



Organic Acidemia Association  
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# Organic Acidemia Association Newsletter

P.O. Box 1008  
Pinole, CA 94564  
510-672-2476  
Fax 866-539-4060

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Carol Barton  
Executive Director  
Isovaleric Acidemia parent  
P.O. Box 1008  
Pinole, CA 94564  
Phone 510-672-2476  
carolbarton@oaanews.org

Kathy Stagni  
Administrative Director  
Propionic Acidemia parent  
13210 35<sup>th</sup> Avenue North  
Plymouth, MN 55441  
Phone 763-559-1797  
kstagni@oaanews.org

Jana Monaco  
Advocacy Liaison  
Isovaleric Acidemia parent  
3175 Ironhorse Dr.  
Woodbridge, VA, 22192  
Phone 703 497 1216  
jana.monaco@verizon.net

Cay Welch  
Glutaric Aciduria type 1 parent  
P.O. Box 427  
Ridgway, CO 81432  
970-316-1780  
cswelch1@verizon.net

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## SAVE THE DATE! July 2012 FOD/OAA Family Conference, Portland Oregon

We are pleased to announce that the OAA and FOD will hold our next joint conference in Portland Oregon, tentatively scheduled for July 20 and 21 of 2012. We've already started fundraising and the Oregon Health and Science University has responded with some very generous pledges as our Premier Sponsor. Thanks OHSU!

I'm sure that everyone who has attended a conference in the past has felt that it benefited them in many ways: to meet other families with the same disorder, the exchange of ideas between families, sampling the food displays, and the information gained from the presentations. I hope you all can plan ahead for this conference next year.

## Financial Statement

Thanks to the enduring support of our members, valued contributors, and with the support of key vendors, the OAA is again able to report solid financial results for calendar year 2010. During the year, we accepted donations that totaled \$57,346 of which \$14,903 was directed to research. The unrestricted contributions which we use to cover our operating expenses were \$4,827 higher than last year which helped cover the cost of the national conference that we held in Atlanta.

As is typical when we hold a national conference, our operating expenses increase dramatically. During 2010 the Atlanta conference drove up our expenses by \$25,157 over those in 2009. We also made grants to Angels for Alyssa (formerly the MMA Research Fund) and the National Kidney Foundation. We ended the year with a healthy fund reserve totaling \$33,965 which will help us prepare for the 2012 conference and ensure the continued availability of the valuable services that we offer to our large and growing OAA family.

<b>OPENING FUND BALANCE</b>		\$26,597
OAA Operating Fund		\$19,131
Research Funds		\$7,466
<b>CURRENT YEAR CONTRIBUTIONS</b>		\$57,346
OAA unrestricted contributions		\$42,443
Research directed contributions		\$14,903
<b>OAA OPERATING EXPENSES</b>		\$40,953
Accounting services		\$1,700
Conferences, conventions, meetings		\$31,281
Printing		\$2,899
Postage and shipping		\$2,757
Internet		\$562
Other expenses		\$1,754
<b>RESEARCH GRANT EXPENSE</b>		\$9,025
Angels for Alyssa (formerly MMA Research Fund)		\$9,000
National Kidney Foundation		\$25
<b>ENDING FUND BALANCE</b>		\$33,965
OAA Operating Fund		\$20,621
Research Funds		\$13,344

## Medical Advisors

Dr. Olaf Bodamer FACMG  
Biochemical Genetics  
University of Miami  
P.O. Box 019132 (M-860)  
Miami, FL 33101

Stephen Cederbaum, MD  
Mental Retardation Research Ctr./NPI  
635 Charles E. Young Dr.  
South Rm 347  
Los Angeles, CA 90095-7332

Carla Cuthbert, PhD  
Newborn Screening Division  
Center for Disease Control  
Atlanta, GA

Richard Hillman, MD  
Univ of Missouri Health Sciences Ctr  
G-1 Metabolism Clinic  
Department of Child Health  
1 Hospital Drive  
Columbia MO 65212

Elaina Jurecki, MS, RD  
BioMarin Pharmaceutical Inc.  
105 Digital Drive  
Novato, CA 94949

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

Dr. Seymour Packman, MD  
Dept of Pediatrics, Box 0748  
Univ of California, San Francisco  
San Francisco CA 94143-0748

Piero Rinaldo, MD, PhD  
Biochemical Genetics Laboratory  
Department of Laboratory Medicine  
Mayo Clinic  
200 First Street SW  
Rochester MN 55905

Mendel Tuchman, MD  
Professor of Pediatrics, Biochemistry &  
Molecular Biology  
Children's National Medical Center  
111 Michigan Avenue, NW  
Washington, DC 20010-2970

Keiko Ueda, MPH, RD, LDN  
Metabolic Dietitian  
Dept. of Pediatrics/Division of Metabolism  
Floating Hospital for Children  
New England Medical Center  
750 Washington Street, NEMC#434  
Boston, MA 02111

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

Jerry Vockley, MD, PhD  
Professor of Human Genetics & Pediatrics  
Chief of Medical Genetics  
Children's Hospital of Pittsburgh  
3705 Fifth Avenue  
Pittsburgh, PA 15213

Dr. Susan Winter, MD  
Valley Children's Hospital  
9300 Valley Children's Place  
C/O Medical Genetics/Metabolism SE11  
Madera, CA 93638

Arthur B. Zinn, MD, PhD  
Center for Human Genetics  
CWRU/University Hospitals of Cleveland  
11100 Euclid Avenue  
Cleveland, Ohio 44106

## Metabolic Outreach Service (MOS)

The MOS has been very active. In March, I provided a 2-day set of workshops in Israel about metabolic diseases, originally directed to pediatric neurologists. However, as time went on and the conference was advertised, pediatricians and geneticists and pediatric house-staff also registered. The conference was sponsored by Assaf Harofeh Medical Center outside of Tel Aviv in conjunction with the Israeli Metabolic Society.

This was a very valuable opportunity for me since I believe such learning experiences can be helpful in getting general and subspecialty physicians to think more about the organic acidemias. I wanted to see what kind of response such a conference would elicit. The conference was a success; 160 people attended and the evaluations are very positive.

During the conference I delivered the following lectures -

- Metabolic approach to encephalopathy
- Newborn screening
- Metabolic approach to lactic acidemia
- Metabolic approach to stroke
- Psychiatric phenotypes in metabolic disease
- Metabolic approach to neonatal seizures and hypotonia
- Elevated CK: A metabolic clue

The workshops were all case-based, interactive, and highly clinical and practical. The majority included some algorithm or set of specific questions to ask to help work through the challenge posed by the lecture topic. Six of them included discussion of the organic acidemias, their detection, diagnosis, and/or management.

The MOS is a diversified educational program that seeks to increase awareness among medical professionals and trainees, as well as encourage an interest in metabolic medicine among medical students. We provide:

- Educational workshops to general and subspecialty physicians and medical students, in a variety of settings
- Patient-As-Teacher Project, scheduling patient forums in which medical audiences hear patients and/or parents speak about their life experiences
- Metabolic Supervision Service, providing high-quality clinical supervision to medical and nutrition professionals without metabolic training who are taking care of patients with organic acidemias

The Organic Acidemia Association is a co-sponsor of the Metabolic Outreach Service.

Mark S. Korson, MD  
Tufts University School of Medicine

## The Inborn Errors of Metabolism (IBEM) Collaborative

Metabolic clinicians in the Region 4 Collaborative (Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin) and colleagues in six other states (New Jersey, Pennsylvania, New York, Missouri, Oklahoma, and South Dakota) recently learned that they have received a five-year grant from the National Institutes of Health to study long-term outcomes for children affected with conditions identified by newborn blood spot screening. Directed by Principal Investigators Cynthia Cameron and Susan Berry, this grant support provides exciting new opportunities for improving outcomes for children identified by newborn blood spot screening (NBS). All of these states screen newborns using tandem mass spectrometry (MS/MS) to identify rare, serious IBEM including organic acidemias.

While long-term follow-up is critical for monitoring health outcomes and evaluating the effectiveness of newborn screening, standards of clinical care for screened conditions have never been subjected to evidence-based study. More information about outcomes for these disorders is essential to a better understanding of the natural history of the conditions and development of best practice models for treatment. The grant allows collection of information about the health outcomes, complications, and life progress of persons that have conditions identifiable by NBS.

This grant provides funding to continue work initiated by the Region 4 Genetics Collaborative Priority 2 Project Workgroup that began building an IBEM Information System with support from the Health Resources and Services Administration (HRSA) Maternal Child Health Bureau Genetic Services Branch. More than 300 persons have already agreed to participation in the project and have allowed collection of ongoing information about the rare IBEM affecting an individual in their family.

With the receipt of this grant, additional families who attend clinics guided by participants in this research will be invited to participate. Participation consists of allowing the site investigators and their team to abstract information about the progress and medical needs of the affected person. Information is stored in a secure, password-protected database; identifiable information about individual persons enrolled in the project is available only to the site investigator responsible for the individual enrolled. Privacy is carefully protected; information about individual participants will be examined in aggregate so that participating centers can accrue information about these rare conditions.

Over time, we hope that the data collected in this project will build the foundation for evidence-based medical practice and care for rare disorders ascertained through NBS because they will provide data to support treatment decisions based on larger cohorts of affected children than can be seen by any individual practitioner or specialty center. With the collaboration of multiple centers over time, a dynamic, longitudinal database will have the power to provide a foundation for evidence-based medical practice and care for rare disorders ascertained through newborn screening.

Our concept is that by developing a core series of agreed-upon strategies that examination of the differences in treatment plans may yield evidence about optimal treatment choices. Further, if families agree, participation in the project provides a point of contact for other research activities and a means to facilitate data collection about those related research activities. We hope to extend our efforts to collaboration with other researchers interested in new strategies for improvement in care for affected persons. We hope this research project will help both clinicians and researchers learn more about the real lives and outcomes of people who have these conditions.

For more information, please see <http://region4genetics.org/>

Or contact:  
Michigan Public Health Institute  
Cynthia Cameron, Principal Investigator  
Director of Systems Reform  
[ccameron@mphi.org](mailto:ccameron@mphi.org)

University of Minnesota  
Susan Berry, MD, Principal Investigator  
Department of Pediatrics  
[berry002@umn.edu](mailto:berry002@umn.edu)



*Dr. Susan Berry with IBEM Poster at ICIEM*

## Kristy Vos

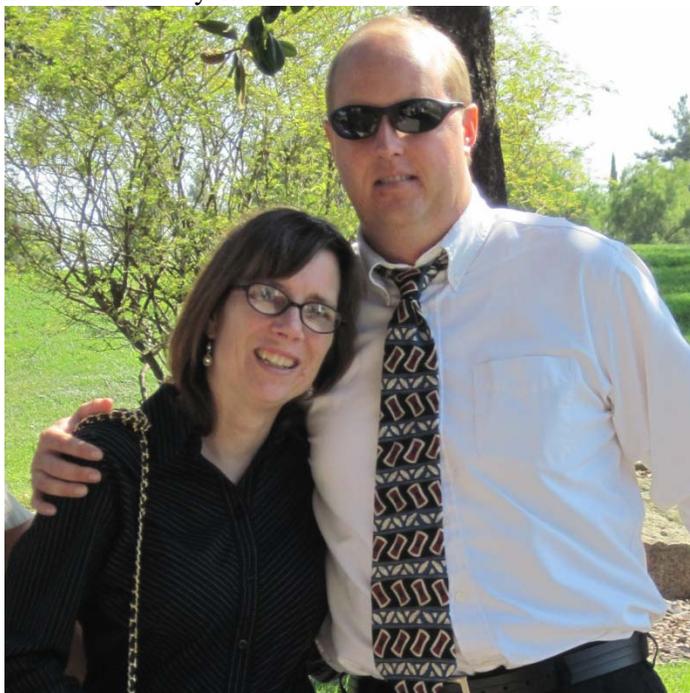
Propionic Acidemia, age 46

I just celebrated my 5<sup>th</sup> year as a Kidney Transplant Survivor. I was diagnosed with Polycystic Kidney Disease and on March 6<sup>th</sup>, 2007 had a successful transplant at Cedars-Sinai Medical Center with my husband as my donor. He wanted to be the first one tested even before I began dialysis and he was a perfect match! In May, we will also be celebrating our 10 Year Wedding Anniversary. I am very blessed to have him.

While the transplant was greatly successful, I have been suffering from numerous other problems such as Headaches, IBS, and other Unexplained Abdominal Issues. I had a Colonoscopy/ Endoscopy performed in January, 2011 which showed I have Melanosis in the Colon, LA Grade Acid Reflux Esophagitis and Acute Gastritis. I have also been in contact with Christina T. Lam M.D. a Clinical Fellow in Medical Genetics at U.C. L.A. who is doing a study on me to see if my Kidney Disease or even if the Early Menopause I've suffered may be due to my Propionic Acidemia.

I am so thankful to Kathy Stagni for putting up with and answering my seemingly endless questions as I work through my many medical issues and also to everyone that puts together the OAA Newsletter. There are times when it is really comforting to remember that we are not alone with our diseases.

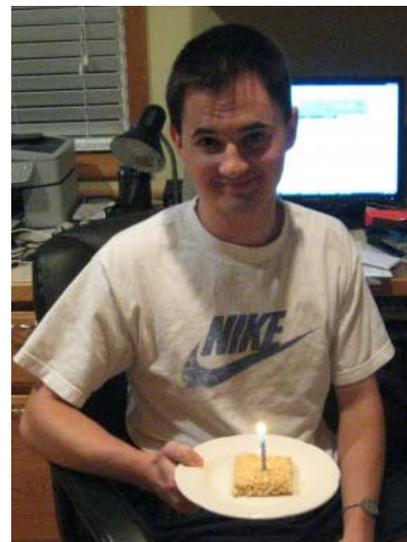
Kristy Vos (pictured below with husband)  
Cypress, CA.  
Luanimals64@yahoo.com



## Tyler Reimers

Methylmalonic Acidemia CblA, age 23

My name is Tyler Reimers. I am 23 years young. I was diagnosed with Methylmalonic Acidemia Cbl-A when I was 6 months old, after I had become very sick and fell into a coma. The coma only lasted a few days, and after a few rough patches of being sick, I am one of healthiest people I know. I am currently a junior at Portland State University. I take 2 classes/8 credit hours this spring term. I also work 21 hours (3, 7 hour days) a week at a retail store.



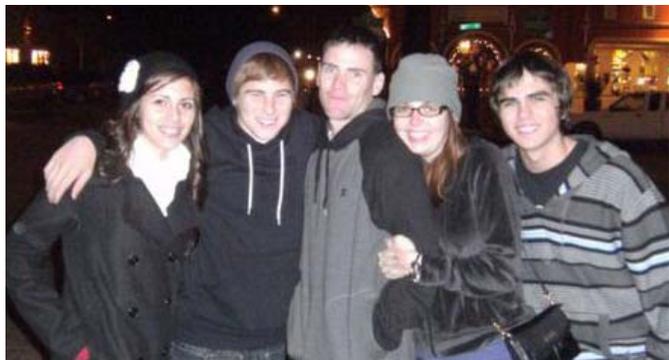
I am currently on low protein diet, though I do have some problems getting enough protein my dietitian recommends. When I was young, my parents made me special formula that I drank (2 or 3 times a day) to get my protein fill. I hated the formula and it was a chore to get me to drink it. I finally gave up on the formula after high school.

After high school, my mom suggested I drink carnation instant breakfast to replace the formula. I hated the instant breakfast and that maybe lasted 6 months or a year, off and on. After the carnation instant breakfast run, I just decided to eat more cheese pizza to keep up the protein intake. Up until a few months ago, the only high protein food I would eat on a regular basis (3 or 4 times a week) was the cheese pizza. My mom found this tasteless protein powder that you mix into some type of juice (I use no pulp orange juice). That has worked very well so far and it has been way better than the carnation instant breakfast and the formula. I drink it about 5 times a week in the mornings (when I have either work or school that day). I usually drink most of it, but the liquid does get a little chunky during the last ¼ of it.

I am very very picky eater. For meals, I usually eat french fries and hamburger buns or cheese pizza. I like different types of snacks, popcorn, cereals, cookies, vanilla ice cream, Popsicle, snow cone, and that's all I can come up with off the top of my head.

Find me on Facebook

**Kerrie Fessler** (pictured second in from the right)  
Propionic Acidemia, Age 27



My name is Kerrie Fessler; I live in North Carolina with my husband Mitch. We have been married since December of 09. My family back home includes my mom, dad, brother, 3 sisters, grand parents, aunts, uncles, the works and guess what, I am the only PA in the family.

I was first diagnosed around 10 months old. I was more sickly as a child but as I grew older the attacks became less. Currently I am supposed to be taking 8 teaspoons

of liquid carnitine a day. I can't really take a full dose at all as it makes me ill still. I take about 1/8-1/4 cup of formula and am suppose to take 1/2 cup a day. I take 80mg of inderal for cardiomyopathy (I was diagnosed early teens with that). The doctors are not sure if it was PA related or not.

I have about 30 grams of protein a day (non complex protein). I do remember when I was little and got sick that sugary drinks would help me kick ketones easier. A little extra dose of carnitine and soda does the trick. Hospital visits were usually from me getting a bug, then getting dehydrated which would kick up an acidotic attack. As I got older visits got less and less.

Now that I am back east I have noticed that the tolerance to carnitine is worse and makes me very nauseated (Zofran-is my new best friend it kicks the nausea/vomiting with no side effects). Drinking formula requires patience in finding something to mix with it. (kool-aid fruit punch-in a blue container). Is the only way I found that works and masks it.

chipmunk16666@yahoo.com

## Cambrooke Foods - Spring 2011



Cambrooke Foods has introduced low protein Pita Pockets. These pocket breads are great for vegetarian sandwiches because they are easy to fill and hold. Try cutting them horizontally in half and then into triangular pieces before baking into pita chips for dipping and snacking.

Try new Cozy Mornings Hot Cereal, made with real apples. This is a wholesome breakfast cereal that is quick and easy to prepare. It is fat and cholesterol free and provides 14 essential vitamins and minerals. It is a source of fiber and has 16 mg of omega 3 fatty acids per serving. Great for babies as a "first food" too, using half of suggested serving amount and preparation liquid. An addition to our ready-to-eat dessert line is Pumpkin Raisin Cookies. These are golden brown homemade cookies - with a pumpkin-spice taste. They are a perfect snack with a hot drink or an after-school treat. If you haven't had the Tweekz (imitation chicken nuggets) in a while, try them again because they now have 32 mg of DHA Omega 3 fatty acids per serving.



Cambrooke is launching Social Media sites this spring. Join your friends and the Cambrooke team on Facebook and Twitter for some friendly and informative dialogue sharing, plus tips and ideas for managing your disorder.

Cambrooke Foods, Inc. toll-free: (866) 4 LOW PRO / (866) 456-9776 fax: (978) 443-1318  
www.cambrookefoods.com orders@cambrookefoods.com

## It's a girl! Elizabeth Brooker

Isovaleric Acidemia, age 29

Beth (isovaleric acidemia, age 29) had a baby girl on Friday the 13<sup>th</sup> of May, measuring 8 lb 2 oz and 20-1/4" long. She is welcomed into the family by her 5 year old brother and 3 year old sister. For Beth, this was the smallest of her 3 babies and the labor and delivery went very well. She had no problems from her IVA although she had a D10 IV as a precaution. Beth found that her special formula and morning sickness didn't mix, so we commend her diligence taking it.



# Conference Report

## PA Consensus Conference

Washington, DC, January 28-30, 2011



This conference was organized by Genetics/Metabolism department of Children's National Medical Center for the purpose of bringing together medical professionals, researchers and support organizations with the goal of developing a consistent standard of care for those diagnosed with Propionic Acidemia. I was asked to attend this conference as a representative of the Organic Acidemia Association and a parent of a 22-year old with propionic acidemia.

Prior to the start of the conference, a SharePoint internet site was created where over 300 journal articles on PA were made available to attendees for pre-reading. Conference leader Dr. Marshall Summar and organizer Dr. Kimberly Chapman were able to plan and hold this conference quickly because of funding available from the ASHG (American Society of Human Genetics) conference that was held in Washington DC last November.

A "consensus" conference seeks to reach a consensus on diagnostic and therapeutic guidelines for Propionic Acidemia based on the most up-to-date information available augmented by the actual experience of experts in the field. The proceedings will be published in the widely read "Pub Med" for physicians to reference when treating a child with propionic acidemia. A similar conference for the urea cycle disorders was held in April of 2000 by Dr. Summar and Dr. Mendel Tuchman. You can read the report here: <http://rarediseasesnetwork.epi.usf.edu/ucdc/documents/Proceedings-UCD-2001.pdf>

For this PA Consensus conference, participants included physicians, researchers, and dieticians—all experts in their chosen field. In addition, representatives from two parent advocacy organizations were invited to participate in the conference.

Conference participants were assigned into one or more of the following "work groups" who will use the information collected during the conference to develop specific recommendations in their relevant discipline. The groups include; diagnostics, acute neonatal, natural history, chronic care and health monitoring, and future/therapeutics.

### Highlights from the sessions ...

Dietrich Matern from the Mayo Clinic discussed the diagnosis of Propionic Acidemia and gave an overview of the Mayo lab in Rochester, Minnesota. The group discussed the incidence of "false positive" test results and state laboratory *cut-off standards* for picking up PA.

Dr. Kimberly Chapman from Children's National Medical Center gave an overview of the acute and neonatal management of PA and included historic therapeutic references. The goal of this focus is to give direction to consulting pediatricians on how to care for a child with PA.

Dr. Loren Pena from the University of Illinois Medical Center at Chicago gave an update on the conditions that are often seen in patients with PA. She cited various journal articles that discussed various treatments for the disorder.

Dr. Reid Sutton from Baylor discussed chronic complications of PA as well as ongoing health monitoring. Dr. Sutton and others described how many medical facilities across the country are using different approaches in treating our kids.

Dr. Chuck Venditti from the National Institute of Health offered an overview on PA research, including the pathway details, and gave us other things that we should think about in correcting the different pathways in both PA and MMA. Liver transplants were discussed as well as current thinking on why this approach might, or might not, be recommended for various patients.

The second day of the conference consisted of a round-table discussion on treatment. Notes from this discussion will be divided by area of focus and forwarded to the various work groups noted above. These approaches will form the "consensus" statements in each discipline with the goal of providing guidance toward a preferred treatment for children and adults living with Propionic Acidemia.

The manuscripts resulting from this meeting's discussions will be submitted for publication in the Journal Molecular Genetics and Metabolism.

Kathy Stagni, Administrative Director, OAA

# Conference Report Society of Inherited Metabolic Disorders (SIMD)

Monterey, CA, Feb 27-March 2, 2011

The Organic Acidemia Association and the Fatty Acid Oxidation Disorders family support groups shared an exhibit table at the Society of Inherited Metabolic Disorders (SIMD) conference. This is the second time I've been able to attend this conference at the Asilomar Conference Grounds near Monterey California, and the third time I've met with this group.

The SIMD is an organization of professionals who deal with organic acidemias and other metabolic disorders. Most of our doctors and nutritionists are members of this group so this is a great opportunity to get to know them better and especially to promote our organizations. Valerie Fulton represented the FOD while I represented the OAA. We took turns attending sessions, mingling, and minding our display table.

## Sunday

After arriving on Sunday afternoon, I set up our display table. We had our quilt, pamphlets, newsletters, magnets, business cards, and "Belly Flops". These were Jelly Belly jelly beans with mutations (conjoined twins and other birth defects). Certain professionals had a lot of fun eating the mutated beans. At one point I came back to the display to find that all the mutated beans were gone and only perfect single beans remained.

After dinner on Sunday, we had three lectures. The first was on the "boot camp" that the SIMD gives to newly qualified doctors entering metabolic fellowship programs. The second was on lab chromatography training programs for the technicians. The third was about the Metabolic Outreach program by Dr. Korson (also presented at our 2011 conference in Atlanta and an update in this newsletter). During the third lecture I discovered that I had accidentally sat next to my daughter's new doctor and nutritionist, whom I had never met.

## Monday

The conference began in earnest on Monday. We started with five lectures on disorders of the carnitine cycle and fatty acid oxidation. After a break there were four lectures on medical foods. The most interesting to me was the one on glycomacropeptides (GMP), a byproduct of cheese manufacture that has no phenylalanine and tastes good. Unfortunately it does have large quantities of isoleucine and valine. Although it is now available for PKU patients, some professionals are wary about it

and are conducting long term studies to follow patients taking it instead of the traditional medical formula.

After lunch, we heard 15 presentations by the travel award winners. These are young researchers who are sometimes quite nervous to be speaking. There were two presentations by doctors from Dr. Venditti's lab at the NIH. One was on the outcome of MMA CblC patients and the other was on their continuing studies of genetherapy in mice.

That evening the exhibits and posters were open and we met with a lot of professionals, reminding them that we exist as a parent support organization.

## Tuesday

Tuesday morning the lectures were on disorders of folate, methionine, biotin, molybdenum, and homocysteine. The exhibits were open again in the afternoon, then the evening presentation was on the Undiagnosed Diseases Program at the NIH. To quote the abstract, "Since its inception in May of 2008, the (program) has reviewed more than 1300 medical records, seen over 280 patients, and made approximately 30 diagnoses, including some ultra-rare metabolic diseases... The program provides hope to a desperate population by offering access to comprehensive and coordinated specialty examinations and state-of-the-art genetic evaluations.

## Wednesday

The last day of the conference included lectures on clinical trials and registries. Trials are complicated by FDA regulations, the small patient population, and lack of funding.

## Posters

There were 118 poster abstracts listed in the conference program. The most interesting to me were:

\* The NIH Undiagnosed Diseases Program. They have identified patients with inborn errors of metabolism, amyloid myopathy, spinocerebellar ataxia, glycosylation disorder, adenosuccinate lyase deficiency, gangliosidosis, and other diseases.

\* Pancreatitis in Organic Acidemias. This is rare a complication of OAs but no correlation has been found as to clinical severity or cause.

\* Cardiomyopathy in Methylmalonic Acidemia. Cardiomyopathy has been identified in PA, but this poster described it being found in one MMA adult. The recommendation is that it should be considered as a potential complication.

(continued next page)

\* Gene Therapy in Propionic Acidemia. This poster repeated what was in our January 2011 newsletter. Using the same techniques as for the MMA mice, gene therapy was effective in PA mice.

\* PA Cells Have Abnormal Krebs Cycle Expression. Patients with PA have signs of energy deficiency and the cells demonstrated decreased gene expression in the Krebs cycle

\* Pregnancy and CblC deficiency. A case study of a woman diagnosed with CblC deficiency after two miscarriages. She had elevated Hcy and MMA but no evidence of protein aversion, visual, or neurologic issues.

\* Short Term Followup for Abnormal NBS Results.

\* Newborn Screening Results Reporting. Both these posters show differences between the state screening programs. The primary physician is contacted by phone, fax, or mail and occasionally a letter is also sent to the parents.

\* MMA and Optic Nerve Atrophy. This poster was affiliated with the NIH MMA study. Five male patients (out of 58) exhibited optic nerve atrophy. There were no apparent triggers like metabolic crisis. One of these patients was an adult who experienced acute visual impairment, which was reversed by antioxidant therapy (coQ10, E, ascorbic acid, thiamine, and N-acetylcysteine).

\* Two Siblings with Cobalamin E deficiency. Despite prenatal diagnosis and treatment in the second sibling, the two children show similar learning disabilities and challenges.

\* Inborn Errors of Metabolism in Adults. This poster describes a survey of positive results between 2000 and 2009 in 205 patients over 60 years of age. Of those 205, 3 had an FOD, 3 had homocystinuria, 3 were found to have PKU.

\* Nutritional Therapies in IEMs

\* Nutritional Guidelines in MSUD.

\* Nutritional Guidelines in PA. All three of these posters report on the progress of different groups in creating treatment guidelines.

\* Bone Density in Treated PKU Patients. PKU patients are at greater risk of osteopenia and osteoporosis. This poster discussed the effect of the new PKU treatment (Kuvan) on bone density. Despite the new treatment and a more liberal protein diet, there didn't seem to be an improvement in density.

\* Renal Failure and Early Menopause in a PA Adult. As the treated OA population ages, this poster discussed possible long term organ failure complications in PA, MMA, and other OAs.

\* Different Clinical Phenotypes in Siblings with 3MGA. Different presentations and symptoms in two children in the same family, with the same disease.

\* Genetic Disorders and Mistaken Diagnoses of Child Neglect or Abuse. Presented by a specialist working in Amish Pennsylvania, where newborn screening has been going on for decades due to a higher than average incidence of genetic errors: "Even within our small group with well-characterized genetic risks, Child Abuse Teams from regional medical centers have mistaken genetic syndromes for shaken baby, medical neglect, and SIDS".

\* Long Term Follow-up of a Patient with CobalaminG. This boy developed kidney issues and multisystem damage despite early diagnosis and treatment.

\* Renal Disease in MMA. Half the MMA patients reported in this French study developed renal disease and many had transplants.

Carol Barton  
Executive Director, OAA

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## 2011 OAA Shirts Available Now!!

Café Press has a large selection of items available with the OAA calendar cover printed on them. They carry long and short sleeve shirts, tees, sweat shirts, bags, ornaments, license plate holders, toys, mugs, magnets... and calendars galore. Be sure to check out the pictures on the insides, too.  
<http://www.cafepress.com/organicacidemia>



# Conference Report

## Genetic Diseases of Children – Advancing Research and Care

New York, March 8-9, 2011

The Department of Health of the state of New York organized this fantastic meeting (New York, March 8-9, 2011) that brought together physicians, researchers, government agencies (including Medicaid), advocacy groups and patients to discuss the current issues in the diagnosis, management and research of genetic diseases of children. A very strong emphasis was placed on rare disorders. The meeting was divided into 5 big topics including: reaching early diagnosis, sharing family experiences and optimizing care and coordination of services to meeting the needs of children living with a genetic disorder and accelerating research. Unfortunately, all the topics were discussed at the same time so it was only possible for me to attend a very small portion of the meeting. I have focused this small summary on two areas: new technologies for treatment and new research initiatives for therapy. I felt it was important to learn about how organic acidemias and other rare disorders are perceived by the funding and research agencies. For those of you who would like to know more on other issues, I will be happy to share information about panelists and discussion topics.

Throughout the meeting, two major ideas helped to summarize the current view of the field of genetic diseases. The first idea, “Whole Genome/exome sequencing for diagnosis: Are we there yet?” focused on the implications of the rapid advances in the field of genetic analysis. Is medicine ready to diagnose based on sequencing the entire genome of a patient? Have we finally come to the age of “genomic medicine”?

Individualized medicine is starting to take shape for many common diseases like cardiovascular or diabetes because we have come to realize that one size doesn't fit it all patients, and we want to know, for example, why some medications are so effective in some patients but not in others. The genetic diseases our children suffer are not any different. As we all know, many of the disorders manifest with multiple symptoms and even with a prenatal or newborn screening, it may sometimes take years to reach correct diagnoses, if any. And even with one clear diagnosis, we always say how similar our children look and yet how different they are!

The very complex picture that we see in our children becomes often an impossible puzzle to solve. Whole-genome analysis can provide the solution to this problem because it rapidly analyzes the millions of bases that our

DNA is composed of. So, instead of making decisions based on population analysis (i.e. based on what is most frequently seen in clinic), doctors will be able to take the next step taking into account the nature of our unique DNA. Many questions arise, as always, with this very promising new technology. Genome-sequencing techniques have improved dramatically in the past 5 years, and the cost is reaching affordable levels. However, there is still need for professionals able to interpret the enormous amount of data that are now being generated; we have now all these data, what do we do with them? How easy will it be to distinguish “signal” from “noise”? Our genomes carry as many as 3.5 million variants (called SNPs) that do not mean disease. The databases have inherent errors themselves and we still don't understand very well when it is useful to do whole genome analysis versus just a panel of 10 genes we think are related to the disease. Lastly, we must never forget that, despite much lower cost, there is always the never-ending obstacle of insurance coverage and, at the moment, the \$15-20K that sequencing a genome costs is still out of reach for the vast majority of families. We certainly need to work on these issues if we want to embrace this very powerful technology.

Second, what is the National Institutes of Health (NIH) doing to facilitate advancements in the field? Is the NIH aware of patients' concerns when it comes down to shaping initiatives that lead to new therapies for complex and rare genetic diseases? The NIH has made a proposal to sequence the genome for every single mendelian disease (a mendelian disease follows the pattern of inheritance of recessive/dominant. In the recessive case, if the two parents have the mutation, the child has 25% probability to inherit the disorder. Anything else that doesn't follow this pattern is known as “non-mendelian”). This approach aims to capture all the variation that exists for each of these diseases and tries to understand disease beyond what we know (can genome variability provide clues about disease variability?).

The Therapeutics for Rare and Neglected Diseases Program (TRND), as part of the new NIH Center for Translational Therapeutics (NCTT), is also a new effort to speed the development of new drugs for rare and neglected diseases. This program aims to bridge the gap between high-risk products (like the drugs destined to small populations of patients like our children) and the pharmaceutical industry. Once basic research has identified a drug target, this program aids in producing new chemicals and methods for screening and assay development.

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There is also room for a patient representative program where a patient representative can apply to sit in a committee and vote in the Food and Drug Administration (FDA) advisory committee meetings. (The FDA is the agency that makes decisions on what new drugs are safe and effective enough to be approved for human use.) A patients' testimonials page is also included. Unfortunately, incoming budget cuts are sure to hamper many of these initiatives.

Despite the "good will" behind all these programs and the excitement they generate, we, the families, must face the reality that, currently, an average 75% of the funds generated to find a cure for one disorder comes from advocacy/patient organizations. In the discussion panels, it was interesting to hear what advocacy groups are doing to accelerate research. Each organization has developed its own protocol: from the one-family effort to raise one million dollars/year to donate to scientists who want to focus on one particular goal (for example, Hanna's Hope Fund) to creating for-profit companies that establish health data-sharing platforms that empower patients manage their own conditions and change the way industry conducts research (for example, PatientsLikeMe, a data-sharing platform where patients can benefit from information generated from other patients, doctors, pharmaceutical companies, researchers and healthcare industry).

Given how small the patient population of some disorders can be, the establishment of more sample repositories as a unique means to accelerate research is also a priority. Biobanking is crucial, but concepts like "privacy" (deciding who will have access to what aspects of our medical history) and "consent" (giving permission for the use of our medical records) are still an issue.

We also have to face the fact that it is still a big challenge to recruit and train young investigators and physicians in the field of genetic diseases because of the lack of incentives. More visibility for rare diseases and funding grants for young investigators were some of the issues that were discussed.

Lastly, some exciting news came from the cellular-approaches panel. Gene delivery is now successful in some disorders (for example, mucopolysaccharidosis) and stem-cell research is a reality in some fields, like dermatology.

Marisa Cotrina, mom to Gabriel, PA

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## California Informal Picnic:

Tilden Park Little Farm, Berkeley, CA May 29 at noon

# Phase 2 Clinical Trial of Ataluren (PTC124®) in Nonsense Mutation Methylmalonic Acidemia: Frequently Asked Questions

by PTC Therapeutics

*(OAA provides this as information only and does not recommend nor endorse this product).*

Q1: What is a nonsense mutation?

A: A nonsense mutation is a premature stop signal in the genetic code that interrupts the body's production of an essential protein. Proteins are essential to the proper working of every cell in the body and they can take many forms, including antibodies, hormones and enzymes. When production of a protein is interrupted by a nonsense mutation, the protein that is created does not function properly and this in turn causes a disease or disorder. The disease caused by the nonsense mutation depends on which protein is incompletely formed.

Methylmalonic academia (MMA) is a rare genetic disorder caused by inadequate levels of the enzyme methylmalonyl-CoA mutase or the cofactor adenosylcobalamin, which causes toxic levels of methylmalonic acid (MMacid) to build up in blood, urine, and other tissues. In MMA caused by a nonsense mutation (nmMMA), production of these enzymes is halted prematurely. It is estimated that nonsense mutations are the basis for the disease in 10 to 15 percent of MMA patients.

Q2: What is ataluren (formerly called PTC124®)?

A: Ataluren is an investigational (experimental) new drug, which means it is being tested as a potential treatment and it has not yet been approved for use by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) or any other regulatory authority. Ataluren is the first potential therapy designed to enable the formation of a functioning protein in a patient with a genetic disorder due to a nonsense mutation. It is taken orally and has the potential to treat the root cause of the disease by overriding the premature stop signal, so that a functional protein can be formed in a patient who has a disease due to a nonsense mutation. In other words, it seems to allow the body to overcome the genetic problem that caused the disorder. Ataluren does not alter a patient's genetic code or introduce genetic materials into the body. In methylmalonic acidemia it may allow production of functioning methylmalonyl CoA mutase and adenosylcobalamin, and thus has the potential to address the underlying cause of the disease. Additional information about ataluren is available at [www.ptcbio.com/ataluren](http://www.ptcbio.com/ataluren).

Q3: What is known about the safety of ataluren?

A: Ataluren has been studied in a variety of clinical trials in healthy volunteers and in patients. For example, it was given to 38 patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) in a Phase 2a trial and it was generally  
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well tolerated. In a Phase 2b pivotal study of 174 boys and young men with nonsense mutation Duchenne and Becker muscular dystrophy (nmDBMD), participants were divided into three groups and received one of two doses of ataluren or placebo for 48 weeks. This trial has been completed and safety data shows that ataluren was well tolerated and no participants discontinued treatment due to an adverse event.

Ataluren was also generally well tolerated by 77 patients with nonsense mutation cystic fibrosis (nmCF) who participated in Phase 2a studies. Adverse events were infrequent and usually mild to moderate in severity. A few patients sometimes had mild burning with urination but this did not result in therapy being interrupted or discontinued. There were no safety concerns based on physical examinations, vital sign measurements, electrocardiograms, or laboratory test results. Based on these results, a Phase 3 double blinded, placebo controlled study of nonsense mutation CF is currently enrolling 208 patients who will each receive ataluren or a placebo for 48 weeks. In this study, a decrease in kidney function has been seen in some patients, in particular when the patients are given intravenous antibiotics called aminoglycosides (for example, tobramycin or gentamicin). These antibiotics have been sometimes known to cause injury to the kidneys. In some cases, therapy was interrupted or discontinued and kidney function returned to normal. Patients were able to restart therapy and their kidney function remained normal.

Q 4: What is known about the efficacy of ataluren?

A: Across the Phase 2a studies in nmDMD and nmCF, ataluren demonstrated activity in that patients treated with ataluren made the missing protein and the protein was localized to the proper location in the cell.

Results of the completed Phase 2b study of 174 boys and young men with nmDBMD show that ataluren slows the loss of walking ability. The primary efficacy measure was 6-minute walk distance (6MWD), a determination of the meters walked by each participant in 6 minutes, as measured periodically throughout the trial. When compared with results in the placebo group after 48 weeks, the mean distance walked by patients treated with ataluren (at a dose of 10 mg/kg morning, 10 mg/kg midday, 20 mg/kg evening) was longer by 29.7 meters (about 97 feet).

Another measure of efficacy indicated that patients receiving ataluren also experienced significantly slower disease progression. By the end of the study, the disease had progressed, defined as persistent 10% worsening in 6MWD, in 44% of patients who received the placebo, compared to only 26% of the patients who received ataluren (at 10 mg/kg morning, 10 mg/kg midday, 20 mg/kg evening).

Q5: What are the goals of the Phase 2 MMA trial of ataluren?

A: This study will evaluate the safety and activity of ataluren in patients with methylmalonic acidemia due to a nonsense mutation. Its main goals are to understand whether ataluren can be tolerated and can decrease MMacid levels.

Q6: Who will be eligible to participate in the trial?

A: To be considered for this trial, patients must be at least 2 years of age, have evidence of MMA based on the presence of characteristic clinical symptoms or signs and an elevated plasma MMacid level (greater than 0.27  $\mu\text{mol/L}$ ), have documented presence of a nonsense mutation in at least one part of the mut, cblA, or cblB gene, and a glomerular filtration rate greater than or equal to 30 mL/min/1.73 m<sup>2</sup>. Additional inclusion and exclusion criteria are listed on [clinicaltrials.gov](http://clinicaltrials.gov) at <http://clinicaltrials.gov/ct2/show/NCT01141075> and will be explained in detail at the trial research centers.

Q7: Where is the trial being conducted and how long will it be accepting patients?

A: The trial will be conducted at ten sites in France, Belgium, Germany, Italy, Switzerland and the United Kingdom. As each site opens, contact information will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and on the clinical trials section of the PTC website, [www.ptcbio.com](http://www.ptcbio.com).

The trial will continue enrolling new patients until the necessary number of participants, (approximately 18) has been reached. The sooner patients enroll in the trial, the faster the trial can be completed, and the sooner the results can be known.

Q8: What will participation in the trial involve?

A: All participants will receive the investigational drug ataluren, a vanilla-flavored powder supplied in an aluminum foil packet. Ataluren is mixed in water and taken by mouth three times a day (at morning, midday, and evening). The amount of drug will be determined by the patient's body weight at the start of the study.

As with some earlier studies of ataluren, two dose levels will be tested, in this case sequentially. This will be done in two four-week cycles, with a break of three weeks in between. Including an initial two-week screening period and a two-week follow-up period, the trial will last approximately 15 weeks for each participant.

Patients will be required to visit the trial site or local laboratory at least weekly during the study. During the visits, participants will provide blood and urine samples for various laboratory tests, including MMacid levels, to evaluate the effects and safety of the drug. They may also be asked questions about their experience in the study.

Q9: Will there be any cost to participate in the trial?

A: All costs of physical examinations, screening assessments, and laboratory and other trial related tests, as well as the cost of the drug, are covered by PTC Therapeutics, the U.S.-based company that makes ataluren.



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Organic Acidemia Association  
13210 - 35<sup>th</sup> Avenue North  
Plymouth, MN 55441

The 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 3 times a year, hosts a Google Group for information exchange and maintains a website. Services are funded by corporation & individual membership 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.

**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 OAA Google Group. Visit the OAAnews.org web site to sign up. This is a private list not open to the general public (but you never know who may be "lurking").



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\* Articles are ALWAYS needed for the newsletter.