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Organic Acidemia Association



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

Parent Support, Education & Awareness www.oaanews.org

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

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Happy New Year! I'm so excited to share that we just received IRB approval for our OAA Natural History Patient Registry. If you signed up to receive information at the OAA conference last summer you will be the first contacted when the registry is ready for your input. We need IRB approval for any media announcements on the registry and once we get everything approved we will be making many announcements encouraging your participation! Below is an update from Dr. Kim Chapman, OAA's principal investigator for our registry:

As many of you know, all of us with OAA and the National Organization of Rare Disorders (NORD) have a registry. For those who are unfamiliar, NORD was awarded a cooperative agreement from the U.S. Food and Drug Administration (FDA) to sponsor a number of rare diseases family group organization's registries which can be used as natural history and have the goal of improving care and shortening the time to approval for therapeutics for these diseases. OAA has been selected for one of these registries. We have been working hard to provide appropriate privacy protection, disease related questions, and patient/family-friendly platform which provides good data. Initial goal was to have the beta test in October of 2016, but that appears to have been optimistic. We are still working on the questions and set up.

Currently, the registry appears to require an initial time commitment for the patient/caregivers to enter information. Physician-initiated patient information entry is not in this first iteration and so we all need to participate. Updates will be on the OAA website.

Thanks to our OAA volunteers who represented us at conferences and Rare Disease Day activities. I attended and exhibited a Rare Disease Day Event in Minnesota, Lillian; mom to Connor represented OAA at an event in Houston Texas. Allison, mom to Issac also represented OAA at the 2016 Rare England Conference in Massachusetts last November. Read her update on page 12.


IN THIS ISSUE

Medical Advisors

WE NEED DISCARDED ORGANS

Livers and kidneys removed from individuals with inherited metabolic disorders during organ transplant are being collected and used for advanced research. If you or yours are scheduled or planning to schedule a transplant, we would like to work with you to obtain those organs, which would otherwise be discarded as medical waste. Please contact Kimberly A Chapman, *kchapman@childrensnational.org* to organize your donation.

Note: we need at least a 4-week lead time to organize organ collection.

NORD Awards New Research Grants for Rare Disease Research

Washington, D.C.—February 24, 2017 The National Organization for Rare Disorders (NORD), the leading independent, nonprofit organization committed to the identification, treatment, and cure of rare disorders, has awarded seven new research grants to fund rare disease research.

For the study of Malonic Aciduria, with support funding raised by The Hope Fund, Lundbeck **"Raise Your Hand"** Campaign, and public donations:

Michael J. Wolfgang, PhD, Johns Hopkins University School of Medicine, Baltimore, MD, Regulation of mitochondrial metabolism by Malonyl-CoA Decarboxylase and Malonyl-CoA Synthetase.

My PA Life!

Hello for those of you who do not know me, my name is Bryan. I am thirty years old and I have Propionic Acidemia. In the beginning doctors did not think anything was wrong with me. They told my mom I was a sleepy baby, but my mom knew that something was wrong. I was officially diagnosed with Propionic Acidemia at Saint Cristopher's hospital when I was only a few months old. Shortly after I would start being seen at Children's hospital of Philadelphia.

When I was really young I suffered a stroke and was in a comma for four days. The doctors said I would never walk or talk. That was not an option for me! Remembering the days of the wheel chair, walker, and speech classes reminds me to be thankful for where I am at today. I am able to walk and talk just fine! However Propionic Acidemia has its effects on me.

Until the age of twenty four I had a feeding tube for a special formula called Propimex -2! Today I am able to drink it by mouth. What I like do is mix it with water, whole milk and strawberry syrup. From my Propionic Acidemia I also suffer from Cardiomyopathy which affects my heart. I'm taking carvedilol 25 mg to keep it under control. I was originally on Lisinopril then I learn that it can be harmful to your kidney's (important to know).

My chronic kidney disease which was not found by my metabolic doctor but is believed to be caused by my Propionic Acidemia is at stage three. The weird thing normally with kidney diseases they only get worse, but mine has actually gotten better. One of the big things is to drink lots of water. I try my best to drink sixty four ounces of water a day.

A lot people have ask me about ammonia and I'll be honest I don't know a lot. My doctors told me that my normal is sixty, I am not sure if that go's all for kid's with Propionic Acidemia. You will know when it's high, you will feel extremely tired and have really bad brain fog. Staying hydrated differently helps along with rest. I would suggest going to your Propionic doctor if gets too high cause I learned from recent experience that normal hospital's don't know anything about it.

That's how Propionic Acidemia affects me. Today I am 30 years old. I work as a cashier at a food store and recently got my own apartment. I exercise daily cause I know how important it is for my muscle, my mind and motor skills. I like yoga but anything you can do will help. I hope this article helps give people hope they can live a somewhat normal life with Propionic Acidemia!

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Fundraising for OAA!

OAA 2017 Calendar available on CafePress.com

OAA's yearly Calendar and other items can be purchased through our CafePress.com shop. A portion of your purchases will help families with rare organic acid disorders.

www.cafepress.com/organicacidemiaassociation

AUTISM + METABOLISM

[STEPHEN G. KAHLER, MD]

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This essay is based on a talk I intended to give at the 2016 FOD-OAA meeting in Denver. It is based on my own observations and those of Dr. Richard Frye, MD, PhD, who directs our Autism Specialty Clinic. In this clinic we see patients diagnosed with autism and attempt to understand the metabolic/biochemical abnormalities that are present in these patients. Using this approach we then implement treatments designed to improve the underlying biochemical abnormalities, and thereby lessen the autism symptoms. Dr. Frye also directs a research laboratory devoted to studying mitochondrial dysfunction in patients with autism.

Autism is now familiar to most Americans, thanks to increased awareness, increased recognition, and what appears to be increasing prevalence. It is a description of how someone's behavior appears to us, not a specific condition with a single cause, or even a specific condition with several possible causes. The fundamental characteristics of what is called autism include problems with communication, problems with relationships with others, and restricted interests and repetitive behaviors, including insistence on sameness. The onset must be in young childhood or earlier.

Within the broad definition of autism, or what some call "the autisms", are a variety of related conditions, which have less severe problems that help to make up the "autism spectrum disorders". In Asperger syndrome communication

is good; in PDD-NOS (pervasive developmental disorder-not otherwise specified) there is less restriction of interests, and less repetitive behaviors. The onset may be sudden, often accompanied by a febrile event; or the symptoms may appear gradually.

The fact that there are families with more than one child with autism, and families in which different members may have different forms of the autism spectrum disorders, suggests that there is a genetic contribution to the autism spectrum. Autistic symptoms are associated with changes (mutations) in a large number of specific genes, and regions of chromosomes, or additional entire chromosomes.

Finally, many children with autism have disturbed intestinal function, with slow intestinal transit and abnormal bowel movements (too runny or too firm). Many children have distinct food aversions, or extremely strong preferences, so that meals are one more example of repetitive behavior.

Among the genes and genetic disorders that can be associated with autism are Rett syndrome, Williams syndrome, tuberous sclerosis, Down syndrome, abnormalities of small genetic regions, and abnormalities of a large number of genes associated with brain function, especially genes involved in the formation of synapses (the areas where two nerve cells make a connection—there are billions in a human brain), and genes involved in certain biochemical processes.

Some of the specific genes contribute to processes to create or transport certain molecules in brain cells (neurons) (for example, creatine), to inactivate excess amounts certain harmful molecules that we make or ingest (e.g., ammonia, phenylalanine), and to provide the energy necessary for proper functioning of neurons (the processes that take place in the mitochondria).

Some of the chemical compounds that contribute to autism in some children are propionic acid and its variations. We all make a lot of propionic acid, generally in the form called propionyl-CoA, and we absorb a very large amount, made by our gut microbes (the "gut flora"), which should be processed in the liver to less dangerous substances, and used for energy. It has been known for a few decades that propionic acid and related compounds can interfere with brain function, and that laboratory animals exposed to an increased amount of propionic acid can exhibit autism-like behavior—restricted repertory of

interests, poor interaction with other animals, and poor communication/vocalizations. This sounds similar to what sometimes happens to children with propionic acidemia, in which propionate accumulates because of genetic alterations in body chemistry (metabolism). There is growing evidence that some children with autism may be being exposed to, or are inadequately responding to, high levels of propionic acid made in the gut. The obvious question is would the autism relent if the propionic acid burden was lower?

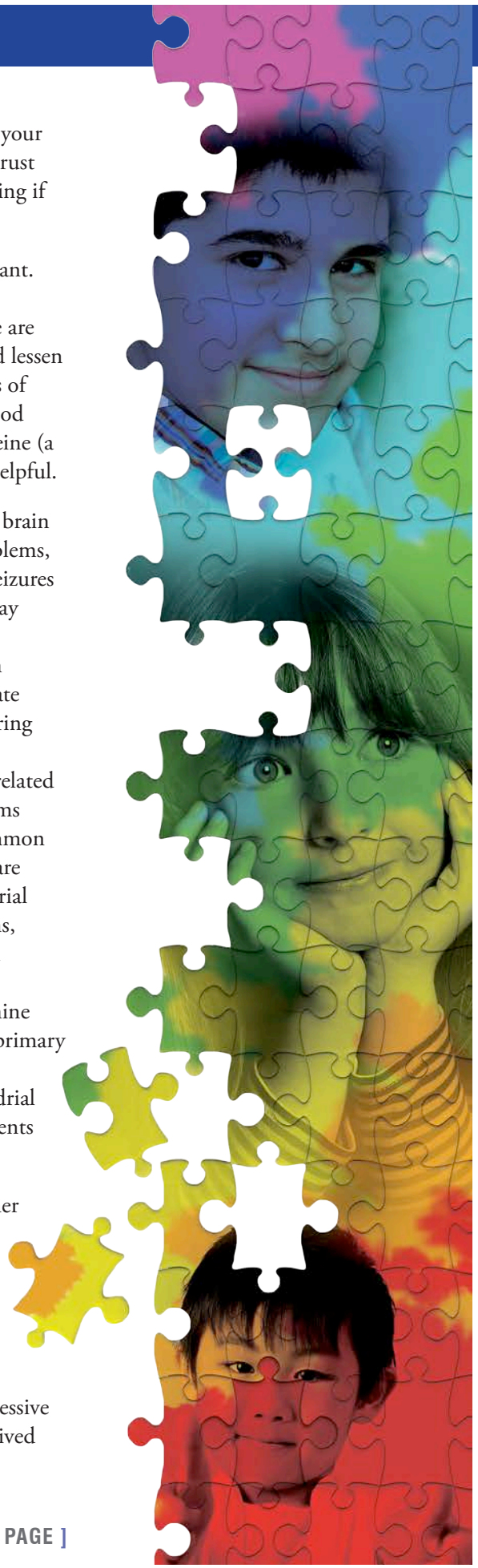
So we investigate children with autism by looking for abnormalities in a wide variety of body compounds (metabolites), analyze their genes for extra, missing, or altered regions, consider if there are dietary habits and intestinal problems that might be contributing, and consider the role of oxidative stress. We can't change a patient's genes, but we may be able to repair some of the problems caused by gene mutations, and we can certainly try to improve abnormal metabolic processes.

One of the early discoveries about metabolism in children with autism is excessive oxidative stress. This is a quick way of saying there is evidence of damage to tissues due to oxygen. Oxygen is essential for life, but it is also a toxic substance that can damage our tissues. This is similar to what happens in a car—oxygen is essential for burning the fuel (gasoline), but it also damages the car—causing rust spots on metal, causing plastic to change and become brittle. We can measure oxidative stress by looking for increased levels of molecules damaged by oxygen. Damaged amino acids, fatty acids, and nucleic acids (the building blocks of DNA, our genetic material) are found in a significant number of children with autism. The connection between this damage and the autistic behavior isn't clear yet—it's very much like your car not running perfectly, finding rust spots on the bumper, and wondering if there is a connection.

Glutathione is our main anti-oxidant. Many children with autism have inadequate free glutathione. There are ways to improve the situation, and lessen the autism symptoms. Large doses of vitamin B12 (even though the blood level is normal), and N-acetylcysteine (a precursor of glutathione) can be helpful.

Mitochondrial dysfunction in the brain can cause subtle and regional problems, or overwhelming brain damage, seizures and coma. In the muscles there may be weakness or hypotonia. When we find this in a child with autism we are especially likely to investigate mitochondrial function by measuring lactic acid (increased level means mitochondrial impairment), and related substances. Mitochondrial problems sometimes respond to certain common nutrients that we can give. These are collectively called "the mitochondrial cocktail". There are several versions, generally including at a minimum carnitine, riboflavin (vitamin B2), coenzyme Q10 (co-Q), and thiamine (vitamin B1). Like children with primary mitochondrial problems, autistic children with impaired mitochondrial function may benefit from treatments that address this.

Altered immune function is another common aspect in some children with autism. This may be expressed as abnormal intestinal immunity, inflammation, abnormal bowel movements, and intolerance of certain foods because of altered digestion or excessive absorption of toxic substances derived from foods.



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AUTISM + METABOLISM

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The foods most commonly involved in this process are proteins present/derived from milk (casein) and wheat (gluten/gliaden). Eliminating these foods from the diet may dramatically improve brain function and lessen autism symptoms. The gut flora includes several hundred different sorts of microbes, all interacting in ways we are barely beginning to understand. If there is excess production of propionate or inability to deal with it, an antibiotic such as metronidazole (Flagyl) may change the numbers of certain microbes, and lessen the production of propionate.

Deficiency of certain nutrients in the brain may also occur. This especially includes the vitamins folic acid and tetrahydrobiopterin, which will lead to altered levels of neurotransmitters, the substances that neurons use to communicate with each other. Serotonin is the neurotransmitter most conspicuously altered in autism (and also depression)—using a low dose of a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine (Prozac) prolongs the action of serotonin, and can lessen symptoms. 95% of the serotonin in the body is made in the intestine, so drugs which influence the bowel may affect serotonin levels.

All of these observations and ideas can be part of understanding autism even in a child who already has a "cause" for autism—Down syndrome, Rett syndrome, propionic acidemia, Angelman syndrome, etc. Of the disorders of most concern to the FOD Family Support Group and the Organic Acidemia Association, for whom I first developed these thoughts, the organic acidemia patients are the more likely to have autistic features. Autism doesn't occur in every patient with propionic acidemia, however, so we must be aware of what other factors might be contributing, and can we improve the situation. Some children with autism with or without a named metabolic error will have a significant improvement if they are only IV feeds (total parenteral nutrition, TPN) for a while. This tells us that something about food or the gut flora is playing a role. Other patients will have a major improvement during and shortly after an illness with fever.

> "There is growing evidence that some children with autism may be being exposed to, or are inadequately responding to, high levels of propionic acid made in the gut. The obvious question is would the autism relent if the propionic acid burden was lower?"

A new drug, sulforaphane, derived from broccoli sprouts, may benefit them (and perhaps others) greatly.

To summarize: Autism is a collection of symptoms, not a specific entity, that occurs in a variety of settings; there are numerous nameable genetic "causes" of autism; autism is a systemic disorder which affects the brain as well as other organs; there are numerous biochemical/metabolic problems which can be found in various combinations in children with autism; these problems may be treatable by diet, nutritional support, medications; autism may occur in children with metabolic disorders, especially some of the organic acidemias; treatments that help improve the metabolic situation may improve the autism symptoms as well; and we must keep in mind that if we can't explain and treat all the symptoms of a patient we may be overlooking something that could offer additional benefit.

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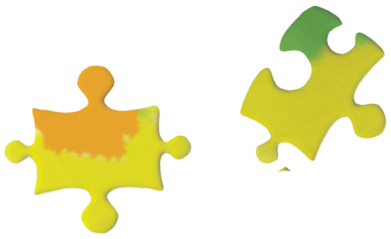

UPDATE: Amber : MMA, Mut 0 | Age 33

As I approach the five-year anniversary of my transplant, I recall all that I went through in the hospital -- people who visited me, workers who went out of their way to get me things I needed, saying beep-beep when coming out of the elevator backwards, communicating by giving a thumbs up or thumbs down with my brother when I couldn't talk. Signing to my mom (I only knew the alphabet, so I was kind of limited lol). Wow, it has been a long time since my most recent update.

I received the white-cane training that I mentioned in my previous update, as I am legally blind. I do go out using a cab or Uber to familiar places. I visit my grandmother. I tried to volunteer at a senior center visiting residents near my home, but because of my low vision, they thought it would not be a good fit for me. Another accomplishment I recently made is that when I go to follow-up appointments, I make my way in to the doctor's office while my mom parks the car.

I went to about four different wound treatment centers over a three year period before my surgical wound finally healed. The scar tissue completely formed after a non-invasive skin graft called "Eric Ericson Expansion Theory." A small amount of skin was scraped from my thigh, and then sprinkled onto the open wound area along with a solution. In about three weeks, the new scar tissue formed.

In the fall of 2016, doctors noticed that my calcium level was critically high…so I was admitted to the hospital and treated with IV saline and an increase in my Sensipar, which brought the calcium level down. However, my calcium level continued to rise and I had to be readmitted on several occasions. In order to solve the hypercalcemia problem, I had to have surgery on November 30, 2016 to remove three and one half of my four parathyroid glands. The surgery took longer than normal because of scar tissue that the surgeon encountered. On December 2nd or 3rd, I was given the antibiotic Linezolid because I had a low-grade fever. This antibiotic caused severe diarrhea. On December 4th at 11:00 p.m., I had a seizure lasting three and a half minutes. I was transferred to SICU. On December 5th at 11:00 a.m., I had another seizure lasting one minute. My mom asked that the Linezolid be stopped since I did not have a fever and my white blood cell count was normal. After researching side effects of Linezolid, we learned that this antibiotic can lead to seizures in people who are predisposed to seizures. We have now added Linezolid as one of my allergy meds. I had no more seizures and was transferred to the transplant unit. I was discharged from the hospital on December 9. My calcium level now seems to be stable.

During my admissions for treatment of the high calcium levels, some medications were skipped for a week -- just many different oversights by different people. I am 33 years old, but these oversights would not have been noticed had my mom not been there with me. I am happy to be home now and doing much better.

PEACE AND LOVE, AMBER
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Grant and Sebastian : Propionic Acidemia Super Heroes | Twins Age 3

Our story with PA started out the same as many of yours. Our sons were born looking perfectly healthy, besides being born six weeks early and being twins. Everyone that saw them thought they looked wonderful and would go home from the NICU rather quickly. However, that all changed on the sixth day of their life. I got a call from the doctor in the NICU that Grant was struggling and had to be put on a ventilator, but they thought it was just a virus of some sort. By the time I got to the hospital he was completely comatose and there were swarms of people around him. They were trying to explain exactly what they thought had happened, but all I could understand at the time was that he was very sick and they didn't know what to do. They were running a lot of labs on him and his twin brother Sebastian to try and see if both boys had a metabolic issue of some sort. We were quickly transferred to another hospital that had dealt with these types of conditions before. While I can remember the whole day perfectly now, in the moment everything was a blur and I seemed to be just a spectator as they hooked both boys up to an abundant amount of machines that seemed so humongous in comparison to their little 4lb bodies. They were too small for traditional dialysis, so they attempted to come up with a plan. Fortunately there was actually a visiting geneticist who was interviewing for a position at the hospital that day, who mentioned he had heard of combining ECMO and dialysis to help patients who were very small. This is what was decided as the best course of treatment for our sons. I will never forget standing over my son as they hooked up IV's and poked and prodded him, all without him making a single, solitary sound. The ECMO and dialysis combination worked, even better than the doctors had anticipated and it seemed that both boys were on their way from catabolic to anabolic. Over the course of the next few weeks, we learned all about PA and the life that would now be our new normal. It was quite the operation at our house to get them fed around the clock, once they came home, thankfully we had and continue to have amazing support from family. The boys have had many hospitalizations since they have come home and have definitely given me lots of new gray hairs, but they have come so far. While our normal is being hospitalized with one or both of them at least once a month, they continue to grow and show us just how determined they are. They both started preschool this year and are riding the bus every day to school. Anyone they come into contact with quickly becomes a new friend. It is so amazing to see how positively they affect the people that they come into contact with. It's as if their personalities and happiness are contagious.

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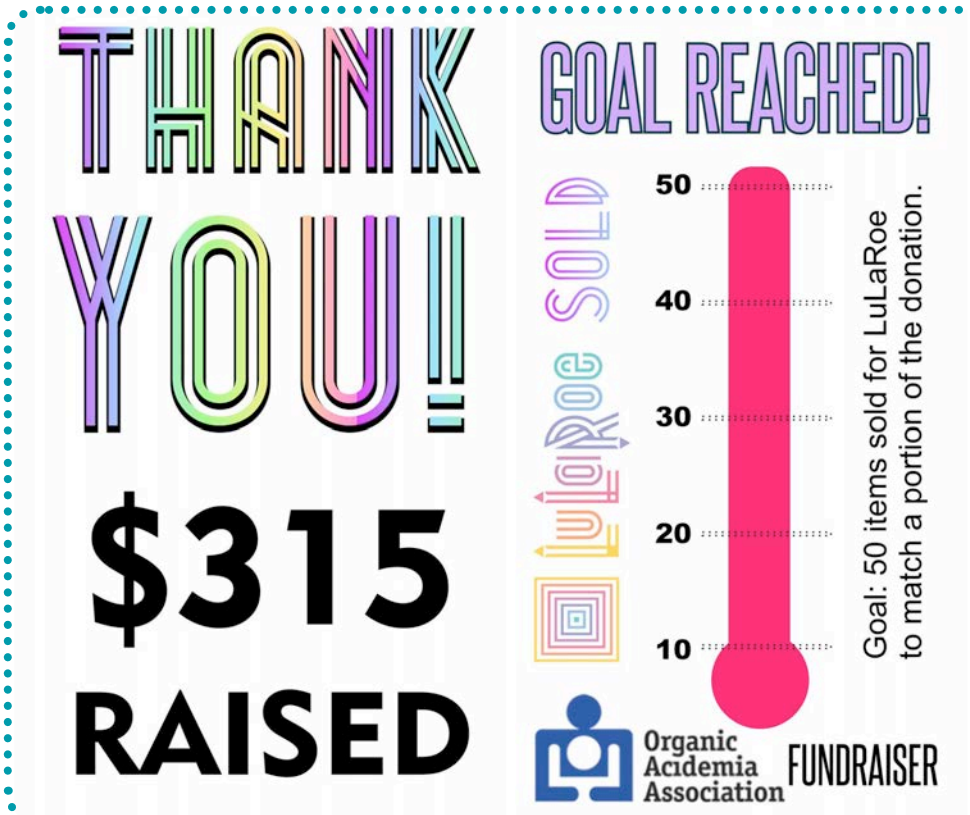

THANKS to AMBER, Mom to Sebastin and Grant, PA for organizing this online FUNDRAISER for OAA!

Olivia : Isovaleric Acidemia | Age 24

Olivia with mom Kerrie

It was the summer of 1992; I was getting ready to enter my Senior Year in high school. I was working at a Kiwanis Camp for disabled children and adults when I became so sick. As soon as I got home from working at the camp I saw my doctor thinking I caught a bug of some sort. He said let's run a pregnancy test too. I was like whatever -- I am so careful. Well this 17 years old was told "you are going to be a mom." I was so sad, scared and not sure how in the world I was going to tell my parents. News was delivered, things became tense…I was pregnant and heading into my last year of school. I tried to hide it. But eventually everyone started to notice. I lost some friends along the way and yet gained others. I turned 18 in Feb, my mom and I were finishing up our last few Lamaze classes and my due date was right around the corner. On April 7th 1992 I had my beautiful daughter Olivia Leigh. Olivia was an 8 pound baby, seemed very healthy. We were discharged immediately and went home. At this time I lived with my mom and dad. My grandparents were visiting as well. We all started to notice that Olivia was not eating much and sleeping all the time. We called up the birthing center and they said you are just a young mom and nervous. I was told babies sleep it is ok. Another couple of days and Olivia was hardly waking up at all. My mom and I rushed her to the emergency room trying to explain something was wrong. The nurse on duty was my guardian angel and no one knew it yet. Later in the night the nurse came in saying she has called OHSU and asked for them to transport Olivia up to Portland immediately.

The infant caravan came in the middle of the night, told me to go home sleep some and then come up to OHSU. My mom made me go home and try to sleep some. After a couple of hours we headed up to the hospital. By the time my mom and I got up to the hospital they had Olivia hooked up to numerous IVs and no one knew what was wrong with her. They had shared they lost her for a brief moment in transit and was able to get her stable. They were not holding onto much hope.

Two weeks of specialists go by and nothing, then a gentleman by the name of Dr. Neil Buist came into her room smelled her and said she is an IVA baby, Isovaleric Acidemia and what I'm smelling is her sweaty sock syndrome. They tested her and that's exactly what she had. My mom asked why the PKU test did not alert them and he explained that the PKU testing was limited. Olivia was a part of a news story when the PKU testing was being expanded to screen multiple metabolic disorders.

We were in and out of the hospital her entire life up to the age of 13. She had several crises. Olivia also had pancreatitis and things were just so hard on her. Things got a little better after about her 13th birthday. Hospital visits became less sporadic and our stays were didn't last as long.

Olivia with her family

Olivia is now 24 years old she has just given birth to a son and is doing ok. Her pregnancy was very hard, hospitalized a few times and had multiple ER visits. But her metabolic team was so good and worked with her so closely.

For my first child and being a teen parent it certainly wasn't what I was hoping for but with the help of the metabolic team and my family Olivia is still with me and I love her deeply.

Thanks for letting me share

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NUTRICIA
Metabolics
Inspiring Futures

February 2017

Attn: Patients using Maxamaid© and Milupa products

Dear Metabolic Families,

Having improved our line of Metabolic formulas to be in line with the latest nutritional guidelines we will **no longer supply our lines of Maxamaid and Milupa products after June of 2017 or until supplies last.**

At Nutricia North America, we work very hard to ensure metabolic patients receive the best possible nutritional support. The past couple of years have been exciting as we have enhanced our product portfolio to grow with patients from infancy to adulthood. We proudly introduced our Periflex© / Anamix© Early Years line for infants with the added benefits of DHA & ARA and prebiotic fiber to be closer to breast milk than ever before*! In addition, we launched the follow-on formulas Periflex© Junior Plus and Anamix© Next, which contain added DHA & a multi-fiber blend.

Although we are confident that these changes are in the best interest of metabolic patients, we certainly understand the challenges that may come with transitioning to new formula. If you are currently using a Maxamaid or Milupa formula please follow the steps below to start your transition:

1. **Contact your clinic/healthcare professional to find other products within our portfolio and start the transition process. Please do not initiate a transition on your own.**
2. If you have questions regarding insurance reimbursement, contact our Reimbursement Care team Monday – Friday 8:30am – 5:00pm EST at 1-800-605-0410.
3. If you have product related questions or need help finding a supplier for your new formula , contact our Customer Service team Monday – Friday 8:30am – 5:00pm EST at 1-800-605-0410

Please know our goal is to provide the best nutrition possible, and we are committed to being the best in specialized nutrition for the metabolic community

Sincerely,

The Nutricia Metabolic Team

*Compared to Nutricia's Periflex Infant and Analog formulas

OAA Formulas included:

METABOLIC CONDITION	PRODUCTS
GA1	XLys. XTrp, Maxamaid
MMA/PA	XMTVI Maxamaid. Milupa. OS 2
IVA	XLeu. Maxamaid

New Drug Relieves TCA Cycle Block In Patients With PA And MMA

JERRY VOCKLEY, M.D., PH.D.

UNIVERSITY OF PITTSBURGH

CLEVELAND FAMILY PROFESSOR OF PEDIATRIC RESEARCH

PROFESSOR OF HUMAN GENETICS, CHILDREN'S HOSPITAL OF PITTSBURGH

CHIEF OF MEDICAL GENETICS DIRECTOR OF THE CENTER FOR RARE DISEASE THERAPY

Propionic acidemia (PA), one of the more common organic acidemias, was first described in 1968 in an infant with severe metabolic acidosis, and many additional patients have since been reported. Propionyl-CoA is an intermediate in the oxidation of four amino acids (i.e., threonine, valine, methionine and isoleucine) as well as odd-chain fatty acids. Propionic acid is also absorbed from the large intestine where it is produced by propiogenic bacteria. Propionic acidemia is due to deficiency of propionyl-CoA carboxylase (PCC), a mitochondrial biotin-containing enzyme that catalyzes conversion of propionyl-coA to D-methylmalonyl-CoA. The disorder is extremely variable and identification through newborn screening is typical in the US. Methylmalonic acidemia (MMA) can be caused by an inherited deficiency of methylmalonyl-CoA mutase, an adenosylcobalamin-requiring enzyme that converts L-methylmalonyl-CoA to succinyl-CoA, or in the metabolic pathway that catalyzes the biosynthesis of adenosylcobalamin from vitamin B12. Patients with PA and MMA are at risk to develop episodes of acidosis caused by accumulation in these two acids when patients have otherwise mild illness or stress. However, they also have an inability to make succinate, the final product in this metabolic pathway, and a key chemical in the tricarboxylic acid (TCA) cycle necessary for cellular energy production. It is likely that this energy deficit leads to significant secondary problems in patients with PA and MMA, including brain damage (in both diseases) and cardiomyopathy (in PA). For the last several years, my laboratory has studied a similar problem that occurs in patients with genetic disorders of long chain fatty acid oxidation (FAO). These patients develop a secondary deficiency of propionate that results in symptoms that include low blood sugar, muscle weakness, and episodes of acidosis. The usual treatment of long chain FAOs is with medium chain triglyceride oil, which can bypass the metabolic block, but doesn't address the propionate deficiency. We have developed a novel drug, triheptanoin that both bypasses the block and restores propionate levels to normal. The drug is currently in clinical trials in patients and results of two phase 2 studies have shown resolution of hypoglycemia, and improvement in muscle and heart symptoms. We have now turned our attention to developing a similar compound to relieve that TCA cycle block in patients with PA and MMA. Ideally, delivering succinate directly as a drug would accomplish this result. Unfortunately, succinate in its pure form is a powder that has an extremely bitter taste and must be taken in large quantities to approach the amount needed to deliver appropriate amounts to cells once ingested. As with triheptanoin, we have elected to make a novel compound in which succinate is attached to another simple chemical, glycerol, to make a high-density oil that can efficiently deliver succinate to the body in a tolerable form. After making nearly three dozen variations, we now have a candidate drug that matches our requirements and are testing it for efficacy in mouse models. If these tests are encouraging, we'll move to the next step to file for FDA approval to move to a clinical trial in patients, with a target to start in the next 1-2 years.

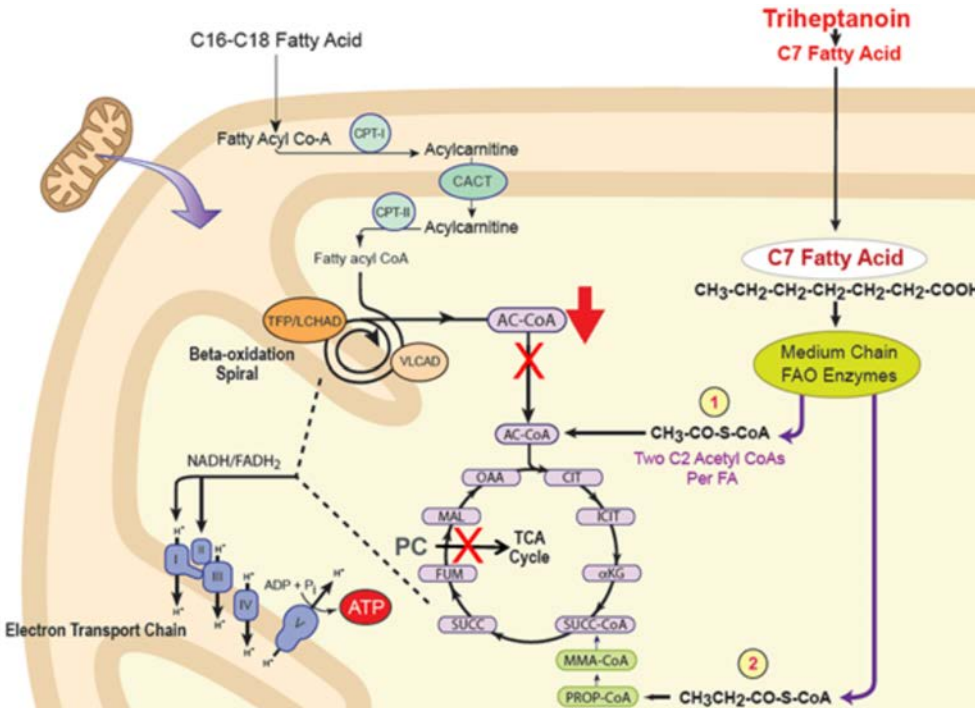

Figure. Entry of propionate into the ICA cycle. Improvement in patients with long chain fatty acid oxidation disorders are seen when they are treated with a drug (triheptanoin) that increases propionate and thus, ultimately, succinate. Our new drug provides succinate directly to the TCA.

OAA Exhibits at Rare New England Conference

November 12 & 13, 2016, South Attleboro, MA

BY: ALLISON WOOD, MOM TO ISSAC, GLUTARIC ACIDEMIA, TYPE 1

A few months ago I was able to represent the Organic Acidemia Association at a conference put on by Rare New England. Rare New England's mission is to bring together New England Families touched by rare and complex disorders. The conference was titled "Staying safe in a medically complex world- Improving communication between patients, families, and medical teams."

The conference hosted a great group of speakers including Dr. Mark Korson who is the co-founder and director of Genetic Metabolic Center for education and Dr. Richard Boles who is a pediatrician with an expertise in genetics. One of the largest issues with having or caring for a patient with a rare or complex disorder is that many of the doctors, who are giving care, have little or no experience with the disease. This can create conflict if the doctor disagrees with the patient or family.

Rare disease patients sometimes have to see a large group of specialists to coordinate care. Wait times can be long for some specialists. One talk addressed ways to "Get the Most out of Your Specialists Visit". Dr. Aurora Richards-Stipnieks had some suggestions as to how to prepare and approach these visits. The first is to be prepared! If you have all the information the doctor will ask on hand, the time the doctor has to spend digging it up is cut way down and you can focus more on your purpose for the visit. This includes having your medication list, list of surgeries, allergies and type of reactions, previous appointment notes from other specialists, copies of lab work, previous imaging and reports, and a list of doctors involved (the best way to reach them and their specialty). Her next suggestion is to really understand what the specialists' capabilities are. Make sure to formulate your questions specific to their specialty and make sure to only bring enough questions which can be answered in that one appointment.

Although this is hard to talk about, one of the issues addressed at this conference was the possibility of parents or patients with a rare disease or complex disorder not being believed by the doctors. Symptoms may not make sense or fit into a box which can cause problems. Dr. Richards-Stipnieks had some suggestions to make sure you protect yourself in these situations.

- Be straightforward with your child and have them lead the appointment
- Have parents switch out appointments if possible
- Respect the physician and ask their opinion
- Keep your emotions in check
- Never say I, always say we
- Do not tell physician about research; ask them if they are interested in reading it

At the conference several speakers talked about the advantages of moving your medical file from a paper binder to an online file that you can put on a USB or CD and bring right to the appointment. This allows the doctors to get all of the information which they can sift through by searching for keywords rather than having to shuffle through papers. You can also easily email all of this information.

There were many other topics addressed at the conference. If anyone would like more information, please feel free to email me at awood@crinet.com. You can find out more about Rare New England on their website *www.rarenewengland.org/index.html*. You can also email them at *info@rarenewengland.org*.

Loree, mom to Jonathan, MMA Mut 0 represents OAA at the 2017 Abbott Nutrition Metabolic Conference in South Carolina

Making Sense of Newborn Screening Cut-off Values

POSTED ON FEBRUARY 28, 2017
IN NEWBORN SCREENING AND GENETICS

Newborn screening is the practice of screening every baby in their first 24-48 hours of life for certain harmful or potentially fatal conditions that are not otherwise apparent at birth. For babies who have abnormal screens for one of these conditions, rapid identification and treatment makes the difference between health and disability – or even life and death. Every year more than 12,000 newborn lives are saved or improved through newborn screening. It is the largest and most successful health promotion and disease prevention system in the country.

How is a screening test different from a diagnostic test?

A screening test looks for abnormal levels that may indicate signs of a disease when no symptoms are present. It tells a patient their risk – normal levels indicate low-risk and abnormal levels indicate high-risk. A diagnostic test determines if, in fact, the disease is present allowing the healthcare provider to make a definitive diagnosis and initiate treatment.

Newborn screening is not a diagnostic test but rather a screening test – it determines whether the baby has a high or low risk of having that disease. If a baby has abnormal screening results, the baby's levels were out of normal range. This immediately cues the healthcare provider to pursue additional diagnostic testing in order to know whether or not the baby has the disease in question.

If a baby has symptoms or family history of a disease, parents should not rely entirely on newborn screening to rule it out; healthcare providers should be consulted for additional diagnostic testing.

What are cut-off values?

As in many scientific tests, cut-off values are used to determine which levels are normal and abnormal. Newborn screening looks for markers of disease and the cut-off levels tell scientists if the amount of markers indicates high or low risk.

How are cut-off values determined and why do they vary from state to state?

Every state newborn screening lab determines the optimal cut-off values for its population. The values are set using a number of factors and considerations such as:

- The disease's prevalence and severity in the state's population,
- Race and ethnic differences in the state (again, relating to a disease's prevalence),
- Environmental factors in the state (temperature or altitude, for example) which can affect testing,
- Differences in the way the laboratory test is performed (methodology),
- And other factors unique to the laboratory and its equipment.

For these reasons, a value in one state newborn screening lab cannot simply be compared to a value in another lab. The value associated with a normal screen in one state's population may differ significantly from the value associated with a normal screening at another lab. That is, the line between normal and abnormal could be different in each state.

For example, Baby A gets a value of 14 which is normal in her state where the cut-off is 16. In a neighboring state, the cut-off is 10 so a 14 would be considered abnormal. However, because of differences in how cut-off values were determined and how the test was performed, Baby A's sample would have screened at 8 in the neighboring state and been considered normal as well.

What are false positives and false negatives?

Sometimes newborn screening will show that a baby has abnormal levels of markers for a disease, but further diagnostic testing is negative. This is a false positive. In extremely rare cases, newborn screening will show normal levels of markers in babies who will eventually develop diseases. This is a false negative or delayed diagnosis.

False positives can be extremely stressful for families. In some cases, the diagnostic process can take several months leading to distress and hardship for the baby and family. False negatives, on the other hand, mean that a baby might begin experiencing symptoms of a condition before being diagnosed. Depending on the condition, these symptoms could cause life-long development delays, permanent disability or even death.

If cut-off values are thought of as a filter, state newborn screening programs work to find the optimal filter to catch as many babies as they can. That may mean catching more babies who are ultimately determined to be healthy to avoid missing others who may later receive positive diagnoses. . So while some false positives are necessary to avoid false negatives, states strive to keep them to a minimum.

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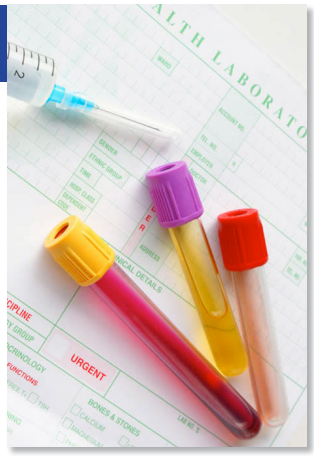


What happens when there is a delayed diagnosis (aka, false negative)?

While delayed diagnoses (aka, false negatives or missed cases) are extremely rare, they are not nonexistent. State newborn screening program staff work to save babies' lives and they take this job extremely seriously. It takes just one delayed diagnosis reported to a newborn screening program to trigger a comprehensive examination of the system. Every effort is made to understand why the case was missed and what, if any, changes can be made to prevent additional delayed diagnoses.

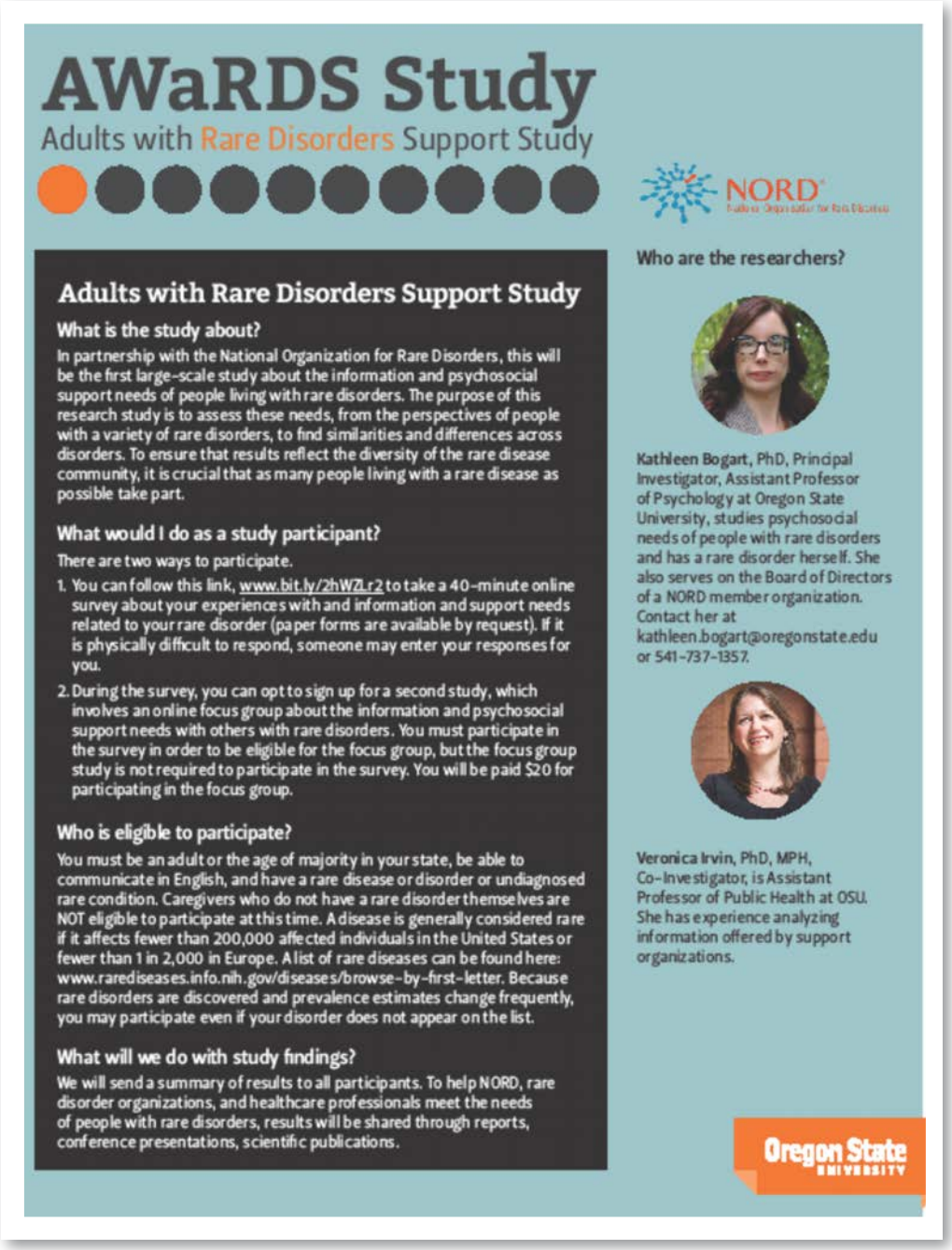
When a delayed diagnosis is reported to the state newborn screening program, the laboratory scientists begin repeating the test to see if they get different results. They retest the bloodspot if it is still available and revalidate the testing equipment to make sure it is functioning properly. If everything is still the same upon retesting, newborn screening laboratory scientists will reevaluate the state cut-off values for the condition, consider altering the sensitivity of the testing equipment and/or determine whether the baby's biology may have affected the screen.

What has been done to prevent delayed diagnoses? Is there more than can be done?

Many states have implemented processes to prevent delayed diagnoses while keeping false positives to a minimum. In most states, when a baby's newborn screening results are abnormal, the test is performed again to confirm that the results. In cases where the value is abnormal but is close to the cut-off, second tier testing may be used. Second tier testing employs a more sensitive test that can eliminate some false positives and delayed diagnoses. But second tier tests are also more expensive, more complex and take more time than the primary method of testing.

Additionally, newborn screening short-term follow-up program staff reviews reports from clinicians of babies' final diagnoses. This information, even if consistent with the baby's newborn screening results, helps the program continue to improve the quality of their testing.

Newborn screening programs around the nation routinely evaluate and examine their processes from beginning to end. There is always room for improvement, and newborn screening programs will continue to seek new advances in technology and methodology while looking to other scientists, clinicians and parents for input



Sigma Tau Pharmaceuticals is now Leadiant Biosciences

GAITHERSBURG, MD.--(BUSINESS WIRE)

Sigma-Tau Pharmaceuticals, Inc., a leader in the development and commercialization of medicines for patients with rare diseases, today announced that the company has changed its name to Leadiant Biosciences, Inc. reaffirming the company's continued strong commitment to the patient communities it serves.

The announcement coincides with Rare Disease Day 2017, a global campaign to raise awareness of rare diseases and improve access to available treatments and medical representation for people, and their caregivers, whose lives are impacted by these conditions. Now in its 10th year, Rare Disease Day is an annual celebration organized by the European Organization for Rare Diseases (EURORDIS) and the National Organization for Rare Disorders (NORD). This year's theme, With Research, Possibilities Are Limitless, underscores the importance of collaborative research in the drug-development process and recognizes the contributions of patients and families in advocating for increased investment in rare disease researh.

> *"Rare Disease Day is the perfect time to unveil our new name and reaffirm our commitment to the study of rare diseases, which has been an integral part of our heritage dating back to 1984 when we became only the fourth company in the world to receive an Orphan Drug Designation in the U.S."*
>
> *Michael Minarich*
> *Chief Executive Officer,*
> *Leadiant Biosciences, Inc.*

"In 2017, Leadiant Biosciences will realize several important and exciting milestones in our product pipeline, as well as continuing multiple ongoing clinical trials."

For more information about the vision, mission and work of Leadiant Biosciences, Inc. visit www.leadiant.com.

About Leadiant Biosciences, Inc.

Leadiant Biosciences, Inc. (formerly Sigma-Tau Pharmaceuticals, Inc.) is a U.S.-based, wholly owned subsidiary of Leadiant Biosciences S.p.A., a research-based pharmaceutical company dedicated to the development and commercialization of medicines for patients with rare diseases. Based in Gaithersburg, Maryland, Leadiant Biosciences, Inc. dedicates considerable scientific and financial resources to the research, development, and distribution of novel and effective therapies that address patient needs and improve quality of life. For more information, visit www.leadiant.com.

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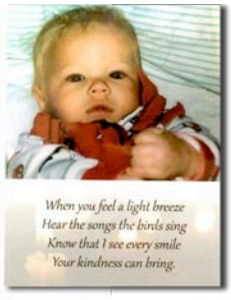

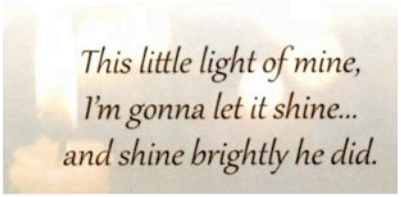

In MEMORIAM

Chad, Propionic Acidemia
May 17, 1993 - December 17, 2016

Twenty-three and a half years filled with joy! So much fun, heartache at times, days of sleep deprivation, medical knowledge and biochemistry I never had thought of. No regrets.

Chat was/is a precious gift to me and all who met him. Was his life cut short? It seems like it, but God is in control and I am so very thankful for 23 years with the most amazing person I have ever met. Blessed to be your mama my "little man." Shine on!

Organic Acidemia Association

9040 Duluth Street
Golden Valley, MN 55427

ANNUAL DONATION CHANGE OF ADDRESS

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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!

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Organic Acidemia Association (OAA) provides information and support to parents and professionals dealing with a set of inborn errors of metabolism collectively called organic acidemias. The OAA is a volunteer organization registered with the IRS as a 501(c)(3) non-profit corporation. Donations to the OAA are tax deductible. OAA publishes a newsletter three times a year, hosts a Google Group for information exchange and maintains a website and Facebook page. Services are funded by corporate & 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.

Find us on: facebook

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.

Google Groups

OAA Internet 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.