

Editorial - Metabolic Conference set for March 18th

The time has finally come! I've been promoting the upcoming New England Connection & Allied Disorders Metabolic Conference for over a year now. I've heard from several families that have booked their flights and are planning to come to Boston in March for this conference. Conference registration forms were mailed out in late January and if you would like to attend and did not receive one, please let me know. If you completed a questionnaire form and have a child with a metabolic disorder, you should have received the conference information. The conference is planned for Saturday, March 18th at the Holiday Inn in Taunton, Massachusetts, a suburb of Boston. This conference is planned mainly for the families of Organic Acidemias, Homocystinuria, and PKU. This is the first year that the OAA has joined forces and has actively promoted this conference to our families. As many of you know, there aren't many conferences available that cover metabolic issues, and with our budget, aren't able to hold a conference on our own. To summarize the agenda, the morning will consist of breakout sessions and the OAA will have Dr. Ampola, Dr. Koch and Dr. Roe take turns to speak to our families on an informal basis. Lunch is provided in your \$25/per person conference fee (they do plan low protein entrees). The afternoon will consist of various speakers, with Dr. Roe again speaking on newborn screening. There are also a wide variety of vendors that will be attending, such as low protein food companies and formula companies, which will provide much information and samples. If you arrive on Friday, March 17th, there is a family gathering/meeting at the hotel. This is the best part of attending a conference to be able to meet and connect with other families that you've communicated with over the years. I hope to see you all in March!

Gene Therapy Trial Halted

(Explanation from the National Urea Cycle Disorders Foundation NUCDF)

The Phase I Gene Therapy for OTC Deficiency has been halted pending the determination of the cause of the unexpected and shocking death of a young man who was to be the final participant needed to complete the study in order to move on to Phase II.

Jesse Gelsinger, an 18-year-old young man with OTC deficiency died on September 17, 1999, while participating in the gene therapy trial at PENN. Jesse was the 18th participant in the study, and received the same infusion dosage as the previous participant, a 19-year-old woman who experienced no ill-effects and showed a 50% increase in her ability to excrete ammonia.

Jesse received the gene therapy on September 13, and experienced the expected initial flu-like reaction which had been documented in other participants. In the days following the infusion, he began to become jaundiced and his organs systematically began to fail. He was placed on hemodialysis and ECMO in an effort to stabilize him, but despite medical interventions he slipped into a coma. Studies revealed decreased blood flow to Jesse's brain, and with his family's consent, he was removed from life support. He passed away on September 17.

Jesse's family allowed an autopsy to be performed in an effort to determine the exact cause of Jesse's death. Preliminary results should be available in two weeks, and the researchers at PENN have said they expect definitive answers within four weeks.

According to Jesse's father, he had long been interested in participating in the gene therapy study, and saw his participation as a way of furthering research into the potential cure that would help newborn children and others like himself with OTC deficiency. His father also said, "He lived for today, because he knew about his illness," and that he lived with the hope for a cure. Jesse had flown to PENN on September 9 for the three day extensive battery of tests before the gene therapy was administered. His father said Jesse was very excited about the trials. "He knew it's the only way to come up with a cure."

We are all devastated at Jesse's loss. He is a hero. We will never forget him or let his death be in vain. We will continue our fight against this disease until our dream and Jesse's dream of a cure is a reality.

(You can read more about this gene therapy trial on NUCDF's website at <http://www.nucdf.org/>)

Cambrooke Foods Announces New Lo-Protein Products

Boston, MA

Driven by the minimal choices available to her son and daughter with PKU, Lynn Paoella has developed a unique line of lo-protein food products soon to be available nationwide. "While I'm grateful to the companies that provide the products to keep our families and community healthy, I've been frustrated by the slim selection, high prices, and bland taste of many low protein food products," explains Lynn Paoella, founder of Cambrooke Foods.

Cambrooke Foods begins shipping their first products, a line of fresh Bagels, Pizza Crusts and Energy Bars, in early 2000. More products will follow, including soups, Freezer-ready dinners, Meat Substitutes, and staples. "It's been very exciting working with food chemists and distributors who have shown me their roadmap to this industry. So much more is possible, given some time and ingenuity."

Lynn expects to develop Cambrooke's offering by enticing the best health food producers to give some of their production time to help the special needs and metabolic diet. So far her hard work is paying off with a new agreement from a national distributor to produce a low-protein bread to her specifications. "There is real satisfaction in knowing that our kids enjoy eating enough to fill their stomachs. Every mother with a PKU child knows the pain of her child going to bed hungry for lack of satisfying food. We're working to make that a thing of the past."

Before bringing these first products to market, Cambrooke Foods received valuable feedback from clinics and conferences from around the country, including over 300 responses were received from the PKU list server indicating your product preferences.

All of their foods are produced in commercial kitchens, analyzed for nutritional and amino acid content and maintain the strictest quality control throughout the production and distribution chain.

You can learn more about Cambrooke Foods, their products and partnership opportunities by visiting their website at www.cambrookefoods.com, or telephone, 508-650-1640.

Gabriele Salvetti

Methylmalonic Acidemia (MMA), Age 8



Gabriele, MMA with his mother, Moncheri Enrica, in Italy.

It is always difficult to tell the story of a sick child.

Gabriele was affected by MMA (Methylmalonic aciduria mut 0), a very rare disease difficult to keep under control. In most patients the metabolic balance is in fact unstable and precarious; most of them need a NG tube to be fed because they tend to refuse food. In fact the Methylmalonic acid, the dangerous substance that organs and tissues of the body secrete, often brings anorexia. All we know is that there is no therapy except for a low protein diet.

Gabriele spent his first eight years of life alternating periods of relative health to longer and longer periods of metabolic unbalance. I can't describe my anguish during these years, as well as my need to help him and better the quality of his life. For years I tried to know everything about this disease. I tried to find an alternative to the diet, in case it should not work anymore. Information was often contradictory and didn't suggest anything other than the diet and those few drugs I already knew. Information about transplants was few and discouraging. His doctors were skeptical and considered a liver transplant as a possibility only in case of life danger. I remember I was frantic during those long months when Gabriele's conditions were worsening and there wasn't any other therapy but the diet. I remember my short stays at home surfing the net trying to find something to help my child. Lots of people emailed me, unknown people offering help and giving me advice and comfort.

Gabriele's condition worsened at the end of February. His doctors made their best effort to rescue him from that pit he was falling into. They tried dialysis first, and then a central line I.V. in the chest and a NG tube to feed him. In the end they surrendered to intensive care. From that moment it was evident that he needed a new liver, and a frantic search for a compatible one started.

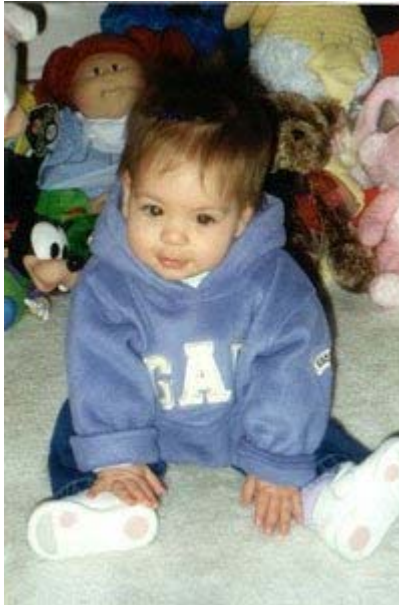
The story has a happy ending, luckily. Gabriele did it. Today he has a new liver and can eat everything he wants. He doesn't need the NG tube and the IV line; he can go to school like his friends and lead a normal life.

I hope Gabriele's experience will give hope to all those parents who are torn by doubts and are uncertain about their children's future. It is still possible to better MMA children's life. We can and we must, but what we need is to pluck up courage, have faith in life and don't give away to despair. We must believe in parents' associations, co-operate, give our own contribution, but most of all we must embrace each other, because only love can perform miracles.

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Bianca Franchi

Propionic Acidemia (PA), Age 11 months



Bianca Franchi, March 15, 1999, 6lbs. 4ozs

Bianca was a full term baby. There were no complications through my pregnancy or through labor. She was delivered in three hours and to our pediatrician's knowledge was a very healthy little girl. There were a few concerns Tony and I had. Bianca did not accept breast-feeding, and slept a lot for the few days we were in the hospital. She only had about 15cc's of Similac. She didn't seem to be wetting diapers, but we were told this was all normal.

On March 18, 1999, three days later, we were discharged from Milford Hospital. When we arrived home, I tried to feed Bianca several times, but had no luck. All she wanted to do was sleep. By dinnertime we were getting more concerned that Bianca was not wetting diapers, or wanting to eat. I telephoned the pediatrician we had chosen. The nurse practitioner explained she was too cozy, to undress her, put

cold wash cloths on her feet and she would be alert enough to eat. We tried all the different techniques and nothing seemed to wake Bianca, or stimulate her to eat. The nurse explained that the office was closing and Bianca should be all right until the morning. They had Bianca scheduled first thing. I then explained to the nurse that Bianca was looking lethargic, she was breathing funny and I thought she was sick. I was advised by her to bring her in the morning, and if I was really concerned to bring her to the local ER. I decided to contact the pediatrician who examined Bianca in Milford Hospital where she was born. The doctor told me to bring her into his office right away. When we arrived, we tried feeding her; she still wouldn't accept a feeding. Her body temperature was 94 degrees and she was lethargic. The pediatrician advised us to bring her to the ER, where they wanted to make her stable. There were several tubes of blood that was drawn and tests that were done. At about 10:00pm the pediatrician advised that she be sent to Yale PICU. The ambulance then transported her to Yale. Bianca was in a traumatic state. Her ammonia was 219, and she had to be intubated. Bianca was using all her energy to breathe. At this point we didn't know what was going to happen but we couldn't help thinking of the worst.

On March 19 we were introduced to Dr. Margretta Seashore, the director of Yale's Genetic Department who explained they might have a diagnosis for Bianca. They introduced us to Propionic Acidemia. We were not expecting anything of this magnitude. Tony and I were stunned to say the least.

After learning more about this disorder, it got easier for us to deal with it as every day passed. Bianca was hospitalized a few times after her initial stay. It was most of the time due to high blood ammonia levels (120). Sometimes we were there for a week straight. There was a lot of guilt felt on our behalf.

Bianca's eating habits were fine in the beginning, but as time passed her eating habits deteriorated. At this point we had the G-Tube placed in Bianca and we have not had to visit the hospital since the tube placement in October. Bianca is eating baby food, baby cookies, and likes to drink from her sippy cup. Her diet consists of Propimex 1, Similac, rice cereal, Carnitor, biotin, and for one week out of each month she gets Flagyl. Bianca is taken to Yale

every two to three weeks for blood work to see if any adjustments need to be made in her formula.

Other than having to be fed with special formula, Bianca is doing well. Bianca is almost on target in every development category. She is now 10 months and looks like she is going to crawl any day. She is a very happy child. Bianca loves to play with her cousins James and Candace who are ages five and three, and most of all loves her NUK. Bianca smiles most of the time, other than when she sees the doctors, and she starts to cry. She is very alert and knows exactly who is who.

Bianca is approaching her first birthday. The time has gone by us so quickly. At one point we didn't know what was going to happen to our daughter and now we are planning a very special event. Talk about being on a roller coaster ride. This has helped us to be stronger people.

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Melissa Stagni

Propionic Acidemia (PA), Age 11



Well, the last time I formally wrote about Melissa was in the April 1995 issue of the newsletter. I thought since I needed to fill some space in this newsletter, I would give you all an update on what's happening with our daughter, Melissa.

Melissa turned eleven years old last November and is currently mainstreamed in a 5th grade classroom in public school here in a suburb of Minneapolis, Minnesota. She is truly a Minnesota kid and loves winter and playing in the snow. Since she has been healthy, and not metabolically unstable for almost "five" (knock on wood) years, I don't tend to cringe when she does go out and play in the cold and snow.

She continues to get all of her nutrition from her "NG" tube. (*NG stands for nasal gastric*) Yes, we have continued the use of an NG versus a G-tube, mainly because, well, we just haven't had any problems. She has been putting down her own NG since she was about four years old...and just recently we moved up to a bigger NG tube (10 French), in order to make her bolus feeding go a little faster, and not so difficult to push with the syringe. Since going to this bigger NG, she has been able to perform the bolus herself! I have to admit, even though I do supervise her, it is a great relief on me and my arm muscles! She is very proud of herself, and I am even "training" her to measure her own formula. Her formula consists of Propimex-2, 80056, whole milk, water, one jar each of Gerber's fruit and meat baby food. I believe adding the "real" foods has contributed to her good health.

Melissa does not really see herself as different, and is a very happy-go-lucky child. She is developmentally delayed and has attended private speech therapy for the past seven years. Her speech has moved up to about a 6-year-old level, and reading is on a 3rd grade level, and math is about a 2nd grade level. She does have private tutoring, and even though she is labeled at school as "Mild-to-Moderate Mentally Impaired," she does function much higher than similar children with this label. She does have good memory skills and is always eager to learn.

She is currently in a Special Olympics Gymnastics team, and last summer proudly won four metals at the state meet. She is also taking swimming lessons, and is on an adapted t-ball team in the summer. She has been involved with Girl Scouts the past few years, but of course, I'm one of her leaders and I'm always advocating for her to be included in typical activities. Her social skills are obviously delayed as well, but after children get to know her, they do enjoy playing with her. She is definitely a "daddy's girl" and enjoys helping her dad work on his car, or go for a motorcycle ride.

She started a new school in our new neighborhood this past fall. I had her dietician, Dorothy Markowitz, come and speak during "Disabilities" week and she did an awesome job explaining "diets" and Melissa's disorder. I think that the kids now have a better appreciation for her. She recently went through some oral surgery, and while we were anxious about her going under anesthesia, she again amazed us by going through this procedure with flying colors. The dentist removed eight of her baby teeth and polished and cleaned her teeth. I had heard of other PA's that have teeth problems, mainly due to the

lack of protein. Her enamel on her teeth is not very strong and her gums had overgrown onto her baby teeth, thus not allowing them to loosen and come out. Thankfully, I found a great dentist who specializes in special needs that has managed to keep her teeth in order. Teeth can be such a "social stigma" to other kids when they don't look good. Another problem with "fitting-in" to school has been an "odor" that she has sometimes, especially when she sweats. I believe it's the Carnitor®, and her metabolic doctor, Sue Berry, is going to look into this, since she has heard of other PA's with this odor problem. If you have any solutions to this, please let me know!

I enjoy sharing my story with all of you, and also producing the OAA newsletter. Knowing that other families can learn from our experiences is so rewarding! Please feel free to call, write, or email us if you have any questions!

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Jessica Stevens Osran

Methlymalonic Acidemia (MMA), Age 7



This should by now be an update, but it is really the first time we have written to OAA regarding Jessica who is now seven years old. Has it been a tough road at times? Yes. But it has been extremely rewarding and fulfilling also. So how to summarize the past seven years in one simple statement? How about: "Life Altering"? Jessica has been a true blessing for our family. Through her sense of humor and strength she has shown us the real meaning of love and family.

Diagnosed at seven weeks of age it started with failure to thrive. Through the standard battery of metabolic screening she had what was determined to be a B12 disorder. Her doctor at the time (who is still her doctor) had a previous patient with Cobalamin C, so miraculously he had experience with the disorder. This was pretty much a stroke of luck as, at the time, only 17 cases had been documented.

Upon release at the time we began, aside from the treatment plan, the only other thing we were told could help her was therapy. So she began the long arduous road called therapy: speech, occupational, physical and vision. At the time O.T., P.T., and speech was provided privately. She had two vision therapists, one by the local school district and the other, by The Lighthouse for the Blind in Chicago. Jessica is and has been a true joy to be around, and usually gains her teachers support very quickly. She discontinued occupational and physical therapy at roughly three years of age. Her therapists felt she was age appropriate.

At one year of age, a routine MRI revealed hydrocephalus. A VP shunt was placed and has been revised only once, last year, when she was six years old.

At six and half Jessica had her first seizure. Ilene and I had sneaked away to England and Paris for one week celebrating our ten-year anniversary. She was left in the care of close family and friends. When we returned, we were informed she did not eat really well, and was a little upset that we were gone, and the air conditioning was broken in our house during the summer heat wave. I believe the seizure was heat and stress related. We agreed to place her on Carbatrol, at half the doctor-recommended dosage. They recommended 200 mg twice daily. We gave her one tablet a day at night in whipped cream. After taking two level tests, morning and night, it was found she had a therapeutic level in her body, in the morning and afternoon. During the treatment period we witnessed maybe one petit mal seizure, it's hard to tell for sure. We continued this treatment until we ran out of Carbatrol recently and just stopped giving it to her in September. She has since been seizure-free.

Presently she receives 45 minutes each of private speech and occupational therapy once a week. At school she gets two hours a week of speech therapy, seeing two different speech therapists, one at her mainstream class, and one at the special Ed class. Jessica can most easily articulate hard consonants. S, Z, CH, and X remain just outside her reach at this time, however she continues to make gains and God willing will have all her speech some day soon. Ilene has promised to have an "S" party when she finally gets her S's. She continues to have some fine motor delays and is once again receiving occupational therapy. Hopefully we can work on writing and shoe tying.

She sees an orientation and mobility therapist monthly, who takes her on walks and to the mall and has introduced her to cane use. The cane has been helpful in crowded places to keep people from bumping into her, and she just loves the attention. It's amazing-- when people see the cane, they just warm up to Jessica. As opposed to without the cane, people generally become angry at bumping into her, as if Jessica was just being careless. They just don't know she can't see well enough to react quickly.

Jessica has a little brother Benjamin, three years old, typically developing. What a breeze, a few sniffles etc. They are great friends and play together, and only occasionally fight with each other (which is, naturally typical sibling behavior and I wouldn't want it any other way).

As far as MMA and Homocystene levels, her doctor, Joel Charrow from Children's Memorial in Chicago, has never really bothered us too much with discussions of actual numbers. He feels her levels are her levels and as long as they are consistent and fairly low (relative to her disorder) then our efforts are better placed on managing her treatment and parenting. Another part of the life lessons here.

Jessica loves to color, and recently has become good at staying in the lines and using a variety of colors. She loves music and reading books, and loves to help around the house (amazing). In fact her little brother is starting to take advantage of this. She was toilet trained by five and half years old, and never made it into the size four diapers.

Jessica's favorite foods are pasta with lots of butter. She likes Parmesan cheese on top, French fries (pie kies she calls them). These two foods have gotten us through at least two years of her life. She likes meat, steak mostly, and doesn't eat too much of it at a time. She pretty much self regulates the amount of protein she eats. She is an extremely active child. Calcium intake continues to worry us a little.

Jessica started taking the bus to school when she was three years old. She loves taking the bus. This year she is repeating kindergarten. Mainstreamed in the morning in her home school, and in a special education kindergarten across town in the afternoon. This has been very successful for her and allowed her to have two school speech therapists in addition to her private speech therapist. She has gotten much better at playing with her peers, however we feel she still has a long way to go compared to her age group. She probably plays with her friends at a three-year-old level.

She was recently determined to have 20/800 vision (not that useful a number since 20 feet is really far for her effective vision). Her new eye doctor, Dr. Zaparakas, felt 5/40 was a more realistic number, and she could probably read 24 point text. This is similar to the text size in typical preschool print.

Jessica is currently on Hydroxycobalamin, 0.75 ML three times a week; Betaine, 1/2 Tsp. three times a day; Carnitine 1 Tsp. twice daily.

Ilene and I are involved in a local support group which meets twice a month. Our group has been together for three years now, and shows no sign of splitting up. We are planning to attend the metabolic conference in March of 2000. Ilene and I are interested in helping anyone in any way we can, please call or write.

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Prenatal Diagnosis of Organic Acidemias with Amniotic Fluid

by Drs. Larry Sweetman & Piero Rinaldo

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Parents of children with an organic acidemia often have questions about the possibilities of prenatal diagnosis in future pregnancies for their organic acid disorder, how it can be done, where, and how accurate it could be. First, it is very important that information be available on the exact biochemical and genetic disorder of the affected child. Prenatal diagnosis for some disorders is well established and known to be reliable but for some disorders there is less experience and the prenatal diagnosis may be experimental. It is also important that the parents have genetic counseling with their physician or genetic counselor in order to identify risk factors, provide a benefit/risk assessment and to consider the possible impact of medical, religious and social issues. Additional information needed is the availability of prenatal diagnosis, an estimate of its cost and whether it is covered by health insurance.

Different approaches to prenatal diagnosis have different requirements for the timing of obtaining the sample, how the sample is collected and how results can be confirmed. Chorionic villous sampling (CVS) by transcervical at less than 10 weeks of pregnancy or transabdominal at greater than 10 weeks has the advantage of being performed earlier in pregnancy and allows direct analysis for some enzyme deficiencies which can be verified later by repeat analysis enzyme assays of the cultured CVS cells. But CVS has a higher risk of fetal loss than amniocentesis, has the possibility of inconclusive results that would require a follow up amniocentesis and may be unreliable in some disorders such as Methylmalonic acidemia.

Amniocentesis is done later in pregnancy, between the 12th and 19th weeks (but usually between 16 and 18 weeks). It is a safer procedure than CVS and gives both amniotic fluid for analysis of diagnostic metabolites and amniocytes that can be cultured for an enzyme diagnosis assay(s) and molecular investigations. A needle is inserted through the mother's abdomen and a small amount of the amniotic fluid surrounding the fetus is drawn into a syringe. This fluid contains small amounts of organic acids and acylcarnitines produced by the fetal kidneys so that careful analysis of the amniotic fluid can be used for rapid prenatal diagnosis just as the urine organic acids can be used for diagnosis of babies and children. The amniotic fluid also contains some fetal cells called amniocytes, which require to be grown for 2-3 several weeks in tissue culture flasks in order to obtain enough of the cells to assay for possible enzyme deficiency. The cells can also be used to look for possible abnormalities in the chromosomes (such as those that cause Down's syndrome) that are not related to the organic acidemias. Because the amniocytes have to be cultured several weeks in order to do an enzyme assay, this method is not as rapid as prenatal diagnosis by analysis of metabolites in amniotic fluid which can usually be done in one to two days after the lab receives the amniotic fluid specimen. But the cultured cells can be a valuable confirmatory test or a backup if there are any questions about the results from the direct analysis of metabolites in the amniotic fluid. Analysis of metabolites in amniotic fluid can

diagnose a fetus affected with an organic aciduria but cannot distinguish between a normal fetus and a fetus that is a heterozygous carrier.

For prenatal diagnosis with amniotic fluid, the metabolites must be assayed with a very sensitive and accurate method in order to determine whether the levels are in the normal range or are elevated into the range of fetuses affected with an organic acidemia. The best method for organic acids in amniotic fluid is gas chromatography-mass spectrometry (GC/MS) with stable isotopically labeled internal standards for accurate quantitation and selected ion monitoring for very sensitive assay required to detect the very low levels of organic acids normally present in amniotic fluid. The best method for acylcarnitines is tandem mass spectrometry (tandem MS) which is very sensitive and the use of internal standards that are labeled with heavy isotopes for accurate quantitation. The choice of whether to measure organic acids or acylcarnitines depends on the organic acidemia and the instrumentation and experience of the laboratory doing the prenatal diagnosis. For some disorders, especially those for which there is limited experience with prenatal diagnosis, it may be best to analyze both organic acids and acylcarnitines. It is also important that the laboratory simultaneously analyze appropriate control specimens. Because the organic acidemias are rare, there are very few laboratories that perform prenatal diagnosis. This means that these few laboratories have considerable experience, which is important for accurate prenatal diagnosis. It is also important to know whether the prenatal diagnosis of for a specific organic acidemia in the first child is well established, such as for Methylmalonic acidemia and Propionic acidemia, and therefore diagnosis from amniotic fluid is known to be very reliable when performed under proper circumstances. Or on the other hand, have very few prenatal diagnosis have been done in the case of other, less common disorders for a disorder been done, and therefore the test should be considered strictly experimental and the reliability has not yet been established? Sometimes the prenatal diagnosis is ambiguous by analysis of metabolites in amniotic fluid and must be followed up with assay for enzyme deficiency in cultured amniocytes. Prenatal diagnosis of unaffected fetuses should always be followed up with routine biochemical testing, usually urinary organic acids or dried blood spot acylcarnitines from the newborn for confirmatory purposes.

We will list the organic acidemias that can be diagnosed prenatally by analysis of amniotic fluid in each of our laboratories and describe how we perform the tests. If you have questions about these or other disorders and whether they can also be diagnosed by enzyme assay, please contact us or have your physician or genetic counselor contact us. We may know other laboratories that can do prenatal diagnosis for the disorders that we do not perform.

Prenatal Diagnosis by the Institute of Metabolic Disease: Larry Sweetman, Ph.D.

For many years, while at the University of California San Diego and at Children's Hospital Los Angeles, Jan Holm and I provided prenatal diagnosis for organic acidemias by GC/MS analysis of organic acids in amniotic fluid:

Disorder	Total	Affected	Not affected
Propionic acidemia	112	23	84
Methylmalonic acidemia	57	8	49
Glutaric aciduria type 1	2	1	1
Glutaric aciduria type 2	5	1	4

At the Institute of Metabolic Disease I now perform these prenatal diagnoses by tandem MS analysis of acylcarnitines in amniotic fluid:

Disorder	Total	Affected	Not affected
Propionic acidemia	10	2	8
Methylmalonic acidemia	10	2	8
Glutaric aciduria type 1	2	0	2
Glutaric aciduria type 2	5	1	4

Tandem MS has the advantage of being more rapid and less expensive than GC/MS and appears to be as reliable.

For information regarding a request of prenatal diagnosis please contact:

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Prenatal Diagnosis by the Biochemical Genetics Laboratory, Mayo Clinic:
Piero Rinaldo, M.D., Ph.D.

Our experience with prenatal diagnosis of organic acidemias is very similar to Dr. Sweetman's and is summarized in the table below, which shows the prenatal diagnoses performed in my laboratory at Yale (1987-1998) and more recently at Mayo (1998-1999). While the majority of diagnoses are based on GC/MS analysis, we also routinely utilize tandem MS for confirmatory purposes, when applicable.

Disorder	Total	Affected	Not affected
Methylmalonic acidemia	83	16	67
Glutaric acidemia type 2	12	5	8
Isovaleric acidemia	6	1	5
Canavan disease	3	1	2
Propionic acidemia	2	0	2
3-Methylglutaconic acid.	1	0	1

In the case of Methylmalonic acidemia, we agree to perform a prenatal diagnosis only if there is a commitment to also have the amniocytes analyzed in the laboratory of Dr. David Rosenblatt (McGill University, Montreal, Canada). Previous knowledge of the complementation group (typically labeled as mut⁰, mut⁻, Cbl A, CblB, CblC, etc), associated homocystinuria, responsiveness to vitamin B12 of the affected child and B12 intake of the mother during the pregnancy are also important to secure an accurate prenatal diagnosis.

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Kaitlin Blake Burns

Propionic Acidemia (PA), Age 1



Hello to everyone!! Our names are Trent and Michelle Burns and we are writing about our daughter Kaitlin Blake Burns who has Propionic Acidemia. She was born January 7, 1999 in Concord, California right outside San Francisco. She was very easy to carry around for nine months, but a very difficult delivery. She ended up being an emergency C-section for the sole reason that she was holding onto her cord so tight she was cutting off her oxygen. For the first two days of life she was the "perfect" baby. Lots of hair, beautiful skin, and the perfect little nose. She did everything she was supposed to do, she slept, nursed well, and was perfection in our eyes. On the second night she became very cranky and hard to calm down. We being new parents of course called in the nurse and she said it was "typical new baby." So we dealt with it.

The next day Kaitlin would nurse a little and then spit up a lot. So being a new mom I called in the nurse again and of course the answer was "typical new baby." As the day went on Kaitlin became very sleepy and was hard to wake. Her breathing became very hard also. I must have called in the nurse a dozen times that afternoon. It took Kaitlin's Grandma to finally get the nurse to take Kaitlin to the nursery and have a doctor look at her. From there it was all down hill.

This is the part of the story all of you know all too well. The part where they tell you your child is very ill. A transport team from Children's Hospital in Oakland was called to take Kaitlin to their NICU. They brought Kaitlin in to see me before they took her to Children's. I had to stay in the hospital another night for my C-section recovery. I remember them opening the little window for me to touch her and before I could put my hand in she reached out for me. Everyone in that room including the doctors was in tears.

Kaitlin stayed in NICU for about three weeks. She was diagnosed with PA a week after birth. Once she got on the Propimex she did great. They kept her at Children's to observe her and then we went home. For the first four months we thought how easy it was to manage. We had only had one minor cold, which set her off metabolically, but not enough to go to the hospital. When Kaitlin was four months, we decided to take our first vacation. We packed up all of her things and drove to Southern California to visit Grandma and Grandpa. Wouldn't you know it, she got sick. Our three-day vacation to the beach ended up being eight days in the PICU at Miller Children's Hospital in Long Beach.

Kaitlin was really sick. They never did figure out what set her off metabolically. Her ammonia rose to somewhere around 600 and she was out of it. That was the first time she had ever had Lactulose and neomycin. She didn't handle either of those too well. She just kept vomiting or had extreme diarrhea. They were having to give her so much fluid that they had to put in a central line. That lasted all of two days. She got a small clot that made her leg swell. If it wasn't one thing, it was something else. Kaitlin had also had so many blood draws that she had to get her first transfusion. What a surreal experience! I remember how pale she was and then all of a sudden neon pink. It was so amazing. She opened her eyes for the first time in six days. Within a couple of hours she was wide awake

and eating from a bottle. The next day we made the well-awaited trip home. Since then, Kaitlin has been in the hospital twelve times and more ER visits than I care to remember.

Our last stay was the whole month of October. Kaitlin all of a sudden just stopped taking her bottle and I couldn't get any fluids into her. This was when we opted for the G-Tube and what a great decision that was. She was handling her feeds OK but we were still having problems with her ammonia and ketones so she stayed in the hospital. She was having so many blood draws done that they had exhausted all of her veins. She was going through IV's and Pick lines like every two days. So we were given the option of a temporary central line or a permanent one. We went with the permanent one and she now has a Port-a-Cath that is a wonderful thing.

Kaitlin still has problems with ammonia and keeping her amino acids normal, so we are still doing weekly blood draws. That is where the port comes in very handy. I was taught how to access it and now I do all of her blood draws at home. She is on many different meds to combat different things. She is on Biotin, Vitamin E, Folic Acid, half a Flintstones vitamin, Sodium Benzoate, and very large doses of Carnitine. She gets the Carnitine every two hours until 1:30 am so it is a full time job. Sometimes I feel more like a stay-home nurse than a stay-home mom.

Overall Kaitlin is doing great! She gets P.T., O.T., and speech therapy once a week in the home, which she loves (someone new to play with!). She is just now starting solid foods which all of you know is very difficult. Nevertheless, we are working through it and she surprises us with her resilience every day. Kaitlin is now one year old and she is learning to pull herself up onto everything and hopefully she will start cruising soon. We couldn't be more thankful to our doctors, dietitians, nurses, case managers, and counselors who have helped us along the way. We are definitely blessed.

Trent and Kaitlin and I are looking forward to meeting all of the families at the conference in March. If anyone would like to ask any questions about Kaitlin or our experiences please feel free to call or write us. We have found that other families who have been through it are a great resource. God Bless, and hope to talk to you soon.

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Joanna Tully

Methlymalonic Acidemia (MMA), 2 years, 8 months



James and Joanna (MMA) Tully (twins)

Hi.

I wondered if you would be interested in an update on Joanna Tully. I have had so much wonderful correspondence with OAA members that I thought you might be interested to hear how she is.

For those of you who don't know us, we are the Tully family and we live on a farm in the providence of Kwa Zulu Natal in South Africa. We have three children, Philippa, who is four, and a half, and the twins, James and Joanna, who are two and eight months. Born at 37 weeks, they weighed 2.6kg and 2.8kg respectively. Joanna had congenital pneumonia and had to be ventilated for eight days. The doctors say that had she had the MMA at birth, she would never have survived the initial illness.

When we brought her home from the hospital at three weeks, we discovered she had a pin-sized cataract in her one eye and were devastated. The ophthalmologist is less concerned. We have it checked annually, but it seems not to have grown and her eyesight is fine. At two months, Joanna was nursing really badly and screaming for what seemed like hours on end. She would put her little mouth over the nipple and then scream and push me away. The midnight to four in the morning sessions nearly drove me insane.

Fortunately for me, my husband was a saint. He took over the night bottle feeds for me and was Jamie's Mom and Dad. This made me very sad. Convinced that there had to be something wrong, I took Joanna to see a pediatrician in Durban. Joanna had been losing or gaining only 50 grams a week. Every clinic visit was awful. Dr. Crutched sent off for a full metabolic screening, convinced that nothing would come of it! He phoned us three weeks later to tell us that Joanna had MMA. From 1976 until 1997 there had only been 18 cases of MMA in South Africa.

Joanna only weighed three and a half kilograms. I began giving her the daily B12 injections and the formula S14 was couriered to us. Three days after her initial dose of B12, she smiled for the first time. She was four months old and it was the best birthday present I could ever have received! In retrospect, all she needed was the B12. It would seem that I could have continued to breast feed and maybe bonded better with her. After such a torrid start, I was only too happy to hand her over to the wonderful Zulu nanny for daytime feeds so that I could spend time with my little baby boy and my other little angel, Philippa. Due to her poor sucking reflex and weakness from the pneumonia, it would take her an hour to drink 25ml of formula initially.

I know that really serious MMA children have levels of up to 1000mol/mmol creatinine and so when I communicated with Elaina Jurecki and Prof. Leonard from London, they made me aware of how lucky we were that Joanna's levels were only 60mol/mmol. They were so encouraging, as were many of you. Thank you.

The levels were, however, still significantly higher than normal. Knowing what some parents have to go through with their MMA children with pumps and hospital time and seizures made me feel guilty for fussing, but I am a Mom who loves my baby as much as each of those parents and I was desperate to learn as much as I could, as there is little or no info in our country and certainly there are no 'metabolic specialists' or dieticians who have dealt with these cases that I could find.

After 10 days of B12, Joanna's levels came down to 20moll/mmol and after a total of seven months; her levels were almost normal. We were able to stop those awful B12 injections and she went onto a completely normal diet. Joanna was and still is very developmentally delayed. She has been to occupational therapy since she was four months old, sat at 14 months, crawled shortly afterwards and took her first step on another one of my birthdays, when she was two years and four months.

Until eight months ago, she was an incredibly irritable, difficult little girl. This all changed once she learned to walk. She is now a busy little girl. Joanna makes sounds and says: "mamama" and very few other consonants. She has been to speech therapy for about nine months and her social interaction and understanding have improved. Her twin James is a real tiger! Jo tries to copy him, so I have a great teacher in him.

Joanna loves the swing and loves to swim. She is our angel sent to teach us patience and the appreciation for all the things that we take for granted. We really do realize how lucky we are and continue to appreciate each new bit of progress as a miracle.

There is a Mum in Port Elizabeth who has a little boy of three years who has MMA that I speak with regularly. She too lives on a farm but does not have access to a computer, so I keep her in touch with OAA news. It helps to know that we all have our good days and our bad days, when we are angry or just sad and we should be allowed to have them!

Looking through an old newsletter some months ago, I came across an article by Dr Charles Roe on two newly discovered disorders. This appeared in the August '98 issue. The profile for the disorder named Methylmalonic semialdehyde dehydrogenase deficiency, fits our little Joanna in many respects. The initial low MMA levels, B12 responsiveness and the psychomotor delay as well as the initial normal levels of carnitine and serum B12. The biochemist and pediatrician agree with me, and think we should try to find out more. Dr Crutchley and I have e-mailed several people in this regard and we eagerly await their replies. If there is no treatment for this disorder, then we shall not pursue the fibroblast testing. Joanna hardly needs any more invasive procedures in her little life.

If anyone out there knows anything about this disorder-prognosis, symptoms, etc., we would be so grateful for the info.

Thank you OAA for being our lifeline.

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The Tully Family, James, Pete, Philippa, Jenny and Joanna (MMA) on their farm in South Africa.

Malik Donovan Lewis

Isovaleric Acidemia, Age 18 months



This is for my grandson: Malik Donovan Lewis – 18 mos. –Isovaleric Acidemia. "Malik I love you dearly—you'll always be my little pumpkin."

Malik Lewis was born July 31, 1999 weighing 7 lb. 15 oz., a strong and healthy baby boy. He is the first born in his family. Malik's parents, friends and relatives welcomed him into the world and all took part in helping to finalize his name. Malik's birth went very well, without complications. He was a beautiful baby boy! The family went home the next day ready to start their new adventure.

Malik was the sweetest little newborn baby with a very soft temperament. The first few days were, as any new parents would expect, a little hectic. Tiana was breastfeeding; she, dad and baby were getting used to their new schedule. Malik brought all the ingredients needed to fill their house with wondrous joy!

I received a call from my daughter on August 4th; she was concerned because Malik wasn't waking up to eat and when she tried he didn't have any interest in eating or staying awake. I told her to keep an eye on him and to call a nurse to get more advice. Tiana called me a few hours later from Children's Hospital (Seattle, Washington) to tell me they had taken Malik to his MD. He was dehydrated and his electrolytes were low so she told them to take him to Children's Hospital to have him examined.

I arrived at the hospital to find my daughter and son-in-law in the hallway of the emergency ward. They were very worried and confused about his condition. The doctors were performing a spinal tap and taking other tests to determine a cause for his condition. Malik's sleepy condition was getting worse and he had no interest in eating. The hospital staff informed us that they were treating him for infection, while waiting for test results. This was the beginning of a very long wait.

Malik's MD came to visit in the morning and because there wasn't any improvement in his condition, asked that they send him to the ICU to keep a closer eye on him. Tiana called to give me this news.

I arrived at the hospital early that morning to find my daughter and son-in-law in tears and so worried about their little son. Malik had been moved to the ICU. We watched as they continued to examine him and tried to find out what was causing him to be so very sick. The doctors were baffled at what was causing him to stay in the lethargic state he was now in. The tests they had performed were all coming back negative. The hospital staff wasn't offering us promising hope; they were very concerned about his well being.

On his first day in ICU, Malik fell into a comatose state. We stayed close to him always, reading to him, talking to him and touching him, hoping to stir some life back into his little body. Malik's breathing was very rapid, as he lay there so helpless. We were so worried

about the way he was breathing. Doctors assured us that it was good that he was breathing on his own; he never needed a respirator to help him.

It seemed every doctor came to see and examine him. Friends and family continued to call to offer their help and support. We just waited while he lay there, waiting for someone to give us some news. It just wasn't coming fast enough.

The second day in ICU the head doctor told us that she noticed an odor about him. She asked us if we noticed this. We all admitted that we did but thought it was medicine or something else; we didn't make the connection of it coming from Malik. She told us that she thought they were going down the wrong path in trying to find a diagnosis; she said the odor could mean that his condition is metabolic. She told us she was going to call Dr. Scott (a Metabolic Specialist) at the University of Washington's Metabolic Clinic to describe Malik's symptoms and get his opinion. She returned and told us Dr. Scott would be there shortly to examine Malik and help with a diagnosis. We were hopeful and anxious to meet him; we needed someone to offer us some hope.

Dr. Scott arrived soon after the phone call. I'll never forget that day and the technique he used as he examined Malik. He picked Malik up a few inches from his small bed and then dropped him onto the mattress. He continued to check his vital signs and then told us Malik had a metabolic disease. He told us he was ordering the necessary blood tests. Malik's ammonia levels had risen to 1500. He told us that he was going to start treating him and that we should see signs of improvement by morning. Dr. Scott assured us he would have a diagnosis soon; he was going to do the lab work necessary himself to speed up the process.

The next day came and Malik wasn't any better, in fact worse. Dr. Scott came in and told us that he had Isovaleric Acidemia, an inherited metabolic disorder. He apologized for Malik's condition and explained that he thought the treatment offered should have helped. Malik's ammonia levels had risen to 1600 by morning. Dr. Scott then decided that dialysis or CVVH (*Continuous Venous Venous Hemoperfusion. This is a method to remove toxic substances from the blood*) was needed to help clean Malik's blood and bring his ammonia level down so he could survive. We stayed close praying and hoping that we would see signs of improvement. We watched the machine continue to clean his blood and continued to read and talk to him letting him know how much we wanted him to wake up. After about thirty-two hours on dialysis, his ammonia level became safe enough to disconnect the machine.

Malik still lay in a coma. We kept waiting to see some sign of life in that little body. Malik's head nurse (Dianne, our loving hero) and I were sitting talking at his bedside; she nudged me to point out that his eyes were wide open and staring at me. What a sight! He opened them shortly and then closed them for another day. The next day his eyes opened and didn't close, he was awake! His little body started responding to life again! The first time he passed gas the unit cheered for his success. It was happening – he was getting better!

Malik stayed in ICU for about nine days; we watched so many babies move on to other rooms. The hospital had become a familiar and somehow comforting place. The staff is so wonderful; the miracles they perform daily are remarkable; they saved his life and I watched them help so many others. They certainly are our heroes!

Malik finally graduated from ICU and was moved to another floor on August 15th. He had a NG tube for feeding. His diet consisted of 160 ml of water, 160 ml of Enfamil Concentrate, 3.4 ml of L-Carnitine, 50 grams of I-Valex mixed with 12 oz of water. He was holding down his formula well. His mom and dad, family and friends stayed by his side; there wasn't a moment when his eyes opened someone was waiting to greet him. It was time to start this thing called "life" again, this time with the right diet.

The family came home on August 25th. His hospital stay lasted twenty days. He came home with his NG tube. He was accepting the bottle but still not strong enough to take in as much as they wanted him to. The NG tube lasted about a week after his release. He was eating on his own and didn't have any trouble keeping his formula down.

Malik is a strong and healthy 18-month-old little boy. His development shows all signs that he's at the stages an 18-month-old should be. He surprises us all including the doctors and nurses that have nurtured us all through this. His formula consists of 320 ml water, 320 ml of Enfamil w/iron, 640 ml of I-Valex and water mixed and 8 ml of Carnitine. He is able to intake 40 ml of Lucien. His metabolic clinic provides him with most of his foods. He is doing great with his diet this far.

Malik has a dedicated, wonderful medical support team. Dr. Scott (his Metabolic Specialist) has cared for him since he diagnosed him and brought him to where he is today, a healthy and happy little boy. Dr. Siegley (his MD), his Nutritionist, and Physical Therapist have been a big part of our lives. We are so thankful for the support we've had from them.

Malik has a new sister (D'Anyia). She was born on December 29, 1999. Dr. Chang (a genetic specialist) followed Tiana's pregnancy and delivered her. All tests were taken right after birth to determine if she had Isovaleric Acidemia. It was a long wait, we found out on New Year's eve at around 8:00 p.m. that she did not have it.

We'll end here, we could brag about this little boy forever; he brightens up a day with his laugh and eagerness to discover the world.

Our lives have been challenged to learn something new. One thing I have learned through all of this is that we are not alone. There are so many families challenged with life-threatening experiences. Our experience wasn't unique; we share in the joy and pain experienced with other families. It has been so helpful to listen to other stories; I hope ours helps in some way.

I've felt so much support since I joined the Association. Thank you so much for sharing your stories and the continued updated medical and personal information. It is truly an inspiration and it gives us so much hope that children born with these diseases can experience a healthy life. Our thoughts are with you all.

Peggy Harris – Malik's Grandmother

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