered ask if your plan is diagnosis driven.
- Other words are exclusions, out-of-pocket, state mandated plans, deductibles, fully insured, self-funded, allowed amounts, suppliers, gap exceptions.

### **2. Difference between Medical and Pharmacy coverage:**

Typically medical foods and dietary supplements are generally covered under your medical benefits and provided by a DME distributor. The medical benefits cover by using the service codes and the diagnosis code. Pharmacy benefits cover by the product alone and not the service. Medical foods and dietary supplements could be challenging for coverage under pharmacy benefits, if the product is not listed in their system and considered over the counter it's not covered. If you pharmacy plan does not cover your product, then use you medical benefits or file for an appeal.

### **3. Reimbursement-Billing issues between insurance company and supplier:**

Receiving bills from your providers could be scary. Don't panic! First make-sure you if you've received a bill from your provider or is it an Explanation of Benefits- EOB statement (not a bill) from your insurance company. Check your EOB and match it with your invoice to determine if the bill is for your deductible or co-insurance. If not, contact your provider immediately and go over your invoices. Look out for any unnecessary charges.

### **4. Verifying Insurance Benefits before placing an order:**

The best way to avoid delays with your medical food orders are to try to verify your benefits and coverage "first" with your insurance carrier before placing an order. Contact your insurance carrier and ask for benefit coverage for Medical Food/ Enteral Formula or nutritional supplements. Include diagnosis code (ICD-10). Mention it's "usually covered under DME". Remember to ask if the plan is diagnosis driven to avoid any misunderstandings.

## 5. Ask for any exclusion on your policy for medical foods:

If there are any exclusions that does not cover your medical foods, it is not the insurance company that you would fight with. This is out of their hands. You will have to go to your employers HR department and ask for a medical food exclusion removal and present your letter of medical necessity explaining your rare genetic disease. Medical food removal template letters can be found at Compassion Works Medical. To make a request, email [raenettef@compassionworksmrs.com](mailto:raenettef@compassionworksmrs.com).

## 6. What is a Gap Exception?

A coverage gap exception is a waiver from a healthcare insurance company that allows a customer to receive medical services from an out of network provider at an in network rate. Usually HMO or EPO plans do not have out-of-network benefits, but if you can't find an in-network provider to supply your medical foods, you could ask your insurance carrier for a gap exception. Also, your out-of-network supplier could request a Gap exception to your insurance company directly. This way is easier!

- One of the best reasons for your waiver is that there aren't any other in-network providers within 100 miles of your residence that can supply your medical foods. Another is that you prefer to use the out-of-network provider because of a strong long-lasting and trusting previous relationship.
- Any request is worth a shot! This also saves time for your out-of-network supplier as well as providing faster medical food service.

## 7. Be prepared for a prior authorization that is required by your insurance carrier:

some policies require prior authorizations from your insurance company before they will cover. Prior authorizations need to be identified as "medical necessary". This is usually provided by your clinic or medical food supplier. Make sure your clinic provides you a letter of medical necessity (LMN) with a prescription and recent progress notes (A.K.A. clinical notes). Your provider usually makes these requests.

- Stay on top of your prior authorization approvals. When they expire, you or your provider will have to request a renewal. This depends on your policy; i.e. month to month, every 3 months, yearly, etc.

## 8. Do you have a government plan such as Medicaid or Medicare?

As most of you already know, Medicaid usually follows all of the state mandated laws and covers 100% for in-network providers and may require a prior authorization. Medicare straight from your state does not cover medical foods "UNLESS fed by a feeding tube and is the sole source of nutrition".

- Want Medicare Coverage?: If you have already have Medicare you can switch to a Managed Medicare Plan in your state such as AARP, UHC, BCBS, Humana, etc. and they could provide your medical food coverage. You may not have to pay any extra premiums. Many patients are able to be covered through their managed Medicare plans. This is NOT a Supplement Plan; it is a Managed plan that has leniency

for medical food coverage. Supplement plans only follow the Medicare straight state plans. Supplement plans will have the word "supplement" on your card or "Complete". Make sure that your plan

is not a supplement as they follow Medicare guidelines. To find a managed Medicare plan in your state by visiting <https://www.medicare.gov/find-a-plan/questions/home.aspx>. Or simply call member services listed on the back of your Medicare card for assistance.

### An extra bonus tip:

From my experience if you are looking for a reliable dietary supplement, medical food and vitamin supplier for all types of rare genetic disorders, I suggest checking out: **Solace Nutrition, LLC**

<https://www.solacenutrition.com>. They are very unique and provide most dietary supplements that you cannot find anywhere else. Ask your provider to search their website for the most appropriate supplement that could help you and your family member's dietary management. Also, most of their products are covered by some insurance companies.

In addition, if you or a family member has an inborn error of metabolism disease such as PKU, TYR, HCU MSUD, I suggest checking out this unique European company: **POA Pharma North America** <http://www.poapharma.com/en>. Their products are also very distinctive comparing to other markets in the USA. Also, most of their products are covered by some insurance companies.

I have experienced success with patients affording products from Solace Nutrition, LLC and POA Pharma North America.

**The tips above are based on actual experiences. I believe there are no true experts with all of the answers.**

So let's face the facts, patients NEED an Advocate, preferably someone with a medical food-insurance background. Patients need champions who can:

**1-TRANSLATE** what's being told

**2-ASK THE RIGHT QUESTIONS** that patients 'don't know to ask'

**3-COMMUNICATE** upwards, downwards and sideways.

For support and questions on medical food insurance coverage for all types of Inherited Metabolic Diseases and rare genetic diseases, please contact:

**Compassion Works Medical**

(973) 832-4736

[raenettef@compassionworksmrs.com](mailto:raenettef@compassionworksmrs.com)



# Nikki Elizabeth

**GLUTARIC ACIDEMIA, TYPE 1**  
**AGE 21**

**H**i, my name is Nikki. I am 21 years old and live in Bethlehem, Pennsylvania. Most of you probably have heard my story, but if you haven't, I will give a brief summary. I was welcomed into this world on June 2, 1997. A few hours after I was born, I was given the O.K. by the doctors to go home. In the next few days, I was living the life of a normal baby. But on day 13, my family was hit with paralyzing news. On June 15th, 1997, my parents got a phone call stating that the Newborn Screening test results had shown that I was diagnosed with a life threatening illness called Glutaric Acidemia Type 1. After being taken to a local pediatrician and discovering that they knew nothing about the disorder, my parents and I were redirected to Dr. Holmes Morton. That evening, my mom and I made the trip to Lancaster, and by night, I was admitted for some tests and MRIs. The next few months consisted of medication schedules and monthly follow-ups. During the first few months of my life, I was hitting every developmental milestone on time. On my 15th visit, everyone was feeling hopeful and starting to believe that they were out of the woods. But on October 18th, 1998, I fell off the back of a rocking horse and was rendered unconscious. A CAT scan was performed, and after it displayed a subdural bleed, my

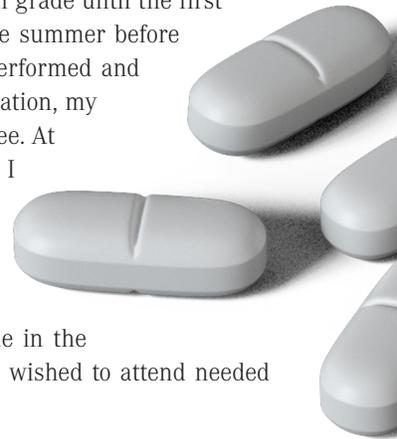
mom and I were taken by helicopter to Lancaster General. During the six days in the hospital, I spiked fevers, went paralyzed on the right side, and apparently screamed uncontrollably. Hours after, I regained movement of my right side, but my fever persisted. After many hours on the phone, Dr. Morton suggested Decadron. Within 24 hours, I was fever free and returned home with a smile on my face.

I don't recall ever being sick. Everything I just stated above I learned from my parents. I don't remember the fall, the tedious food charts, and I definitely do not remember the helicopter ride. Everything I remember about my childhood was normal. I got to take part in everything my sister and friends were doing. I got to decide what to eat, I ran around on the playground, and except for reading comprehension problems, I was able to learn alongside of my classmates in school.

From the time I could remember to seventh grade, medically, I was fine. My GA1 never restricted me from taking part in anything. But when eighth grade hit, painful headaches, which are common in GA1 patients, started. I had headaches most days. They weren't unbearable, but they were painful enough that they caused concentration issues in school. These headaches went from eighth grade until the first part of freshman year of high school. The summer before high school started, I had a spinal tap performed and then was put on Diamox. With this medication, my headaches resolved and I was headache free. At this time, I was relieved and happy that I could once again focus on school. From 9th-12th grade, I was lucky enough to attend the Lehigh Valley Charter High School for Performing Arts where I studied vocals, and played alto saxophone in the band. For this school, every student who wished to attend needed to audition.

For the next two years of high school, I was headache free. But on the third day of senior year, the headaches returned worse than ever. It was third period and I was in my Vocal Techniques class doing warmups. All of a sudden, it felt like I was shot in the right temple. I stopped singing and just stood there in pain. The rest of the day, I got progressively worse. By sixth period, I was resting my head on my desk because I was in so much pain. Never has a day gone so slow. By the time the school day was over, I felt like I could barely stand. I walked in my house and automatically burst into tears because of how bad the pain was.

From that day on, the headaches continued to worsen. To try and relieve the headaches, I started with Over-the-Counter (OTC) medications like Tylenol, Advil, and Excedrin Migraine. Tylenol and Advil didn't do anything. Excedrin Migraine sort of helped my head but it made me really nauseous. After the OTC medications failed to work, we attended appointment after appointment. I saw my family doctor, eye doctor, massage therapist, cranial sacral therapist, and neurologist. Every appointment ended with them saying that they had no idea what was causing the headaches. I try to be a positive person, but during this time, it was hard to stay hopeful. One year and eight months, I lived with a headache that never went away. I went to sleep with it and I woke up with it. I lost any desire for a social life and was basically living life feeling like a ghost. I feel like I was just existing instead of living. I was constantly in agonizing pain, and my constant goal was to just



make it through the day. During this time, I stopped reading, knitting, and basically anything else that required a lot of concentration. By the time I'd get home, I'd be exhausted and in so much pain. Every day I was taking three Aleve to help take the edge off, but they never fully resolved the pain. Even during this time, I went to school, attended play rehearsals, and worked as an administrative assistant at a modeling and acting agency.

More months passed where more ideas were tried and more tests were done, but still there was no relief in sight. Our last resort was to go see Dr. Li, a neurosurgeon, at Lehigh Valley Cedar Crest. In the first appointment, I wasn't too hopeful. He looked at my MRI charts and told me that he did not see anything that seemed worth operating on. Since I was born, I have had two arachnoid cysts on either side of my brain. But they were never thought of as harmful. The first tip from him was to combine Tylenol and Aleve. Then he told me that he would see me in a few weeks.

Leaving the hospital, I was devastated. I really was hoping that he would know what to do. In the next few weeks, I did as he asked. But as you can probably guess, it did nothing. We went back for our follow-up visit, and I told him that there had been no relief. And by this point in my life, on a scale from 1-10, my headaches were usually ranging from a 7-9. In this appointment, he looked at my charts again, and said that he would perform cyst fenestration surgery, but there were no guarantees that this would be the cure. He sat down and explained in great detail how the surgery was going to go. With where the cyst was, he said that he'd be able to go in through my right eyebrow to drain the cyst. By this point in my life, I was desperate and just wanted relief. After going home and talking it through, I made the decision to go through with the surgery.

On May 19, 2016, I was admitted to the hospital to undergo brain surgery. I remember going in feeling super hopeful, even though Dr. Li told me that this might all be for nothing. Still, I remained hopeful and smiled the whole way to the operation room. The surgery took longer than expected due to the consistency of the cyst. Dr. Li was expecting the cyst to be like a balloon. He thought that once he reached it, it would pop causing some of the pieces to not be collected. But instead, the cyst was a gooey consistency, meaning it took longer than expected to retract all of it. After the surgery, Dr. Li explained to my parents that the cyst was the size of a golf ball and it was actually wrapped around my 3rd cranial nerve, something that was not seen on the MRI. After I woke up from surgery, I was extremely nauseous. The doctors were giving me fluids because I couldn't keep anything down. I remember the whole stay being so uncomfortable. I had all these lines in me, I couldn't see out of my right eye, I was nauseous, and I was so exhausted. Throughout the day and night, doctors were coming in and trying to pry my eye open and talk to me. The night spent in the hospital was anything but relaxing, but I wouldn't change anything about what happened. Thanks to the surgery, I am now living headache free. Although

I will admit I still get the occasional headache, but it usually results from not eating enough or not drinking enough water.

It's been almost three years since my surgery, and I can honestly say I am living my happiest life. Two years ago, I earned my associates degree after studying communications at Northampton Community College. Now out of school, I work as a part time stylist at David's Bridal in Whitehall. From the time I started until now, I have remained their top seller and have achieved Circle of Excellence two years in a row. For those of you wondering, Circle of Excellence is awarded to those who manage to sell \$200,000 in a year. Along with being a stylist, I am also pursuing my dream of becoming an actor. Lately, I've been making frequent trips into NYC for various roles on TV shows. **FUN FACT:** I can actually be spotted in season 3, episode 4 of BULL on CBS.

There's not a day that goes by without realizing how lucky I am. I hear about my childhood and can't help but feel grateful. I don't know where I would be without my parents' love and commitment. Hearing about the daily routines, charts, medications, and constant trips to Lancaster makes me have so much respect for all the parents out there who are making sure that their kids have the happiest and healthiest lives. I also thank Dr. Morton for saving me more than once. If it wasn't for him, I can guarantee my life would be very different from what it is now. Knowing about my past now gives me such respect and admiration for everyone who worked tirelessly to allow me to be the person I am today.

Over the years, I have been thrown many obstacles, but I never let them get me down. My entire life I've had a positive, optimistic attitude. I see the good in every day and let nothing stop me from achieving my dreams. I strongly believe that's how I was able to make it through some of the toughest times in my life. I never gave up and I always believed that something good was going to come of every situation, even if it didn't seem that way at first.



*I want nothing more  
in my life than to  
give you all hope.*

For those who have read my story or are just reading my story now, I want nothing more in my life than to give you all hope. Over the years, people have shared their stories with me and my family speaking of how I am the reason their child is alive. People from all around the world have told me that my story gave them hope and have also said that because of my story, they found the Clinic for Special Children. Let me just say, I am so humbled and honored. I can't help but get teary eyed every time I hear that my story made an impact on someone. To everyone that has followed my story over the years, again, I just want to say thank you.

NIKKI  
BETHLEHEM, PENNSYLVANIA  
[83hrichakn@gmail.com](mailto:83hrichakn@gmail.com)



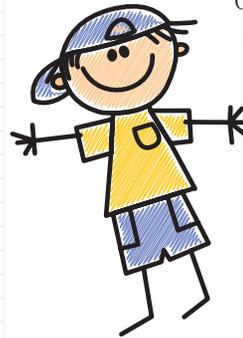
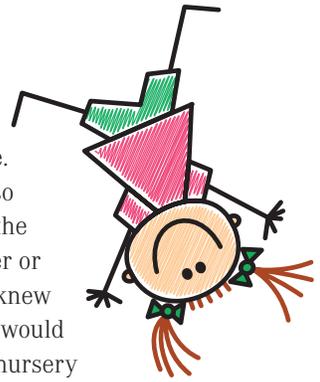
# Moriarty

## ISOVALERIC ACIDEMIA

AGE 2

Moriarty was born to what we thought to be healthy, despite her dad asking about a weird smell that I dismissed as him being crazy because to me she smelled like a typical baby. Two days in the hospital and we were getting ready to go home when her dad again mentioned something he thought was weird to the nurse, holding our discharge paperwork. Moriarty had been in a billiblanet pretty much 12 hours after she was born so we did see much of her other than her face, but while changing her diaper he noticed she was breathing weird. The nurse being absolutely amazing decided it would be best to put off discharging her for the slight difference in breathing and have her checked out at the nursery. Within a few minutes she came back to let us know that Mo would be staying a few more days and they would let us know what was going on with her. I did end up using the last day my insurance would pay for to stay at the hospital with her, only to be told the next morning that they had run every test they could

think of and nothing was coming back positive. I've never been so fearful of losing something so perfect, I sat in the nursery with her as long as the nurses would let me. I was not allowed to touch her or sit to close as they weren't feeding her until they knew something and every time she knew I was close would start screaming, causing a chain reaction in the nursery and disrupting all the other babies. On day 4 I finally left the hospital to take a shower and get non hospital food, I was gone for 10 minutes when the doctor called and I thought I lost my baby. It was much better news than anticipated, but not very insightful. He said that a doctor called from Phoenix Children's Hospital and told him Moriarty needed to be transported as soon as possible and I was needed to sign the release, though the birthing hospital doctor did not get a reason as to why she was being requested at another hospital. I was terrified to watch my baby go in an ambulance to a hospital 45 minutes away, but knew it was necessary to keep her alive.



Once at PCH everything was different, the most amazing doctor waited for us to get to the NICU and very calmly told us our daughter has Isovaleric acid CoA dehydrogenase deficiency. To which my sleep deprived brain took as an insult, but was quickly corrected. I had never been so relieved to hear someone explain such, what at the time seemed, a complicated thing my child would be living with. The doctor explained that she would be fine and she would be starting a special formula as soon as the mixing people could get it ready. Finally after

four days of being terrified and not being able to touch my daughter I got to hold and feed her. It was later explained that Mo had pretty much gone straight into a metabolic crisis and when the Doctor initially called to have her transported he was not sure what state he was getting her in. After about 3½ weeks we got the good news that she was perfectly fine and we shouldn't worry about any adverse effects from her initial crisis. Completely terrified that we would screw something up at home, we took our little Mo to the clinic and called pretty much any time she so much as hiccupped. After about three months and getting into the routine of formulas, medicines and figuring out her personality, we realized it would be much easier to care for her than we thought. We didn't have anything out of the ordinary of keeping up with Mo until her sister went to school and brought home a stomach virus, which landed Mo in the hospital when she was about a year old.

Now at 2½ she has only had two other hospitalizations, one at 2 for not having her formula for a week and one on January 2nd of 2019 for a weird random vomiting episode in the middle of the night. So far Moriarty has been a normal child, aside from being extremely smart. She potty trained herself before she was 2 and is currently working on her alphabet after mastering 4 colors. Mo does have a hatred of meat, she has tried most kinds and did have little stint where she liked the Bar S bun length hot dogs, but that passed pretty quickly. She now has a new Metabolic specialist after seeing the same one for the last two years. She seems to like



him a bit more and only cried once during her first check with him. Currently she has 14 grams of protein from food followed with her 2mls of Levocarnitine, the generic Carnitor three times a day with 350 milligrams of Glycine twice a day and does amazing with it. We had a very long three month fight when trying to switch from IVA Anamix Early Years to the Next and even tried Isovactin to no avail. She went about a month with no formula at all and one day all she wanted was her Early Years milk. She very happily drinks about 16 ounces a day and calls it her milk while shunning regular milk.

Aside from her very strong will power and attitude she is a very happy girl and shown us that caring for her is no different from caring for our older daughter who is unaffected. The hardest thing to deal with is when Mo does get sick and needs the extra attention our older daughter feels left out and lashes out after she knows her sister is okay. Mo's sister did have a hard time when she was born and felt like she was unloved because of the time I spent at the hospital and is still showing those signs of feeling unloved. She is 7 and only somewhat understands why Mo needs more attention but fully understands why she cannot have protein. She is a big help when other people are around and try to give things to Mo and acts as a body guard against all people/food that is being brought to Mo and they have a great bond, just need to work on balancing our time after giving the extra attention to Moriarty. I did not know until recently how different our experience with the diagnosis of IVA was from others, I thought it was normal for any OA kid to be diagnosed in the hospital until we spoke with the new Doctor. I feel like dealing with a crisis before the diagnosis is the biggest challenge we could have faced and it will make anything else we have to go through that much easier when it comes to IVA related illnesses with Mo.



KAITLYN  
PHOENIX, ARIZONA  
[kaitlyn.winn23@yahoo.com](mailto:kaitlyn.winn23@yahoo.com)

A **NEW** Metabolic Balancer App to replace the DietWell App to help people living with Metabolic disorders to feel balanced, feel better with key functionality to create recipes, track phe and protein intake, share information with friends and learn about Cambrooke products and much more. In addition to all the features and user interface enhancements, with this new release we have rearranged recipes, meals ingredients, food items and their classification to make the new app more relevant, efficient and organized.

**Metabolic Balancer** – is designed to assist in the dietary management of Phenylketonuria (PKU) and other inborn errors of protein metabolism where tracking exact protein is essential in the management of a specific metabolic disorder. This iPhone app guides you through your meals, snacks, and formula intake by offering phenylalanine (phe), dietary protein, formula protein equivalent (P.E.), and calorie information for over 7500 food items, specially manufactured low protein food products, metabolic formula products, Cambrooke recipes and meals, along with your Kuvan® intake, blood levels and wellness - all at the touch of your fingertips.

## Use Metabolic Balancer to:

### 1. Improve dietary compliance-learn about the phe content of your food in order to make better choices.

Metabolic Balancer provides a quick reference to more than 7500 food items. Know what each portion or recipe actually contains. Know when you need to adjust your dietary phe intake. Save your favorite foods to Favorites or add new items, recipes and meals.

### 2. Prepare diet log and export it via email in preparation for clinic visit.

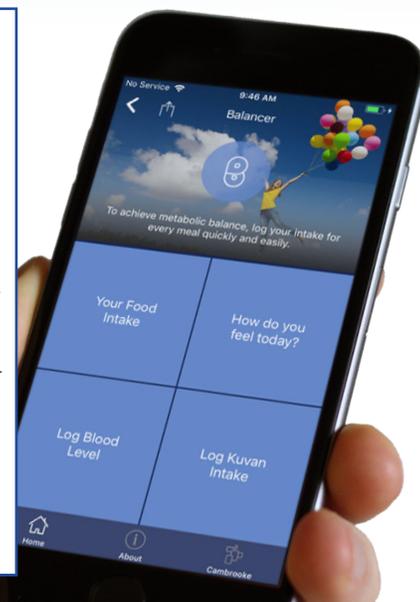
You can now easily record your dietary protein, supplemental protein, and Kuvan® intake along with your blood levels and wellness using this handy iPhone app. Many U.S. metabolic clinics recommend 3-5 days of dietary records before the clinic visit.

### 3. Plot data overtime.

Metabolic Balancer app can help you better understand how dietary compliance correlates to your overall feeling “wellness”.

#### METABOLIC BALANCER FEATURES:

- Over 7500 USDA and manufacturers' product data. Includes data on many specialty low protein food items and formula.
- Log data for multiple users.
- Easy search.
- Save your frequently used food items or recipes to Favorites.
- Add new food items, recipes or meals.
- Share custom items, recipes & meals with friends.
- Track of your Kuvan® intake, blood levels and daily wellness.
- Monitor your daily goals with the graphing feature.
- Review, edit, and export to email (by date range) daily log entries by user.
- Enter quantities in three convenient units: gram, ounce, or serving size.
- All data is contained within the app. No Wi-Fi connection is needed except when downloading updates or exporting logs via email.



# Natural Histories and Registries: the good, the bad and the oiy.

Kimberly A Chapman, MD, PhD

Children's National Rare Disease Institute, Washington D.C.

[kchapman@childrensnational.org](mailto:kchapman@childrensnational.org)

**S**o you are thinking in enrolling yourself or your care into a research study, thank you for helping us understand your family's disorder. We are going to start a new section to the newsletter to talk about research.

Let's start with what research is. It is a system or process in which the goal is to better understand something in the world around us. We divide research into clinical (that which affects the patient directly) and basic (that which studies fundamental processes, e.g. studying the Krebs cycle or how cells talk to each other). Today we are going to talk about a subset of clinical research. As part of this discussion, we are going to examine the expected benefits and risks from this subset of clinical research—observational studies.

The two big, most basic categories of clinical research, basically research that which is designed to understand the natural course of a disorder (observational) and that which tries to impact that natural course (interventional). Sometimes, the research protocol tries to do both, especially if little is known about a particular disorder or if a disorder is generally lethal to almost all with the disorder.

So from this point forward, we are going to ignore issues of interventional studies—these are clinical trials in which an intervention, like a medication or a device is tested to see if it works better than current practice and address these at a future date, and focus on observational studies.

Observation studies have several flavors, the shallow, the medium and the deep evaluations. In general, observational studies collect information about an individual (like an individual with an organic acidemia and their family). They can collect information at one particular time in many individuals or can follow an individual or cohort of individuals over time. The best designed studies to gather natural history—what happens in the disorder with current interventions over time—follows individuals through time, but these can take a long time so some studies are designed to look at many individuals who are at different points in their disorder at one moment in time and makes assumptions about impact of time on the disorders. Either of these studies can be shallow, medium or deep in terms of how much information they gather.

A study which is designed to take a shallow look at a disorder looks for the most basic facts (i.e. disorder, genotype, current health) and often is fairly short in length (and so can take less time to complete the initial forms). This can gather information once or over time from the same individuals. The benefit from this study is that it can provide a “google earth” view of the disorder and takes little time from each participant to gather the information (like minutes). The problem is it is a shallow look at the disorder and so rare complications or occurrences are unlikely to be identified.

A study which is more in depth (a deep information study) tries to examine every possible thing about a disorder and collects a lot of data on each participant often over the course of days. Often times this type of study also gathers biological specimens (i.e. laboratory, biopsy, etc.) and radiological data (i.e. X-ray, MRIs, etc.). Dr. Venditti's natural history studies (for



MMA and PA) at NIH are an example of this type of study. Again individual participants can be studied over time (like Dr. Venditti's studies) or deeply once. This is like getting a magnifying glass out on a walk through the neighborhood and studying as much as possible as closely as possible. You learn lots about lots of things but it takes lots of time and produces much data. The benefits with these studies is rare occurrences or small changes are more likely to be identified. The disadvantage is it takes lots of time from the participant and is very expensive for the researcher.

The type of study which sits between these two in the continuum of studies is the medium study. It is like the view one has walking down the street in one's neighborhood, some detail (the designs on the houses), but not lots of specifics (no idea how many ants on the sidewalk). Our natural history registry with NORD is an example of this type of study. It does not gather as much information as the deep study, but more than a shallow study. It tries to gather enough information that common rare occurrences can be identified, but has less time commitment (more measured in an hours).

Each of these observation studies have some risks. Consent to participate in research of this type should include a list of the risks identified and possible mitigations for these risk.

Privacy and confidentiality are two of the biggest risks with observational studies. Those observational studies which include laboratory and radiology as a component also have risk associated with these procedures.

Some common privacy risks in these types of studies include 1) how safe are my data and will someone outside the study be able to see them and identify that it belongs to me, 2) can I be identified by my data and how are my data being protected? Data here can mean your name, your address, connecting the disorder to you, your health history, your date of birth, etc. You can understand why these privacy issues could be concerning and why you as a participant (or your care) should be aware of this risk.

Most reputable registries and natural history studies tell you how and where your information is stored and protected as part of the consent. They are aware of the concern. In fact, the European Union has just required much more strict privacy rules for any registry or natural history study which has anyone who is lives in the EU or storage in the EU (it is called the General Data Protection Regulations, if you want to look at them).



Despite the risks which can be associated with observational research, there is much that has and to be learned by these studies. None of this discussion is to dissuade you from participating, it is merely to help you make an informed choice.

As a research scientist who takes care of patients, I **NEED** you to help us take better care of individuals with Organic Acidemias. As you know, many fundamental questions about these disorders still exist. We do not know the natural history of these disorders well. We do not have adequate medications and interventions. We cannot tell you whether you or your care is going to be severe or mild, have a decompensation in the next 2 weeks or not, or develop a particular complication. This is not to say that we are not getting better, but more information is necessary. Thanks for all the help you provide to us.



## ABOUT DR. KIMBERLY A CHAPMAN, MD, PHD

Dr. Chapman is an associate professor at Children's National Rare Disease Institute in Washington, DC where she takes care of patients, runs clinical trials (predominately registries and natural histories, but also some interventional trials) and has a basic science laboratory which studies the interaction of the propionate pathway and Krebs's cycle. She enjoys swimming and knitting in her free time. Dr. Chapman is happy to answer any of your questions about the topics in the research corner. These discussions are meant to be helpful and reflect her opinion and experiences.



**Children's National**  
Health System

# Point-of-Care Ammonia Monitoring from a single drop of blood

Natalia Gomez-Ospina & Matthew W. Kanan

Department of Pediatrics, Medical Genetics, Stanford School of Medicine  
[gomezosp@stanford.edu](mailto:gomezosp@stanford.edu) | [mkanan@stanford.edu](mailto:mkanan@stanford.edu)

Thomas R. Veltman

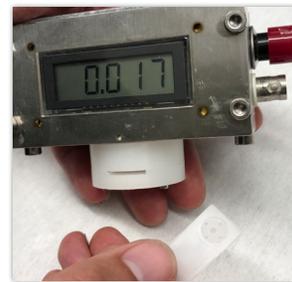
Department of Chemistry, Stanford University  
[tveltman@stanford.edu](mailto:tveltman@stanford.edu)

Hyperammonemia (elevated blood ammonia) frequently occurs secondary to organic acidemia and is responsible for a large portion of brain damage and death in these patients.<sup>i</sup> The underlying cause is thought to be the accumulation of organic acyl-CoA derivatives,<sup>ii,iii</sup> which inhibit the enzyme N-Acetylglutamate Synthetase and deplete acetyl CoA. Both of these effects cause a reduction of N-acetylglutamate levels, which results in dysregulation of the normal nitrogen metabolism that is responsible for converting ammonia to urea for subsequent excretion. Timely intervention to reduce ammonia levels is essential to improve neurodevelopmental outcomes<sup>iv,vi</sup> but diagnosing hyperammonemic infants before an acute crisis is extremely challenging with the standard clinical ammonia test. The standard assay requires intravenous access for at least 1 mL of blood and must be performed in specialized clinical labs. Obtaining samples requires an extremely skilled phlebotomist since accurate values can only be obtained from draws performed without a tourniquet, and patient distress or a slow-flowing venipuncture can contribute to inaccuracies. Additionally, blood is unstable and releases ammonia over time, and therefore samples must be transported on ice and processed rapidly to avoid false elevations.

Patients diagnosed with acidemia require lifelong management to minimize hyperammonemic crises. Current clinical guidelines indicate that suspected patients should be sent to a metabolic treatment center as soon as possible, and transport teams should be equipped with ammonia scavengers and Carbaglu to continue management.<sup>vii</sup> Thus, any suspected hyperammonemic crisis may result in transport to a metabolic center. Frequently, patient families may be hours away from such a center. Finally, uncertainty in a patient's ammonia status is a source of significant stress for parents. The symptoms of hyperammonemia are non-specific, and caloric management can be difficult when children are physically active. Illness can also be a trigger for hyperammonemia, and parents frequently report concern over the uncertainty of the wellbeing of their children.

Our work has focused on addressing all of the above issues through the development of a point-of-care ammonia testing device. The

availability of a user-friendly and accurate ammonia monitor is of longstanding interest to the organic acidemia community, but technical challenges have heretofore kept other proposed devices from achieving success. Our breakthrough came with the recognition that ammonia could be measured in small volumes of whole blood simply by alkalizing the blood sample and monitoring the concentration of ammonia released from the sample. We have built a series of prototypes to validate this detection scheme, culminating in a handheld device that produces accurate ammonia readings in less than a minute from a single drop of blood.



The device is as easy to use as a blood glucose meter, and because we are detecting ammonia in the gas phase, typical interferents in the blood that can cause inaccurate readings with the conventional plasma ammonia test do not influence our results. Furthermore, the immediate readout eliminates complications from sample handling and permits the immediate evaluation of the patient's status with respect to their ammonia treatment regimen. With the device in hand, we were further motivated to devise a measurement protocol that would provide the easiest access to patient samples with a minimum of effort and as little discomfort as possible, as routine venipuncture can be challenging and traumatic for acidemia patients. Fortunately, we discovered that sampling with a skin prick from the underside of the patient's earlobe is completely painless and produces ammonia values that match those measured from a concurrent venous draw. For patients who have an indwelling line placed, access is not as significant of a barrier, however indwelling lines come with an increased risk of infection, and therefore their use is not appropriate in all settings. In the future, we envision shifting the treatment paradigm to closer monitoring of ammonia levels in acidemia patients with the objective of reducing hospitalization frequency and parent stress while improving the quality of life for affected families.

## CITATIONS

<sup>i</sup> Filipowicz, Heather R.; Ernst, Sharon L.; Ashurst, Carrie L.; Pasquali, Marzia; Longo, Nicola. Metabolic changes associated with hyperammonemia in patients with propionic acidemia. *Molecular Genetics and Metabolism*. 88 (2006) 123-130.

<sup>ii</sup> Coude, Francois X.; Sweetman, Lawrence; Nyhan, William L. Inhibition by propionyl-coenzyme A of N-acetylglutamate synthetase in rat liver mitochondria. *J. Clin. Invest.* 64 (1979) 1544-1551.

<sup>iii</sup> Stewart, Peter M.; Walsler, Mackenzie. Failure of the normal ureagenic response to amino acids in organic acid-loaded rats: proposed mechanism for the hyperammonemia of propionic and methylmalonic acidemia. *J. Clin. Invest.* 66 (1980) 484-492.

<sup>iv</sup> Msall, Michael; Batshaw, Mark L.; Suss, Richard; Brushlow, Saul W.; Mellits, E. David. Neurologic outcome in children with inborn errors of urea synthesis. *N. Engl. J. Med.* 310 (1984) 1500-1505.

<sup>v</sup> Picca, Stefano; Dionisi-Vici, Carlo; Abeni, Damiano; Pastore, Anna; Rizzo, Cristiano; Orzalesi, Marcello; Sabetta, Gaetano; Rizzoni, Gianfranco; Bartuli, Andrea. Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators. *Pediatr. Nephrol.* 16 (2001) 862-867.

<sup>vi</sup> Vergano, Samantha A.; Crossette, Jonathan M.; Cusick, Frederick C.; Desai, Bimal R.; Deardorff, Matthew A.; Sondheimer, Neal. Improving surveillance for hyperammonemia in the newborn. *Mol. Genet. Metab.* 110 (2013) 102-105.

<sup>vii</sup> Chapman, Kimberly A.; Gropman, Andrea; MacLeod, Erin; Stagni, Kathy; Summar, Marshall L.; Ueda, Keiko; Mew, Nicholas Ah; Franks, Jill; Island, Eddie; Matern, Dietrich; Pena, Loren; Smith, Brittany; Sutton, V. Reid; Urv, Tiina; Venditti, Charles; Chakrapani, Anupam. Acute management of propionic acidemia. *Mol. Genet. Metab.* 105 (2012) 16-25.

# Help Us Teach Physicians

## ABOUT ORGANIC ACIDEMIAS

**FACT!**

- Teaching about metabolic diseases in medical school and residency programs is poor.
- Most patients live and die without a diagnosis being made, especially when the disease presents in adulthood.
- Patients cannot access effective therapies unless a proper diagnosis is made.
- The sooner a diagnosis is made and treatment begun, the better the outcome.

### WE NEED YOUR HELP!

We at VMP Genetics believe in the power of “patient-teaching” and are bringing patients and families into lectures and presentations – at conferences and in the classroom. While doctors teach facts, patients tell stories. Story-telling is a more compelling teaching method with better recall over time than didactic lecturing. We also believe that doctors are more likely to make a diagnosis if they have already seen a patient and heard her/his story. Story-telling can be live or taped.

### WE ARE LOOKING FOR...

- Patients and/or family members who are interested in telling their stories in local medical classroom settings...**  
We are developing a Patient Teacher Registry. If a medical school faculty member is looking to introduce the patient story in a teaching session, the Registry can tell him/her if there are patient-speakers in the area and what diagnoses they have.
- Patients and/or family members who are interested in having their stories videotaped...** As we secure funding, we are interested in recording stories that reflect the broader patient experience. The more variety in the stories, the richer the learning potential.
- Videos of patients and families telling their stories...**  
A 5-or 10-minute clip can be downloaded into a lecture about that disease or relevant biochemistry to enhance the learning potential of the session.

Please help us in our efforts to raise awareness about Organic Acidemias through this innovative educational outreach to the medical community. For more information about this project, please contact us at:

[PatientTeacherRegistry@vmpgenetics.com](mailto:PatientTeacherRegistry@vmpgenetics.com)

Mark Korson, MD, VMP Genetics, Director of Education  
Jacob Athoe, Genetic Counseling Student, Boston University Genetic Counseling Program



# Organic Acidemia Association

9040 Duluth Street  
Golden Valley, MN 55427

[oanews.org](http://oanews.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.

### 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.



## 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.



## 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 [OANews.org](http://OANews.org) web site to sign up.

